Clinical trial results:
A Multicenter, Single Arm, Open Label Study to Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients From Birth to < 1 Year With Influenza-Like Symptoms

Summary

EudraCT number	2018-002154-70
Trial protocol	PL ES FI BG
Global end of trial date	31 July 2023

Results information

Result version number	v1
This version publication date	14 February 2024
First version publication date	14 February 2024

Trial information

Trial identification

Sponsor protocol code	CP40559

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03653364
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?	Yes
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	03 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the safety of a single dose of baloxavir marboxil in paediatric population.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Costa Rica: 6
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	South Africa: 25
Worldwide total number of subjects	48
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	47
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in this study at 15 investigative sites in 7 countries (Costa Rica, Finland, Mexico, Poland, South Africa, Spain, and the United States) from 23 January 2019 to 03 April 2023.

Pre-assignment

Screening details:

A total of 49 paediatric participants from birth to <1 year with influenza-like symptoms were enrolled in this study to receive baloxavir marboxil. Out of the 49 participants, one participant was screened and enrolled by accident but was not dosed.

Period 1

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

Arms

Arm title	Baloxavir Marboxil

Arm description:

Participants received a single oral dose of baloxavir marboxil on Day 1 based on body weight and age. Participants aged ≥ 3 months to <12 months old received baloxavir marboxil, 2 milligrams per kilograms (mg/kg). Participants from birth to < 4 weeks old and ≥ 4 weeks to < 3 months old received baloxavir marboxil, 1 mg/kg.

Arm type	Experimental
Investigational medicinal product name	Baloxavir Marboxil
Investigational medicinal product code	RO7191686
Other name	Xofluza
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single, oral dose of baloxavir marboxil, 2 mg/kg administered in participants aged ≥ 3 months to <12 months and 1 mg/kg was administered in participants from birth to < 4 weeks old and ≥ 4 weeks to < 3 months.

Number of subjects in period 1	Baloxavir Marboxil
Started	48
Completed	46
Not completed	2
Adverse event, serious fatal	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants received a single oral dose of baloxavir marboxil on Day 1 based on body weight and age. Participants aged ≥ 3 months to <12 months old received baloxavir marboxil, 2 milligrams per kilograms (mg/kg). Participants from birth to < 4 weeks old and ≥ 4 weeks to < 3 months old received baloxavir marboxil, 1 mg/kg.	

Reporting group values	Baloxavir Marboxil	Total	
Number of subjects	48	48	
Age categorical Units: participants			
Age Continuous Units: days			
arithmetic mean	206.5		
standard deviation	± 106.08	-	
Sex: Female, Male Units: participants			
Female	23	23	
Male	25	25	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	15	
Not Hispanic or Latino	22	22	
Unknown or Not Reported	11	11	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	26	26	
White	21	21	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Baloxavir Marboxil
Reporting group description:	
Participants received a single oral dose of baloxavir marboxil on Day 1 based on body weight and age. Participants aged ≥ 3 months to <12 months old received baloxavir marboxil, 2 milligrams per kilograms (mg/kg). Participants from birth to < 4 weeks old and ≥ 4 weeks to < 3 months old received baloxavir marboxil, 1 mg/kg.	
Subject analysis set title	Baloxavir Marboxil: Birth - <4 weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants from birth to < 4 weeks old received a single oral dose of baloxavir marboxil, 1 mg/kg on Day 1.	
Subject analysis set title	Baloxavir Marboxil: ≥ 4 weeks - <3months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged ≥ 4 weeks to < 3 months old received a single oral dose of baloxavir marboxil, 1 mg/kg on Day 1.	
Subject analysis set title	Baloxavir Marboxil: ≥3 months - <12 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged ≥ 3 months to <12 months old received a single oral dose of baloxavir marboxil, 2mg/kg on Day 1.	

Primary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]
End point description:	
An AE=untoward medical occurrence in participant administered a pharmaceutical product that does not necessarily have causal relationship with treatment. It can therefore be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of medicinal/investigational product, whether or not considered related to medicinal (investigational) product. A SAE=significant hazard, contraindication, side effect that is fatal/life-threatening, requires hospitalization/prolongation of existing hospitalization, results in persistent/significant disability/ incapacity, is congenital anomaly/ birth defect, is medically significant /requires intervention to prevent one or other of outcomes listed above. Safety-evaluable Population included all participants who received at least 1 dose of treatment regardless of whether they had any follow-up assessments.	
End point type	Primary
End point timeframe:	
From Day 1 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: Only descriptive statistics were planned for this study.

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: participants				
AEs	23			
SAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Baloxavir Marboxil and S-033447

End point title	Plasma Concentrations of Baloxavir Marboxil and S-033447

End point description:

Plasma concentrations of baloxavir marboxil (BM) (pro-drug) and S-033447 (active metabolite) was evaluated and collected as per the age group. S-033447 is an active metabolite of baloxavir marboxil. Pharmacokinetic (PK)-evaluable population included all participants in the Intent-to-Treat (ITT) population who had at least one post-dose drug concentration measurement at a scheduled visit timepoint. Here, 9999 signifies that SD was not evaluable as only 1 participant was analyzed. Here, 99999 signifies that zero participants were analyzed at the specified timepoint. Number analyzed per timepoint are unique number of participants out of all the assessed participants with data available for analysis at specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

0.5 to 2 hours post dose on Day 1; 24 hours (Day 2) and 72 hours (Day 4) post dose, Day 6 and Day 10

End point values	Baloxavir Marboxil: Birth - <4 weeks	Baloxavir Marboxil: ≥ 4 weeks - <3months	Baloxavir Marboxil: ≥3 months - <12 months	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	31	
Units: nanograms per milliliters (ng/mL)				
arithmetic mean (standard deviation)				
BM: 0.5 to 2 hours (Day 1) (n=1,7,31)	0 (± 9999)	0.94 (± 1.971)	0.96 (± 2.429)	
BM: 24 hours (n=1,4,13)	0 (± 9999)	0 (± 0)	0 (± 0)	
BM: 72 hours (n=0,4,18)	99999 (± 99999)	0 (± 0)	0 (± 0)	
BM: Day 6 (n=0,5,22)	99999 (± 99999)	0 (± 0)	0 (± 0)	
BM: Day 10 (n=1,2,10)	0 (± 9999)	0 (± 0)	0 (± 0)	
S-033447: 0.5 to 2 hours (Day 1)(n=1,7,31)	26.90 (± 9999)	25.53 (± 18.867)	96.51 (± 94.828)	
S-033447: 24 hours (n=1,4,12)	38.50 (± 9999)	27.95 (± 19.821)	57.96 (± 45.592)	
S-033447: 72 hours (n=0,4,18)	99999 (± 99999)	8.57 (± 8.182)	19.95 (± 18.409)	
S-033447: Day 6 (n=0,5,22)	99999 (± 99999)	3.87 (± 2.170)	4.91 (± 3.922)	
S-033447: Day 10 (n=1,2,10)	0.84 (± 9999)	0.33 (± 0.464)	1.60 (± 1.684)	

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:

9999: Data analysis is still ongoing. Once the data is available the results for this endpoint will be posted.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: ng*h/mL				
arithmetic mean (standard deviation)	9999 (± 9999)			

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:

9999: Data analysis is still ongoing. Once the data is available the results for this endpoint will be posted.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: hours				
median (full range (min-max))	9999 (9999 to 9999)			

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:

9999: Data analysis is still ongoing. Once the data is available the results for this endpoint will be posted.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: hours				
geometric mean (geometric coefficient of variation)	9999 (± 9999)			

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:

9999: Data analysis is still ongoing. Once the data is available the results for this endpoint will be posted.

End point type	Secondary

End point timeframe:

Up to Day 10

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: ng/mL				
arithmetic mean (standard deviation)	9999 (± 9999)			

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=time taken from start of treatment to a point at which following criteria were met & remained for at least 21.5 hours:
• Score 0 (no problem) or 1 (minor problem) for cough & nasal symptoms for items 14 & 15 of Canadian Acute Respiratory Illness & Flu Scale [CARIFS]);
• A "yes" response to following question on CARIFS: "Since last assessment has the participant been able to return to day care/school, or resume his/her normal daily activity in same way as performed prior to developing the flu?";
• First return to afebrile state (tympanic temperature ≤37.2°C).
Median time was estimated from Kaplan-Meier curve. Intent-to-Treat Influenza-Infected (ITTi) population, a subset of ITT set was used for analysis. 9999=upper limit of confidence interval (CI) was not calculated due to low number of participants with events. Participants who withdrew prior to an event of interest/did not experience resolution of symptoms were censored at last observation time point.

End point type	Secondary

End point timeframe:

Day 1 up to Day 15

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)	163.7 (122.5 to 9999)			

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 was defined 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?" and

remaining so for at least 21.5 hours. Median time was estimated from the Kaplan-Meier curve. ITTi population, subset of ITT was used for analysis. Overall number analyzed is the number of participants with data available for analysis. Participants who withdrew prior to an event of interest or did not experience resolution of symptoms were censored at the last observation time point. Here, 9999 signifies 95% CI could not be calculated due to low number of participants with events.

End point type	Secondary

End point timeframe:

Day 1 up to Day 15

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
median (confidence interval 95%)	140.7 (72.2 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Symptoms

End point title	Duration of Symptoms

End point description:

The efficacy of baloxavir marboxil was evaluated by duration of symptoms i.e. alleviation of all symptoms as defined by score of 0 (no problem)/1 (minor problem) & remaining so for at least 21.5 hours, for all 18 symptoms (Poor appetite; Not sleeping well; Irritable, cranky, fussy; Feels unwell; Low energy, tired; Not playing well; Crying more than usual; Needing extra care; Clinginess; Headache; Sore throat; Muscle aches or pains; Fever; Cough; Nasal congestion, runny nose; Vomiting; Not interested in what's going on; Unable to get out of bed) specified in the CARIFS questionnaire. Median time was estimated from the Kaplan-Meier curve. ITTi population, a subset of ITT set was used for analysis. Here, 9999 signifies that the upper limit of CI was not calculated due to low number of participants with events. Participants who withdrew prior to an event of interest or did not experience resolution of symptoms were censored at the last observation time point.

End point type	Secondary

End point timeframe:

Day 1 up to Day 15

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)	163.7 (71.0 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Fever

End point title	Duration of Fever

End point description:

Duration of fever was defined as the 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 after onset. Participants who did not have fever at baseline or whose body temperature was not collected were excluded from the analysis. Median time was estimated from the Kaplan-Meier curve. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Day 1 up to Day 15

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hours				
median (confidence interval 95%)	23.1 (22.3 to 44.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Influenza Virus Titer Over Time

End point title	Change from Baseline in Influenza Virus Titer Over Time

End point description:

Change from baseline in influenza virus titer (log10TCID50/mL) was defined as the change from baseline in influenza virus titer on Days 2, 4, 6, 10, and 29. If influenza virus titer was less than the lower limit of quantification (LLOQ), the virus titer was imputed as 0.749 (log10TCID50/mL). Only participants with a positive virus titer on Day 1 were included in this analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Number analyzed per timepoint are unique number of participants out of all the assessed participants with data available for analysis at specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 4, 6, 10, and 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: log10 TCID 50/mL				
arithmetic mean (standard deviation)				
Baseline (n=10)	3.58 (± 1.81)			
Change From Baseline at Day 2 (n=10)	-2.50 (± 1.70)			
Change From Baseline at Day 4 (n=10)	-2.60 (± 1.95)			
Change From Baseline at Day 6 (n=10)	-2.43 (± 1.40)			
Change From Baseline at Day 10 (n=10)	-2.83 (± 1.81)			
Change From Baseline at Day 29 (n=4)	-1.69 (± 1.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Requiring Antibiotics

End point title	Number of Participants Requiring Antibiotics

End point description:

The number of participants who required antibiotics for influenza related complication are reported here. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Influenza-Related Complications

End point title	Number of Participants with Influenza-Related Complications

End point description:

The influenza related complications include death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cessation of Viral Shedding by Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

End point title	Time to Cessation of Viral Shedding by Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

End point description:

Time to cessation of viral shedding by RT-PCR, in hours, was defined as the time between the initiation of study treatment and first time when the virus ribonucleic acid (RNA) by RT-PCR qualitative result was negative (no cycle threshold [Ct]-value detectable). Participants who did not have a negative result by the last observation time point were treated as censored at that time point. For the participants with multiple virus types, this endpoint was defined as the time between the initiation of the study treatment and first time when the virus RNA by RT-PCR qualitative result was negative for all virus types. One day was converted into 24 hours. Median time was estimated from the Kaplan -Meier curve. Participants with a positive virus RNA on Day 1 are included in this analysis. ITTi population, subset of ITT was used for analysis. Overall number analyzed is the number of participants with a positive virus RNA on Day 1.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
median (confidence interval 95%)	219.1 (141.6 to 695.5)			

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 was defined as the time, in hours, between the initiation of any study treatment and first time when the influenza virus titer was below the limit of detection (0.75 log10 tissue culture infectious dose (TCID)50/milliliters [mL]). Participants whose virus titers did not reach the limit by the last observation time point were treated as censored at that time point. One day was converted into 24 hours. Median time was estimated from the Kaplan-Meier curve. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
median (confidence interval 95%)	24.5 (24.2 to 68.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Amount of Virus RNA (RT-PCR) Over Time

End point title	Change from Baseline in the Amount of Virus RNA (RT-PCR) Over Time

End point description:

Change from baseline in the amount of virus RNA was defined as the change from baseline in the amount of virus RNA on Days 2, 4, 6 and 10. If the amount of virus RNA is less than the lower limit of quantification, the amount of virus RNA was imputed as the relevant LLOQ (log10 viral particles per mililiter (vp/mL)). If a participant was infected with multiple virus types, the sum of virus RNA (log10 vp/mL) was used for analysis. Participants with a positive virus RNA by RT-PCR on Day 1 were included in this analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Number analyzed per timepoint are unique number of participants out of all the assessed participants with data available for analysis at specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 4, 6, and 10

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: log10 vp/mL				
arithmetic mean (standard deviation)				
Baseline (n=14)	6.46 (± 1.91)			
Change From Baseline at Day 2 (n=12)	-2.26 (± 1.00)			
Change From Baseline at Day 4 (n=12)	-1.93 (± 1.99)			
Change From Baseline at Day 6 (n=9)	-1.76 (± 2.40)			
Change From Baseline at Day 10 (n=6)	-3.30 (± 3.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Positive Influenza Virus Titer Over Time

End point title	Percentage of Participants with Positive Influenza Virus Titer Over Time

End point description:

Percentage of participants positive for influenza virus titer at each visit were defined as the percentage of participants whose influenza virus titer was not less than the LLOQ (0.75 log10TCID50/mL) or positive among those assessed for influenza virus titer on Days 2, 4, 6, 10 and 29. Participants with a positive influenza virus titer on Day 1 were included in this analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analyzed is the number of participants with a positive influenza virus titer on Day 1. Number analyzed is the number of participants with data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 4, 6, 10, and 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
Baseline (n=10)	100			
Day 2 (n=10)	40			
Day 4 (n=10)	20			
Day 6 (n=10)	30			
Day 10 (n=10)	0			
Day 29 (n=4)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive by RT-PCR Over Time

End point title	Percentage of Participants Positive by RT-PCR Over Time

End point description:

Percentage of participants positive by RT-PCR at each visit was defined as the percentage of participants with a positive qualitative result among those assessed by RT-PCR on Days 2, 4, 6, 10 and 29. Participants with a positive RT-PCR result on Day 1 were included in this analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analyzed is the number of participants with a positive RT-PCR result on Day 1. Number analyzed is the number of participants with data available for analysis at the specified timepoint. Percentages are rounded off.

End point type	Secondary

End point timeframe:

Baseline, Days 2, 4, 6, 10, and 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of participants				
number (not applicable)				
Baseline (n=14)	100			
Day 2 (n=13)	92.3			
Day 4 (n=13)	92.3			
Day 6 (n=14)	64.3			
Day 10 (n=14)	42.9			
Day 29 (n=7)	0			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

AUC in virus titer was calculated using the trapezoidal method. Twenty-four hours of time was converted into one day. Participants with a positive virus titer on Day 1 were included in this analysis. The LLOQ and lower limit of detection was defined as 0.75 log10TCID50/mL for flu A and 0.75 log10TCID50/mL for flu B. If a participant was infected with multiple virus types, the sum of those virus titers will be used for analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analyzed is the number of participants with a positive virus titer on Day 1.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: log10 TCID 50/mL*hours				
arithmetic mean (standard deviation)	-871.25 (± 681.03)			

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) was defined as AUC of change from baseline in the amount of virus RNA (RT-PCR). AUC was calculated using the trapezoidal method similar to AUC in virus titer. Participants with a positive RT-PCR result on Day 1 were subjected to this analysis.If the amount of virus RNA is less than the lower limit of quantification, the amount of virus RNA was imputed as the relevant LLOQ (log10 viral particles per mililiter (vp/mL)). If a participant was infected with multiple virus types, the sum of those the amount of virus RNA was used for analysis. ITTi population is a subset of ITT participants who had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study. Overall number analyzed is the number of participants with a positive RT-PCR result on Day 1.

End point type	Secondary

End point timeframe:

Day 1 up to Day 29

End point values	Baloxavir Marboxil			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: log10 vp/mL*hours				
median (standard deviation)	-287.41 (± 356.35)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 29

Adverse event reporting additional description:

Safety-evaluable Population included all participants who received at least one dose of treatment regardless of whether they had any follow-up assessments.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Baloxavir Marboxil

Reporting group description:

Participants received a single oral dose of baloxavir marboxil on Day 1 based on body weight and age. Participants aged ≥ 3 months to <12 months old received baloxavir marboxil, 2 mg/kg. Participants from birth to < 4 weeks old and ≥ 4 weeks to < 3 months old received baloxavir marboxil, 1 mg/kg.

Serious adverse events	Baloxavir Marboxil		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Baloxavir Marboxil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 48 (22.92%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2019	1. An exploratory objective was added to evaluate palatability of the oral suspension. 2. Exclusion criteria regarding participant weight was updated. 3. Polyvalent cation containing products were added as cautionary therapy and 4. Prescreening influenza and COVID-19 tests were included.
01 June 2020	1. Prescreening Influenza and COVID-19 test were added. 2. Screening requirement for fever was modified.
27 April 2022	1. A rapid antigen test to detect SARS-CoV-2 infection at prescreening was added. 2. Minimum number of participants recruited into cohort III was updated to 3 participants as this was judged to be sufficient. 3. Requirement of fever at screening was removed. 4. Pre-screening window was increased from 24 hours to 48 hours for influenza and SARS-CoV-2 testing. 5. Negative SARS-CoV2 results from either PCR or rapid antigen test could be used to confirm eligibility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported