Clinical trial results:
A Phase III, Randomized, Double-Blind Placebo-Controlled, Multicenter Study To Evaluate the Efficacy and Safety of Baloxavir Marboxil in Combination With Standard-of-Care Neuraminidase Inhibitor in Hospitalized Participants With Severe Influenza

Summary

EudraCT number	2018-001416-30
Trial protocol	BG EE CZ SE BE DE FR FI HU ES RO
Global end of trial date	16 March 2020

Results information

Result version number	v1 (current)
This version publication date	30 September 2020
First version publication date	30 September 2020

Trial information

Trial identification

Sponsor protocol code	CP40617

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03684044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333,, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG,, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

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	30 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of baloxavir marboxil plus a standard of care (SOC) neuraminidase inhibitor (NAI) compared with matching placebo plus a SOC NAI

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	08 January 2019
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	Argentina: 8
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 71
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Serbia: 49
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Turkey: 2

Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	363
EEA total number of subjects	155

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)	11
Adults (18-64 years)	191
From 65 to 84 years	129
85 years and over	32

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

366 participants enrolled into the study and 363 actually received any treatment. All patients who received any study treatment are included in the safety analysis. Patients that received at least one dose of study treatment and were centrally assessed RT-PCR positive for influenza at any time point where included in the efficacy analysis.

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 at least two doses of baloxavir marboxil or its matching placebo on Day 1 and 4. A third dose of Baloxavir or its matching placebo will be given on Day 7 for participants who have not improved according to protocol defined criteria on Day 5 Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5

Arm type	Experimental
Investigational medicinal product name	Baloxavir marboxil
Investigational medicinal product code	
Other name	Xofluza
Pharmaceutical forms	Tablet, Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Baloxavir marboxil will be administered as a weight-based dose on Days 1 and 4. A third dose of Baloxavir or its matching placebo will be given on Day 7 for participants who have not improved according to protocol defined criteria on Day 5

Arm title	Placebo

Arm description:

Participants will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants will receive Baloxavir marboxil matching placebo.

Number of subjects in period 1	Baloxavir Marboxil	Placebo
Started	239	124
Completed	217	104
Not completed	22	20
Adverse event, serious fatal	4	7
Physician decision	1	-
Consent withdrawn by subject	11	9
Adverse event, non-fatal	3	-
Patient Not Available	-	2
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants will receive at least two doses of baloxavir marboxil or its matching placebo on Day 1 and 4. A third dose of Baloxavir or its matching placebo will be given on Day 7 for participants who have not improved according to protocol defined criteria on Day 5 Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5	
Reporting group title	Placebo
Reporting group description:	
Participants will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5	

Reporting group values	Baloxavir Marboxil	Placebo	Total
Number of subjects	239	124	363
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	8	3	11
Adults (18-64 years)	134	57	191
From 65-84 years	79	50	129
85 years and over	18	14	32
Age Continuous Units: Years			
arithmetic mean	58.0	61.6	
standard deviation	± 19.8	± 20.3	-
Sex: Female, Male Units:			
Male	122	68	190
Female	117	56	173

End points

End points reporting groups

Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants will receive at least two doses of baloxavir marboxil or its matching placebo on Day 1 and 4. A third dose of Baloxavir or its matching placebo will be given on Day 7 for participants who have not improved according to protocol defined criteria on Day 5 Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5	
Reporting group title	Placebo
Reporting group description:	
Participants will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5	

Primary: Time to Clinical Improvement

End point title	Time to Clinical Improvement
End point description:	
Time to Clinical Improvement is defined as Time to Hospital Discharge OR Time to NEWS2 (National Early Warning Score 2) of ≤ 2 maintained for 24 hours.	
End point type	Primary
End point timeframe:	
Up to Day 35	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (confidence interval 95%)	97.5 (75.9 to 117.2)	100.2 (75.9 to 144.4)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4666
Method	Gehan Wilcoxon
Parameter estimate	Median difference (net)
Point estimate	-2.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.4
upper limit	25.9

Secondary: Response Rates of the 6-Point Ordinal Scale at Day 7

End point title	Response Rates of the 6-Point Ordinal Scale at Day 7

End point description:

The ordinal scale categories are: Category 1) Discharged (or "ready for discharge") Category 2) Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen/non-invasive ventilation Category 3) Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen/non-invasive ventilation Category 4) ICU without mechanical (invasive) ventilation (or "ready for ICU admission") Category 5) Mechanical (invasive) ventilation Category 6) Death

End point type	Secondary

End point timeframe:

Day 7

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	108		
Units: percentage of participants				
number (not applicable)				
Category 1	49.2	45.4		
Category 2	22.6	24.1		
Category 3	20.1	22.2		
Category 4	4.0	1.9		
Category 5	3.5	4.6		
Category 6	0.5	1.9		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6326
Method	Cochran-Mantel-Haenszel

Secondary: Time to Clinical Response

End point title	Time to Clinical Response

End point description:

Time to Clinical Response is based on temperature ranges, oxygen saturation, respiratory status, heart rate, and hospitalization status.

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (confidence interval 95%)	138.3 (120.0 to 161.1)	145.1 (128.0 to 187.2)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs. Placebo
Comparison groups	Baloxavir Marboxil v Placebo
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3272
Method	Gehan Wilcoxon
Parameter estimate	Mean difference (net)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.9
upper limit	17.7

Secondary: Percentage of Participants on Mechanical Ventilation

End point title	Percentage of Participants on Mechanical Ventilation

End point description:

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: percentage of participants				
number (not applicable)	5.3	6.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Mechanical Ventilation

End point title	Duration of Mechanical Ventilation

End point description:

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (full range (min-max))	150.25 (18.0 to 465.0)	91.00 (24.0 to 407.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Requiring ICU Stay

End point title	Percentage of Participants Requiring ICU Stay

End point description:

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: percentage of participants				
number (not applicable)	4.3	3.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of ICU Stay

End point title	Duration of ICU Stay

End point description:

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (full range (min-max))	138.55 (23.7 to 362.0)	71.78 (18.7 to 139.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinical Failure

End point title	Time to Clinical Failure

End point description:

Time to clinical failure, defined as the time to death, mechanical ventilation, or ICU admission, corresponding to ordinal scale categories 6, 5, and 4, respectively, from baseline. Here 99999 represents data that was not available as very few patients experienced a clinical failure event and the median time to clinical failure could not be estimated

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hospital Discharge

End point title	Time to Hospital Discharge

End point description:

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (confidence interval 95%)	166.7 (144.7 to 190.7)	167.3 (146.4 to 211.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Post-Treatment Influenza-Related Complications

End point title	Percentage of Participants with Post-Treatment Influenza-Related Complications

End point description:

Influenza-related complications included pneumonia, myositis or rhabdomyolysis, encephalitis or encephalopathy, myocarditis and/or pericarditis, otitis media, sinusitis, exacerbation of COPD/asthma, sepsis, acute lung injury or acute respiratory distress syndrome.

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: percentage of participants				
number (not applicable)	10.6	14.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality Rate at Day 7

End point title	Mortality Rate at Day 7

End point description:

End point type	Secondary

End point timeframe:

Up to Day 7

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: percentage of participants				
number (confidence interval 95%)	0.5 (0.01 to 2.65)	2.6 (0.55 to 7.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality Rate at Day 28

End point title	Mortality Rate at Day 28

End point description:

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: percentage of participants				
number (confidence interval 95%)	1.9 (0.53 to 4.85)	5.3 (1.96 to 11.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to NEWS2 of ≤ 2 maintained for 24 hours

End point title	Time to NEWS2 of ≤ 2 maintained for 24 hours
End point description:	
A score of 0 (Range 0 - 3) indicates normal health conditions.	
End point type	Secondary
End point timeframe:	
Up to Day 35	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	114		
Units: hours				
median (confidence interval 95%)	106.3 (88.3 to 138.3)	127.2 (77.4 to 156.3)		

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 virus titer is defined as the time, in hours, between the initiation of study treatment and first time when the influenza virus titer is below the limit of detection (0.75 log10 TCID50/mL)	
End point type	Secondary
End point timeframe:	
Screening (baseline) and on Days 2, 3, 4, 5, 7, and 10	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	78		
Units: hours				
median (confidence interval 95%)	23.9 (23.2 to 24.5)	63.7 (46.4 to 68.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Influenza Virus Titer at Each Timepoint

End point title	Change from Baseline in Influenza Virus Titer at Each Timepoint

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained from nasal swabs. If influenza virus titer was less than the lower limit of quantification, the virus titer was imputed as 0.749 (log10TCID50/mL). A lower value indicates lower viral titer.

End point type	Secondary

End point timeframe:

Days 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	78		
Units: log10 TCID50/ml				
number (not applicable)				
Day 2	-2.36	-1.00		
Day 3	-2.70	-1.93		
Day 4	-2.88	-2.50		
Day 5	-3.01	-2.81		
Day 7	-3.00	-2.95		
Day 10	-3.02	-3.06		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Positive Influenza Virus Titer at Each Timepoint

End point title	Percentage of Participants with Positive Influenza Virus Titer at Each Timepoint

End point description:

Influenza virus titer is the quantity of influenza virus in a given volume within the samples obtained from nasal swabs. If influenza virus titer was less than the lower limit of quantification, the virus titer was imputed as 0.749 (log10 TCID50/mL). A lower value indicates lower viral titer.

End point type	Secondary

End point timeframe:

Days 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	78		
Units: percentage of participants				
number (not applicable)				
Day 2	37.7	80.3		
Day 3	18.6	53.4		
Day 4	7.9	26.7		
Day 5	1.3	20.8		
Day 7	2.7	5.8		
Day 10	1.4	1.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve in Virus Titer

End point title	Area Under the Curve in Virus Titer

End point description:

End point type	Secondary

End point timeframe:

Days 1, 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	77		
Units: log10 TCID50/mL*hours				
arithmetic mean (standard deviation)	291.68 (± 176.68)	332.04 (± 183.63)		

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, in hours, is defined as the time between the initiation of study treatment and first time when the virus RNA by RT-PCR is below the limit of detection (2.05 for flu A and 2.83 for flu B log10 virus particles/mL). Here 999999 represents data that were not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Screening (baseline) and on Days 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	111		
Units: hours				
median (confidence interval 95%)	216.3 (211.3 to 239.8)	261.1 (236.4 to 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Amount of Virus RNA (RT-PCR) at Each Timepoint

End point title	Change from Baseline in the Amount of Virus RNA (RT-PCR) at Each Timepoint

End point description:

If the amount of virus RNA was less than the lower limit of quantification, the amount of virus RNA was imputed as 2.18 for flu A and 2.93 for flu B (log10 virus particles/mL)

End point type	Secondary

End point timeframe:

Days 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	111		
Units: log10 virus particles/mL				
number (not applicable)				
Day 2	-0.98	-0.66		
Day 3	-1.54	-1.19		

Day 4	-2.35	-1.84		
Day 5	-2.91	-2.39		
Day 7	-3.15	-2.96		
Day 10	-3.69	-3.21		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive by RT-PCR at Each Timepoint

End point title	Percentage of Participants Positive by RT-PCR at Each Timepoint

End point description:

If the amount of virus RNA was less than the lower limit of quantification, the amount of virus RNA was imputed as 2.18 for flu A and 2.93 for flu B (log10 virus particles/mL)

End point type	Secondary

End point timeframe:

Days 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	111		
Units: percentage of participants				
number (not applicable)				
Day 2	95.6	96.3		
Day 3	90.0	93.3		
Day 4	88.1	87.9		
Day 5	79.9	85.4		
Day 7	69.6	68.0		
Day 10	46.7	50.5		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Days 1, 2, 3, 4, 5, 7, and 10

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	106		
Units: log10 virus particles/mL				
arithmetic mean (standard deviation)	676.40 (± 371.72)	740.15 (± 484.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A serious adverse event (SAE) is any significant hazard, contraindication, side effect that is fatal or life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly/ birth defect, is medically significant or requires intervention to prevent one or other of the outcomes listed above.

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	124		
Units: percentage of participants				
number (not applicable)				
AEs	45.2	50.0		
SAEs	12.1	15.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with AEs and SAEs Leading to Discontinuation

from Treatment	
End point title	Percentage of Participants with AEs and SAEs Leading to Discontinuation from Treatment
End point description: Discontinuation from study treatment.	
End point type	Secondary
End point timeframe: Up to Day 35	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	124		
Units: percentage of participants				
number (not applicable)				
AEs	1.3	3.2		
SAEs	0.8	1.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Post-Treatment ALT and AST Above Baseline and >3 × ULN, >5 × ULN, >10 × ULN	
End point title	Percentage of Participants with Any Post-Treatment ALT and AST Above Baseline and >3 × ULN, >5 × ULN, >10 × ULN
End point description: ALT = alanine aminotransferase AST = aspartate transaminase	
End point type	Secondary
End point timeframe: Up to Day 35	

End point values	Baloxavir Marboxil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	124		
Units: percentage of participants				
number (not applicable)				
AST(U/L) or ALT (U/L) >3 x ULN	4.6	8.9		
AST(U/L) or ALT (U/L) >5 x ULN	0.8	3.2		
AST(U/L) or ALT (U/L) >10 x ULN	0	1.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Baloxavir (Active Metabolite) at Specified Time Points

End point title	Plasma Concentration of Baloxavir (Active Metabolite) at Specified Time Points[1]

End point description:

Here 999999 represents data that were not estimable.

End point type	Secondary

End point timeframe:

Day 1, 2, 4, 5, 7 and 8

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: PK parameters were not estimated for the Placebo arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 - 30 minutes postdose	37.82 (± 23.61)			
Day 1 - 2 hours postdose	75.06 (± 52.16)			
Day 1 - 4 hours postdose	95.85 (± 58.36)			
Day 1 - 10 hours postdose	64.47 (± 39.47)			
Day 2 - 24 hours postdose	53.36 (± 37.42)			
Day 4 - Predose	24.26 (± 15.87)			
Day 4 - 30 minutes postdose	49.16 (± 52.07)			
Day 4 - 2 hours postdose	109.66 (± 95.22)			
Day 4 - 4 hours postdose	117.69 (± 60.54)			
Day 4 - 10 hours postdose	94.08 (± 49.71)			
Day 5 - 24 hours postdose	77.98 (± 42.89)			
Day 7 - predose	23.31 (± 25.87)			
Day 8 - 24 hours postdose	105.00 (± 999999)			
Visit 8	28.37 (± 61.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration to Time Curve From Time 0 to 72 hours (AUC0-72) of Baloxavir

End point title	Area Under the Concentration to Time Curve From Time 0 to 72 hours (AUC0-72) of Baloxavir[2]

End point description:

End point type	Secondary

End point timeframe:

Day 1, 2, 4, 5, 7 and 8

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: PK parameters were not estimated for the Placebo arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Hours(h)*nanogram(ng)/milliliter (mL)				
geometric mean (geometric coefficient of variation)				
Visit 1 (Day 1)	2820 (± 70.5)			
Visit 4 (Day 4)	3170 (± 53.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Baloxavir

End point title	Maximum Plasma Concentration (Cmax) of Baloxavir[3]

End point description:

End point type	Secondary

End point timeframe:

Day 1, 2, 4, 5, 7 and 8

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: PK parameters were not estimated for the Placebo arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Visit 1 (Day 1)	86.3 (± 64.6)			

Visit 4 (Day 4)	123 (± 51.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Half-Life (T1/2) of Baloxavir

End point title	Apparent Half-Life (T1/2) of Baloxavir[4]

End point description:

Here 999999 represents data that were not estimable.

End point type	Secondary

End point timeframe:

Day 1, 2, 4, 5, 7 and 8

Notes:

[4] - 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: PK parameters were not estimated for the Placebo arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Hours (h)				
geometric mean (geometric coefficient of variation)				
Visit 1 (Day 1)	18.9 (± 999999)			
Visit 4 (Day 4)	23.4 (± 12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration at 24 hours (C24) of Baloxavir

End point title	Concentration at 24 hours (C24) of Baloxavir[5]

End point description:

Here 999999 represents data that were not estimable.

End point type	Secondary

End point timeframe:

Day 1, 2, 4, 5, 7 and 8

Notes:

[5] - 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: PK parameters were not estimated for the Placebo arm.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Visit 1 (Day 1)	43.9 (± 74.4)			
Visit 4 (Day 4)	67.1 (± 66.8)			
Visit 6 (Day 7)	105 (± 999999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Day 35	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Baloxavir Marboxil

Reporting group description:

Participants will receive at least two doses of baloxavir marboxil or its matching placebo on Day 1 and 4. A third dose of Baloxavir or its matching placebo will be given on Day 7 for participants who have not improved according to protocol defined criteria on Day 5 Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5

Reporting group title	Placebo

Reporting group description:

Participants will be assigned in a 2:1 ratio to receive baloxavir marboxil or matching placebo. Study treatment will be given in combination with SOC NAI (i.e., oseltamivir, zanamivir, or peramivir) in accordance with local clinical practice. SOC NAI will be administered to cover a minimum of treatment exposure from Day 1 to Day 5

Serious adverse events	Baloxavir Marboxil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 239 (12.13%)	19 / 124 (15.32%)	
number of deaths (all causes)	4	7	
number of deaths resulting from adverse events			
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral ischaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 239 (0.84%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 239 (0.84%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 239 (1.26%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 239 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 239 (0.42%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 239 (0.42%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral artery embolism			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 239 (2.93%)	5 / 124 (4.03%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 239 (0.84%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection viral			
subjects affected / exposed	1 / 239 (0.42%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 239 (0.00%)	1 / 124 (0.81%)	
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: 3 %

Non-serious adverse events	Baloxavir Marboxil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 239 (18.41%)	27 / 124 (21.77%)	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	6 / 239 (2.51%)	5 / 124 (4.03%)	
occurrences (all)	7	5	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 239 (3.77%)	2 / 124 (1.61%)	
occurrences (all)	11	2	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	10 / 239 (4.18%)	6 / 124 (4.84%)	
occurrences (all)	10	6	
Diarrhoea			
subjects affected / exposed	8 / 239 (3.35%)	6 / 124 (4.84%)	
occurrences (all)	8	7	
Nausea			
subjects affected / exposed	7 / 239 (2.93%)	4 / 124 (3.23%)	
occurrences (all)	9	4	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 239 (2.09%)	4 / 124 (3.23%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 239 (3.77%)	5 / 124 (4.03%)	
occurrences (all)	9	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2019	Major updates included the change from study sample size from approximately 240 to approximately 366, the endpoint "time to clinical response" was moved from an exploratory endpoint to secondary endpoint, and section was added to summarize post-marketing safety data that identified hypersensitivity reactions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported