# EU Clinical Trials Register

## 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

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## 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

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## 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 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: 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: 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: 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: 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: 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: 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: 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: 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: 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

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## 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

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## 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.<br>2. Exclusion criteria regarding participant weight was updated.<br>3. Polyvalent cation containing products were added as cautionary therapy and<br>4. Prescreening influenza and COVID-19 tests were included. |
| 01 June 2020 | 1. Prescreening Influenza and COVID-19 test were added.<br>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.<br>2. Minimum number of participants recruited into cohort III was updated to 3 participants as this was judged to be sufficient.<br>3. Requirement of fever at screening was removed.<br>4. Pre-screening window was increased from 24 hours to 48 hours for influenza and SARS-CoV-2 testing.<br>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