Clinical trial results:
A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients 1 to <12 Years of Age With Influenza-Like Symptoms

Summary

EudraCT number	2018-002169-21
Trial protocol	ES PL
Global end of trial date	03 April 2019

Results information

Result version number	v1
This version publication date	12 October 2019
First version publication date	12 October 2019

Trial information

Trial identification

Sponsor protocol code	CP40563

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03629184
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	09 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2019
Global end of trial reached?	Yes
Global end of trial date	03 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the safety of a single dose of baloxavir marboxil with 5 days of oseltamivir administered twice daily.

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	20 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	Costa Rica: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	United States: 161
Worldwide total number of subjects	173
EEA total number of subjects	8

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)	16
Children (2-11 years)	157
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

173 participants were enrolled and dosed in this study.

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). Oseltamivir matching placebo will also be administered orally twice daily (BID) for 5 days.

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

Dosage and administration details:

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

Investigational medicinal product name	Oseltamivir matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Oseltamivir matching placebo was administered orally twice daily (BID) for 5 days

Arm title	Oseltamivir

Arm description:

Participants will receive oseltamivir orally BID for 5 days (based on body weight). Baloxavir marboxil matching placebo will also be administered orally on Day 1

Arm type	Active comparator
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	Tamiflu
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants received oseltamivir orally BID for 5 days (based on body weight)

Investigational medicinal product name	Baloxavir marboxil matching placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Baloxavir marboxil matching placebo was administered orally on Day 1

Number of subjects in period 1	Baloxavir Marboxil	Oseltamivir
Started	115	58
Completed	112	57
Not completed	3	1
Consent withdrawn by subject	2	1
Physician decision	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). Oseltamivir matching placebo will also be administered orally twice daily (BID) for 5 days.	
Reporting group title	Oseltamivir
Reporting group description:	
Participants will receive oseltamivir orally BID for 5 days (based on body weight). Baloxavir marboxil matching placebo will also be administered orally on Day 1	

Reporting group values	Baloxavir Marboxil	Oseltamivir	Total
Number of subjects	115	58	173
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	9	7	16
Children (2-11 years)	106	51	157
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	6.10	6.02	
standard deviation	± 2.90	± 3.20	-
Sex: Female, Male Units: Subjects			
Female	60	32	92
Male	55	26	81
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	1	0	1
Black or African American	6	5	11
Native Hawaiian or other Pacific Islander	0	1	1
White	98	51	149
Multiple	4	0	4
Unknown	5	1	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	52	27	79
Not Hispanic or Latino	63	31	94

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). Oseltamivir matching placebo will also be administered orally twice daily (BID) for 5 days.

Reporting group title	Oseltamivir

Reporting group description:

Participants will receive oseltamivir orally BID for 5 days (based on body weight). Baloxavir marboxil matching placebo will also be administered orally on Day 1

Primary: 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)[1]

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	Primary

End point timeframe:

Up to Day 29

Notes:

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

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	58		
Units: percentage of participants				
number (not applicable)				
Adverse Events (AEs)	46.1	53.4		
Serious Adverse Events (SAEs)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Baloxavir Marboxil - Sparce PK Population

End point title	Plasma Concentrations of Baloxavir Marboxil - Sparce PK Population[2]

End point description:

Concentration data are provided by body-weight groups for participants receiving Baloxavir Marboxil only. Values below lower limit of quantification (0.5 ng/mL) are set to zero. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Days 1 (Post-Dose), 2, 4, 6 and 10

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: Concentration data are provided for participants receiving Baloxavir Marboxil only.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: ng/mL				
arithmetic mean (standard deviation)				
5 - <10 kg (Day 1) (n=1)	0.000 (± 99999)			
5 - <10 kg (Day 2) (n=1)	0.000 (± 99999)			
5 - <10 kg (Day 4) (n=0)	99999 (± 99999)			
5 - <10 kg (Day 6) (n=1)	0.000 (± 99999)			
5 - <10 kg (Day 10) (n=0)	99999 (± 99999)			
10 - <15 kg (Day 1) (n=16)	0.073 (± 0.2001)			
10 - <15 kg (Day 2) (n=7)	0.000 (± 0.0000)			
10 - <15 kg (Day 4) (n=9)	0.000 (± 0.0000)			
10 - <15 kg (Day 6) (n=13)	0.000 (± 0.0000)			
10 - <15 kg (Day 10)(n=3)	0.000 (± 0.0000)			
15 - <20 kg (Day 1) (n=22)	0.090 (± 0.2386)			
15 - <20 kg (Day 2) (n=13)	0.000 (± 0.0000)			
15 - <20 kg (Day 4) (n=7)	0.000 (± 0.0000)			
15 - <20 kg (Day 6) (n=17)	0.000 (± 0.0000)			
15 - <20 kg (Day 10) (n=3)	0.000 (± 0.0000)			
>=20 kg (Day 1) (n=58)	0.048 (± 0.1936)			
>=20 kg (Day 2) (n=34)	0.000 (± 0.0000)			
>=20 kg (Day 4) (n=25)	0.000 (± 0.0000)			
>=20 kg (Day 6) (n=56)	0.000 (± 0.0000)			
>=20 kg (Day 10) (n=6)	0.000 (± 0.0000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of S-033447 - Sparce PK Population

End point title	Plasma Concentrations of S-033447 - Sparce PK Population[3]

End point description:

Concentration data are provided by body-weight groups for participants receiving Baloxavir Marboxil only. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Days 1 (Post-Dose), 2, 4, 6 and 10

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: Concentration data are provided for participants receiving Baloxavir Marboxil only.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: ng/mL				
arithmetic mean (standard deviation)				
5 - <10 kg (Day 1) (n=1)	45.700 (± 99999)			
5 - <10 kg (Day 2) (n=1)	45.800 (± 99999)			
5 - <10 kg (Day 4) (n=0)	99999 (± 99999)			
5 - <10 kg (Day 6) (n=1)	3.110 (± 99999)			
5 - <10 kg (Day 10) (n=0)	99999 (± 99999)			
10 - <15 kg (Day 1) (n=16)	49.084 (± 53.6689)			
10 - <15 kg (Day 2) (n=7)	42.900 (± 16.5227)			
10 - <15 kg (Day 4) (n=9)	9.233 (± 5.3879)			
10 - <15 kg (Day 6) (n=13)	2.965 (± 1.6480)			
10 - <15 kg (Day 10) (n=3)	0.367 (± 0.6351)			
15 - <20 kg (Day 1) (n=22)	64.160 (± 73.6320)			
15 - <20 kg (Day 2) (n=13)	67.729 (± 46.7346)			
15 - <20 kg (Day 4) (n=7)	15.840 (± 10.8285)			
15 - <20 kg (Day 6) (n=17)	4.829 (± 3.6562)			

15 - <20 kg (Day 10) (n=3)	1.110 (± 1.9226)			
>=20 kg (Day 1) (n=58)	29.899 (± 26.1558)			
>=20 kg (Day 2) (n=34)	56.287 (± 40.4073)			
>=20 kg (Day 4) (n=25)	18.674 (± 11.2179)			
>=20 kg (Day 6) (n=56)	7.397 (± 5.0530)			
>=20 kg (Day 10) (n=6)	3.953 (± 2.2536)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Baloxavir Marboxil - Extensive PK Population

End point title	Plasma Concentrations of Baloxavir Marboxil - Extensive PK Population[4]

End point description:

Concentration data are provided by body-weight groups for participants receiving Baloxavir Marboxil only. Values below lower limit of quantification (0.5 ng/mL) are set to zero. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Days 1 (Post-Dose), 2, 4, 6 and 10

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: Concentration data are provided for participants receiving Baloxavir Marboxil only.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.5 - 2 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 4 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 6 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 2 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 4 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 6 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 10 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 0.5 - 2 hrs (10 - <15 kg) (n=4)	0.000 (± 0.0000)			
Day 1, 4 hrs (10 - <15 kg) (n=2)	0.000 (± 0.0000)			

Day 1, 6 hrs (10 - <15 kg) (n=1)	0.000 (± 99999)			
Day 2 (10 - <15 kg) (n=3)	0.000 (± 0.0000)			
Day 4 (10 - <15 kg) (n=1)	0.000 (± 99999)			
Day 6 (10 - <15 kg) (n=3)	0.000 (± 0.0000)			
Day 10 (10 - <15 kg) (n=1)	0.000 (± 99999)			
Day 1, 0.5 - 2 hrs (15 - <20 kg) (n=4)	0.000 (± 0.0000)			
Day 1, 4 hrs (15 - <20 kg) (n=1)	0.000 (± 99999)			
Day 1, 6 hrs (15 - <20 kg) (n=1)	0.000 (± 99999)			
Day 2 (15 - <20 kg) (n=2)	0.000 (± 0.0000)			
Day 4 (15 - <20 kg) (n=1)	0.000 (± 99999)			
Day 6 (15 - <20 kg) (n=3)	0.000 (± 0.0000)			
Day 10 (15 - <20 kg) (n=0)	99999 (± 99999)			
Day 1, 0.5 - 2 hrs (>=20 kg) (n=10)	0.051 (± 0.1600)			
Day 1, 4 hrs (>=20 kg) (n=9)	0.062 (± 0.1863)			
Day 1, 6 hrs ((>=20 kg) (n=6)	0.000 (± 0.0000)			
Day 2 (>=20 kg) (n=5)	0.000 (± 0.0000)			
Day 4 (>=20 kg) (n=4)	0.000 (± 0.0000)			
Day 6 (>=20 kg) (n=9)	0.000 (± 0.0000)			
Day 10 (>=20 kg) (n=0)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of S-033447 - Extensive PK Population

End point title	Plasma Concentrations of S-033447 - Extensive PK

End point description:

Concentration data are provided by body-weight groups for participants receiving Baloxavir Marboxil only. Values below lower limit of quantification (0.5 ng/mL) are set to zero. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Days 1 (Post-Dose), 2, 4, 6 and 10

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: Concentration data are provided for participants receiving Baloxavir Marboxil only.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1, 0.5 - 2 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 4 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 6 hrs (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 2 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 4 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 6 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 10 (5 - <10 kg) (n=0)	99999 (± 99999)			
Day 1, 0.5 - 2 hrs (10 - <15 kg) (n=4)	10.768 (± 14.7987)			
Day 1, 4 hrs (10 - <15 kg) (n=2)	49.500 (± 13.0108)			
Day 1, 6 hrs (10 - <15 kg) (n=1)	41.000 (± 99999)			
Day 2 (10 - <15 kg) (n=3)	28.933 (± 14.7514)			
Day 4 (10 - <15 kg) (n=1)	2.230 (± 99999)			
Day 6 (10 - <15 kg) (n=3)	3.131 (± 2.2828)			
Day 10 (10 - <15 kg) (n=1)	0.000 (± 99999)			
Day 1, 0.5 - 2 hrs (15 - <20 kg) (n=4)	93.883 (± 152.5431)			
Day 1, 4 hrs (15 - <20 kg) (n=1)	72.900 (± 99999)			
Day 1, 6 hrs (15 - <20 kg) (n=1)	80.300 (± 99999)			
Day 2 (15 - <20 kg) (n=2)	42.640 (± 47.6024)			
Day 4 (15 - <20 kg) (n=1)	12.200 (± 99999)			
Day 6 (15 - <20 kg) (n=3)	2.663 (± 1.5387)			
Day 10 (15 - <20 kg) (n=0)	99999 (± 99999)			
Day 1, 0.5 - 2 hrs (>=20 kg) (n=10)	19.923 (± 27.0980)			
Day 1, 4 hrs (>=20 kg) (n=9)	69.198 (± 55.7220)			
Day 1, 6 hrs ((>=20 kg) (n=6)	65.527 (± 43.0799)			
Day 2 (>=20 kg) (n=5)	57.980 (± 37.8922)			
Day 4 (>=20 kg) (n=4)	21.775 (± 3.7968)			
Day 6 (>=20 kg) (n=9)	6.240 (± 3.3702)			

Day 10 (>=20 kg) (n=0)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration to Time Curve from Time 0 to Infinity (AUC0-inf) of baloxavir marboxil and S-033447

End point title	Area Under the Concentration to Time Curve from Time 0 to Infinity (AUC0-inf) of baloxavir marboxil and S-033447
End point description:	
End point type	Secondary
End point timeframe:	
Up to Day 10	

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Pending				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[6] - Results will be provided from the pop-PK report before 03-Apr-2019.

[7] - Results will be provided from the pop-PK report before 03-Apr-2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of baloxavir marboxil and S-033447

End point title	Maximum Plasma Concentration (Cmax) of baloxavir marboxil and S-033447
End point description:	
End point type	Secondary
End point timeframe:	
Up to Day 10	

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Pending				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[8] - Results will be provided from the pop-PK report before 03-Apr-2019.

[9] - Results will be provided from the pop-PK report before 03-Apr-2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax) of baloxavir marboxil and S-033447

End point title	Time to Maximum Plasma Concentration (Tmax) of baloxavir marboxil and S-033447

End point description:

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Pending				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[10] - Results will be provided from the pop-PK report before 03-Apr-2019.

[11] - Results will be provided from the pop-PK report before 03-Apr-2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Half-Life (T1/2) of baloxavir marboxil and S-033447

End point title	Apparent Half-Life (T1/2) of baloxavir marboxil and S-033447

End point description:

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Pending				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[12] - Results will be provided from the pop-PK report before 03-Apr-2019.

[13] - Results will be provided from the pop-PK report before 03-Apr-2019.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Alleviation of Influenza Signs and Symptoms

End point title	Time to Alleviation of Influenza Signs and Symptoms

End point description:

Time to alleviation of influenza signs and symptoms is defined as the length of time taken from the start of treatment to the point at which all of the following criteria are met and remain so for at least 21.5 hours: - A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15 of the Canadian Acute Respiratory Illness and Flu Scale [CARIFS]) - A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" - First return to afebrile state (tympanic temperature ≤37.2 degree Celsius [°C])

End point type	Secondary

End point timeframe:

Up to Day 15

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	43		
Units: hours				
median (confidence interval 95%)	138.1 (116.6 to 163.2)	150.0 (115.0 to 165.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Fever

End point title	Duration of Fever

End point description:

Length of time taken by participants to return to afebrile state [tympanic temperature ≤ 37.2°C] and remaining so for at least 21.5 hours.

End point type	Secondary

End point timeframe:

Up to Day 15

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	43		
Units: hours				
median (confidence interval 95%)	41.2 (24.5 to 45.7)	46.8 (30.0 to 53.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Symptoms

End point title	Duration of Symptoms

End point description:

The clinical efficacy of baloxavir marboxil is evaluated by duration of symptoms i.e., alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire).

End point type	Secondary

End point timeframe:

Up to Day 15

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	43		
Units: hours				
median (confidence interval 95%)	66.4 (43.7 to 76.4)	67.9 (45.8 to 88.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Return to Normal Health and Activity

End point title	Time to Return to Normal Health and Activity

End point description:

Time to Return to Normal health and activity' is identified by a 'Yes' response to the following question on the CARIFS: "Since the last assessment has the patient been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?"

End point type	Secondary

End point timeframe:

Up to Day 15

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	43		
Units: hours				
median (confidence interval 95%)	116.5 (94.9 to 138.0)	111.6 (80.8 to 138.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Influenza-Related Complications

End point title	Frequency of Influenza-Related Complications

End point description:

Influenza related complications include death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis.

End point type	Secondary

End point timeframe:

Up to Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	43		
Units: count of events				
Total	6	4		
Death	0	0		
Hospitalization	0	0		
Sinusitis	1	0		
Otitis Media	3	3		
Pneumonia	1	0		
Bronchitis	1	0		
Encephalitis/Encephalopathy	0	0		
Febrile Seizures	0	1		
Myositis	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Influenza-Related Complications

End point title	Percentage of Participants with Influenza-Related Complications

End point description:

Influenza related complications include death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis.

End point type	Secondary

End point timeframe:

Up to Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	43		
Units: percentage of participants				
number (not applicable)				
Total	7.4	7.0		
Death	0	0		
Hospitalization	0	0		
Sinusitis	1.2	0		
Otitis Media	3.7	4.7		
Pneumonia	1.2	0		
Bronchitis	1.2	0		
Encephalitis/Encephalopathy	0	0		
Febrile Seizures	0	2.3		
Myositis	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Requiring Antibiotics

End point title	Percentage of Participants Requiring Antibiotics

End point description:

End point type	Secondary

End point timeframe:

Up to Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	43		
Units: percentage of participants				
number (not applicable)				
Total	4.9	4.7		
Bronchitis	0	0		
Otitis Media	2.5	4.7		
Pneumonia	1.2	0		
Sinusitis	1.2	0		

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 any study treatment and first time when the influenza virus titer is below the limit of detection. Number of patients with post-baseline Virology assessment and a positive virus titer on Day 1 were included in this analysis. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 - Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	37		
Units: hours				
median (confidence interval 95%)				
Virus Titer	24.2 (23.5 to 24.6)	75.8 (68.9 to 97.8)		

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 any study treatment and first time when the virus RNA by RT-PCR is below the limit of detection.

Number of patients with post-baseline Virology assessment and a positive RNA at Day 1 were included in this analysis. Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 - Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	39		
Units: hours				
median (confidence interval 95%)	242.5 (235.8 to 262.8)	238.9 (214.0 to 286.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Influenza Virus Titer at Day 2, 4, 6, 10, 15, 29

End point title	Change from Baseline in Influenza Virus Titer at Day 2, 4, 6, 10, 15, 29

End point description:

Influenza virus titer (log10TCID50/ML) 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:

Baseline, Day 2, 3 (optional), 4, 6, 10, 15 (optional), 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	38		
Units: log10TCID50/ML				
arithmetic mean (standard deviation)				
Baseline (Baloxvir Marboxil n=67/Osetamivir n=38)	4.43 (± 1.36)	4.27 (± 1.48)		
Day 2 (Baloxvir Marboxil n=64/ Osetamivir n=37)	-3.59 (± 1.34)	-1.79 (± 1.54)		
Day 3 (Baloxvir Marboxil n=3 / Osetamivir n=2)	-2.83 (± 0.58)	-2.63 (± 0.88)		
Day 4 (Baloxvir Marboxil n=61 / Osetamivir n=31)	-3.53 (± 1.38)	-3.27 (± 1.54)		
Day 6 (Baloxvir Marboxil n=63 / Osetamivir n=35)	-3.55 (± 1.32)	-3.52 (± 1.50)		
Day 10 (Baloxvir Marboxil n=4 / Osetamivir n=4)	-3.66 (± 1.40)	-3.50 (± 1.42)		

Day 15 (Baloxvir Marboxil n=4 / Osetamivir n=4)	-3.75 (± 0.54)	-3.63 (± 1.45)		
Day 29 (Baloxvir Marboxil n=4 / Osetamivir n=4)	-3.50 (± 1.43)	-3.75 (± 1.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Amount of Virus RNA (RT-PCR) at Day 2, 4, 6, 10, 15, 29

End point title	Change from Baseline in the Amount of Virus RNA (RT-PCR) at Day 2, 4, 6, 10, 15, 29

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). Here 99999 represents results data which was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Baseline, Day 2, 3 (optional), 4, 6, 10, 15 (optional), 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	40		
Units: log10 virus particles/mL				
arithmetic mean (standard deviation)				
Baseline (Baloxvir Marboxil n=76/Osetamivir n=40)	6.46 (± 1.50)	6.86 (± 1.02)		
Day 2 (Baloxvir Marboxil n=70 / Osetamivir n=39)	-1.74 (± 1.13)	-1.12 (± 1.12)		
Day 3 (Baloxvir Marboxil n=4 / Osetamivir n=2)	-1.78 (± 1.50)	-2.21 (± 0.94)		
Day 4 (Baloxvir Marboxil n=61 / Osetamivir n=30)	-2.40 (± 1.50)	-2.47 (± 1.35)		
Day 6 (Baloxvir Marboxil n=60 / Osetamivir n=30)	-2.73 (± 1.78)	-3.32 (± 1.27)		
Day 10 (Baloxvir Marboxil n=35 / Osetamivir n=15)	-3.55 (± 1.62)	-3.81 (± 1.19)		
Day 15 (Baloxvir Marboxil n=2 / Osetamivir n=1)	-1.24 (± 3.06)	-4.44 (± 99999)		
Day 29 (Baloxvir Marboxil n=1 / Osetamivir n=0)	2.18 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Positive Influenza Virus Titer at Day 2, 4, 6, 10

End point title	Percentage of Participants with Positive Influenza Virus Titer at Day 2, 4, 6, 10

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 2, 3 (optional), 4, 6, 10

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	43		
Units: percentage of participants				
number (not applicable)				
Baseline	82.7	88.4		
Day 2	12.3	65.1		
Day 3 (optional)	1.2	2.3		
Day 4	19.8	20.9		
Day 6	9.9	4.7		
Day 10	1.2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive by RT-PCR at Day 2, 4, 6, 10, 15, 29

End point title	Percentage of Participants Positive by RT-PCR at Day 2, 4, 6, 10, 15, 29

End point description:

End point type	Secondary

End point timeframe:

Day 2, 3 (optional), 4, 6, 10, 15 (optional), 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	43		
Units: percentage of participants				
number (not applicable)				
Baseline	93.8	93.0		
Day 2	86.4	90.7		
Day 3 (optional)	4.9	4.7		

Day 4	76.5	74.4		
Day 6	72.8	65.1		
Day 10	40.7	34.9		
Day 15 (optional)	2.5	2.3		
Day 29	1.2	0		

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:

Area under the curve (AUC) in virus titer was calculated using the trapezoidal method.

End point type	Secondary

End point timeframe:

Day 1 - Day 29

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	37		
Units: log[TCID/mL]*hours				
arithmetic mean (standard deviation)	-863.81 (± 543.37)	-849.29 (± 684.43)		

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:

AUC in virus RNA (RT-PCR) is defined as AUC of change from baseline in the amount of virus RNA (RT-PCR) from Day 1 to Day 10. AUC is calculated using the trapezoidal method similar to AUC in virus titer.

End point type	Secondary

End point timeframe:

Day 1 - Day 10

End point values	Baloxavir Marboxil	Oseltamivir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	39		
Units: log VPs/mL*hours				
arithmetic mean (standard deviation)	-381.53 (± 338.53)	-353.31 (± 304.01)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline (Day 1) until 28 days after the last dose of study drug (29 days)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Oseltamivir
Reporting group description:	
Participants will receive oseltamivir orally BID for 5 days (based on body weight). Baloxavir marboxil matching placebo will also be administered orally on Day 1	
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). Oseltamivir matching placebo will also be administered orally twice daily (BID) for 5 days.	

Serious adverse events	Oseltamivir	Baloxavir Marboxil	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)	0 / 115 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Oseltamivir	Baloxavir Marboxil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 58 (22.41%)	15 / 115 (13.04%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 58 (1.72%)	6 / 115 (5.22%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	9 / 58 (15.52%)	7 / 115 (6.09%)	
occurrences (all)	10	7	
Infections and infestations			

Otitis Media subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5	3 / 115 (2.61%) 3	

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