Clinical trial results:
A Phase IIIB, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Clinical Efficacy Study of Baloxavir Marboxil for the Reduction of Direct Transmission of Influenza From Otherwise Healthy Patients to Household Contacts

Summary

EudraCT number	2018-004056-37
Trial protocol	ES GB GR HU PL FR BG
Global end of trial date	10 May 2024

Results information

Result version number	v1 (current)
This version publication date	15 December 2024
First version publication date	15 December 2024

Trial information

Trial identification

Sponsor protocol code	MV40618

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03969212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of a single, oral dose of baloxavir marboxil (BXM) compared with a placebo to prevent secondary within-household transmission of influenza A/B.

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	10 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Israel: 148
Country: Number of subjects enrolled	Poland: 85
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Türkiye: 230
Country: Number of subjects enrolled	United States: 1310
Country: Number of subjects enrolled	Bulgaria: 1041
Country: Number of subjects enrolled	Costa Rica: 6
Country: Number of subjects enrolled	Mexico: 44
Country: Number of subjects enrolled	South Africa: 112
Country: Number of subjects enrolled	China: 441
Country: Number of subjects enrolled	Japan: 668
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	India: 2
Worldwide total number of subjects	4134
EEA total number of subjects	1172

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	433
Adolescents (12-17 years)	495
Adults (18-64 years)	3063
From 65 to 84 years	132
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

Participants with acute influenza infection (Index participants [IPs]) and their household contacts (HHCs) took part in the study across 142 investigative sites in 15 countries from 10 October 2019 to 10 May 2024. A total of 4138 participants, 1457 IPs, and 2681 HHCs, were included in the study.

Pre-assignment

Screening details:

IPs received baloxavir marboxil or placebo in a 1:1 ratio, and their evaluable HHCs were assessed for influenza symptoms. No treatment was administered to the HHCs. Of the 1345 HHCs enrolled in 'Baloxavir Marboxil:HHCs', 1305 completed the study. Baseline data was not collected for 4 HHCs, hence only 1341 HHCs are presented in the disposition.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo: IPs

Arm description:

IPs were randomized in this arm to receive a single dose of matching placebo orally as a tablet or oral suspension based on their weight and age.

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

Dosage and administration details:

Single, oral dose of matching placebo administered according to age and weight of IPs.

Arm title	Baloxavir Marboxil: IPs

Arm description:

IPs were randomized in this arm to receive a single dose of baloxavir marboxil orally based on their weight and age.

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

Dosage and administration details:

Single, oral dose of baloxavir marboxil administered according to age and weight of IPs.

Arm title	Placebo: HHCs

Arm description:

HHCs related to IPs randomized to the placebo arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm	
Arm title	Baloxavir Marboxil: HHCs

Arm description:

HHCs related to IPs randomized to the baloxavir marboxil arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Placebo: IPs	Baloxavir Marboxil: IPs	Placebo: HHCs
Started	731	726	1336
Treated	726	723	0 [1]
Completed	699	688	1300
Not completed	32	38	36
Consent withdrawn by subject	7	13	5
Physician decision	-	-	1
Adverse Event	1	-	-
Other	22	23	28
Lost to follow-up	2	2	2
Protocol deviation	-	-	-

Number of subjects in period 1	Baloxavir Marboxil: HHCs
Started	1341
Treated	0 [2]
Completed	1301
Not completed	40
Consent withdrawn by subject	11
Physician decision	-
Adverse Event	-
Other	26
Lost to follow-up	2
Protocol deviation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: HHCs were not treated in this study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: HHCs were not treated in this study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo: IPs
Reporting group description:	
IPs were randomized in this arm to receive a single dose of matching placebo orally as a tablet or oral suspension based on their weight and age.	
Reporting group title	Baloxavir Marboxil: IPs
Reporting group description:	
IPs were randomized in this arm to receive a single dose of baloxavir marboxil orally based on their weight and age.	
Reporting group title	Placebo: HHCs
Reporting group description:	
HHCs related to IPs randomized to the placebo arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.	
Reporting group title	Baloxavir Marboxil: HHCs
Reporting group description:	
HHCs related to IPs randomized to the baloxavir marboxil arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.	

Reporting group values	Placebo: IPs	Baloxavir Marboxil: IPs	Placebo: HHCs
Number of subjects	731	726	1336
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	31.2	30.5	34.7
standard deviation	± 15.8	± 15.2	± 18.4
Gender Categorical			
Units: Subjects			
Female	377	389	740
Male	354	337	596
Ethnicity			
Units: Subjects			
Hispanic or Latino	83	83	169
Not Hispanic or Latino	646	633	1133
Unknown or Not Reported	2	10	34
Race			
Units: Subjects			
American Indian or Alaska Native	7	7	9
Asian	196	190	370
Black or African American	28	19	47
White	483	495	817
Multiple Race	3	0	9
Unknown	14	15	74
Native Hawaiian or other Pacific Islander	0	0	10

Reporting group values	Baloxavir Marboxil: HHCs	Total	
Number of subjects	1341	4134	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	35.3		
standard deviation	± 18.6	-	
Gender Categorical Units: Subjects			
Female	709	2215	
Male	632	1919	
Ethnicity Units: Subjects			
Hispanic or Latino	153	488	
Not Hispanic or Latino	1145	3557	
Unknown or Not Reported	43	89	
Race Units: Subjects			
American Indian or Alaska Native	8	31	
Asian	364	1120	
Black or African American	46	140	
White	871	2666	
Multiple Race	5	17	
Unknown	47	150	
Native Hawaiian or other Pacific Islander	0	10	

End points

End points reporting groups

Reporting group title	Placebo: IPs

Reporting group description:

IPs were randomized in this arm to receive a single dose of matching placebo orally as a tablet or oral suspension based on their weight and age.

Reporting group title	Baloxavir Marboxil: IPs

Reporting group description:

IPs were randomized in this arm to receive a single dose of baloxavir marboxil orally based on their weight and age.

Reporting group title	Placebo: HHCs

Reporting group description:

HHCs related to IPs randomized to the placebo arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.

Reporting group title	Baloxavir Marboxil: HHCs

Reporting group description:

HHCs related to IPs randomized to the baloxavir marboxil arm were evaluated for influenza transmission (either virological or symptomatic) up to Day 9 of the observation period without any treatment being administered.

Subject analysis set title	Placebo: Household
Subject analysis set type	Per protocol

Subject analysis set description:

All households of randomized IPs who received matching placebo, with the IP being PCR positive at screening and with at least one HHC enrolled for the full study.

Subject analysis set title	Baloxavir Marboxil: Household
Subject analysis set type	Per protocol

Subject analysis set description:

All households of randomized IPs who received baloxavir marboxil, with the IP being PCR positive at screening and with at least one HHC enrolled for the full study.

Primary: Percentage of HHCs With Virological Influenza Transmission by Day 5

End point title	Percentage of HHCs With Virological Influenza Transmission by Day 5[1]

End point description:

The virological transmission was determined based on Polymerase Chain Reaction Positive (PCR+) influenza test results. Percentage of HHCs who tested PCR+ for influenza by Day 5 post IP randomization with virus subtype matching with that of the respective IP, irrespective of being symptomatic or asymptomatic are reported. The primary household contacts analysis set (PAS-HC) included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B, received the study drug, and where all contacts were PCR negative at baseline.

End point type	Primary

End point timeframe:

Baseline (Day 1) to Day 5

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1098	1118		
Units: percentage of HHCs				
number (confidence interval 95.38%)				
HHC with endpoint positive	13.42 (10.66 to 16.76)	9.50 (7.40 to 12.13)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo

Statistical analysis description:

The odds ratio (OR) shown represents the odds of Baloxavir Marboxil (BMX) versus the odds of Placebo.

Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Generalized estimating equation (GEE)
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.68
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.5
upper limit	0.93

Secondary: Percentage of Households (HHs) With Virological Influenza Transmission at Household Level by Day 5

End point title	Percentage of Households (HHs) With Virological Influenza Transmission at Household Level by Day 5

End point description:

Percentage of households with at least one HHC who met the primary endpoint of virological transmission by Day 5 are reported. Primary Households Analysis Set (PAS-HH) included all households of randomized IPs that were PCR+ at screening and with at least one HHC enrolled for the full study. The IPs should be a part of the Primary Index Patients Analysis Set (PAS-IP) which includes all randomized IPs with at least one HHC in the PAS-HC. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B, received the study drug, and where all contacts were PCR negative at baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 5

End point values	Placebo: Household	Baloxavir Marboxil: Household		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	544[2]	548[3]		
Units: percentage of HHs				
number (not applicable)	19.5	15.5		

Notes:

[2] - Number analyzed represents the number of households analyzed for this endpoint.

[3] - Number analyzed represents the number of households analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo

Statistical analysis description:

The OR shown represents the odds of BMX versus the odds of Placebo.

Comparison groups	Placebo: Household v Baloxavir Marboxil: Household
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds Ratio (BMX vs Placebo)
Point estimate	0.76
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.55
upper limit	1.06

Secondary: Percentage of HHCs With Symptomatic Influenza Transmission by Day 5

End point title	Percentage of HHCs With Symptomatic Influenza Transmission by Day 5[4]

End point description:

Virological transmission was determined based on PCR+ influenza test results. Percentage of HHCs who were PCR+ for influenza by Day 5 post IP randomization with virus subtype matching with respective IP & develop symptoms at any time during the study are reported. HHCs ≥12 years old were symptomatic if 1. Presence of temperature ≥38.0 Celsius & 1 respiratory symptom or 2. Presence of one respiratory symptom & 1 general systemic symptom (headache, feverishness or chills, muscle or joint pain, fatigue), with /without a fever. HHCs ≥2 & <12 years old were symptomatic if the presence of temperature was ≥38.0 Celsius & upper respiratory tract infection signs or symptoms (cough, nasal congestion, or rhinorrhea). Symptoms must be either new, or have worsened versus baseline (BA) in HHC with BA symptoms due to a preexisting comorbidity. PAS-HC=unvaccinated HHCs who were linked to HHs where IP was BA PCR+ for influenza A/B, received study drug, & where all contacts were PCR negative at BA.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 5

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: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1098	1118		
Units: percentage of HHCs				
number (confidence interval 95.38%)	7.61 (5.66 to 10.17)	5.80 (4.10 to 8.15)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo
Statistical analysis description:	
The OR shown represents the odds of BMX versus the odds of Placebo.	
Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	GEE model
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.75
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.5
upper limit	1.12

Secondary: Percentage of Households With Symptomatic Influenza Transmission at Household Level by Day 5

End point title	Percentage of Households With Symptomatic Influenza Transmission at Household Level by Day 5
End point description:	
Percentage of households with at least one HHC who meets the symptomatic transmission by Day 5 endpoint are reported. PAS-HH included all households of randomized IPs that were PCR+ at screening and with at least one HHC enrolled for the full study. The IPs should be a part of the PAS-IP which includes all randomized IPs with at least one HHC in the PAS-HC. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B, received the study drug, and where all contacts were PCR negative at baseline.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Day 5	

End point values	Placebo: Household	Baloxavir Marboxil: Household		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	544[5]	548[6]		
Units: percentage of HHs				
number (not applicable)	11.9	8.6		

Notes:

[5] - Number analyzed represents the number of households analyzed for this endpoint.

[6] - Number analyzed represents the number of households analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo

Statistical analysis description:

The OR shown represents the odds of BMX versus the odds of Placebo.

Comparison groups	Placebo: Household v Baloxavir Marboxil: Household
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds Ratio (BMX vs Placebo)
Point estimate	0.69
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.46
upper limit	1.04

Secondary: Percentage of HHCs With Symptomatic Influenza Transmission by Day 9

End point title	Percentage of HHCs With Symptomatic Influenza Transmission by Day 9[7]

End point description:

Data are reported for the percentage of HHCs who met the virological transmission by Day 9 endpoint and developed symptoms at any time during the study. HHCs ≥12 years were symptomatic if they had 1. temperature ≥38.0°C & one respiratory symptom or 2. one respiratory and one systemic symptom, with/without fever. HHCs ≥2 & <12 years were symptomatic if with a temperature ≥38.0°C and upper respiratory symptoms. Symptoms must be either new, or have worsened versus baseline in HHC with baseline symptoms due to a preexisting comorbidity. PAS-HC included unvaccinated HHCs who were linked to households where IP was baseline PCR+ for influenza A or B, received study drug, and where all contacts were PCR negative at baseline. Overall number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 9

Notes:

[7] - 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: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1037	1079		
Units: percentage of HHCs				
number (confidence interval 95.38%)	8.26 (6.10 to 11.09)	6.15 (4.37 to 8.58)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo
Statistical analysis description:	
The OR shown represents the odds of BMX versus the odds of Placebo.	
Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2116
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.73
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.48
upper limit	1.09

Secondary: Percentage of HHCs With Virological Influenza Transmission by Day 9

End point title	Percentage of HHCs With Virological Influenza Transmission by Day 9[8]

End point description:

Virological transmission was determined based on PCR+ influenza test results. Data are reported for percentage of HHCs who tested PCR+ for influenza by Day 9 post IP randomization with virus subtype matching with the respective IP, irrespective of being symptomatic/asymptomatic including: 1. all HHC meeting primary endpoint, AND 2. all HHC cases detected after Day 5 meeting following criteria: 2a. included HHC case was in an HH where another HHC had already met the primary endpoint OR 2b. included HHC case was PCR+ bearing an amino acid substitution of isoleucine for another amino acid at position 38 (I38X) in the polymerase acidic (PA) protein (PA/I38X substitution) or amino acid substitution of threonine to lysine at position 20 in the PA protein for influenza B only (PA/T20K), indicating transmission of virus with reduced susceptibility. PAS-HC analysis set used for this endpoint. Overall number analyzed=number of HHCs with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 9

Notes:

[8] - 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: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1038	1081		
Units: percentage of HHCs				
number (confidence interval 95.38%)	15.40 (12.20 to 19.27)	10.77 (8.41 to 13.71)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo
Statistical analysis description:	
The OR shown represents the odds of BMX versus the odds of Placebo.	
Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2119
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.66
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.48
upper limit	0.91

Secondary: Percentage of Households With Any Virological Infection at Household Level by Day 9

End point title	Percentage of Households With Any Virological Infection at Household Level by Day 9
End point description:	
Virological infection at HH level were defined as the HHs with at least one HHC who met the endpoint of any virological infection by Day 9. PAS-HH included all households of randomized IPs that were PCR+ at screening and with at least one HHC enrolled for the full study. The IPs should be a part of the PAS-IP which includes all randomized IPs with at least one HHC in the PAS-HC. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B, received the study drug, and where all contacts were PCR negative at baseline.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Day 9	

End point values	Placebo: Household	Baloxavir Marboxil: Household		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	544[9]	548[10]		
Units: percentage of HHs				
number (not applicable)	24.3	20.1		

Notes:

[9] - Number analyzed represents the number of households analyzed for this endpoint.

[10] - Number analyzed represents the number of households analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo
Statistical analysis description:	
The OR shown represents the odds of BMX versus the odds of Placebo.	
Comparison groups	Placebo: Household v Baloxavir Marboxil: Household
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds Ratio (BMX vs Placebo)
Point estimate	0.79
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.59
upper limit	1.06

Secondary: Percentage of HHCs With Any Virological Infection by Day 9

End point title	Percentage of HHCs With Any Virological Infection by Day 9[11]
End point description:	
Virological infection was defined as HHCs who tested PCR+ for influenza by Day 9 post IP randomization based on PCR influenza test results. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B and received study drug and where all contacts were PCR negative at baseline. Overall number analyzed is the number of participants with data available for analysis.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to Day 9	

Notes:

[11] - 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: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1040	1071		
Units: percentage of HHCs				
number (confidence interval 95.38%)	18.68 (15.36 to 22.53)	13.98 (11.31 to 17.16)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo
Statistical analysis description:	
The OR shown represents the odds of BMX versus the odds of Placebo.	
Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.71
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.53
upper limit	0.94

Secondary: Percentage of Households With Any Symptomatic Infection at HH Level by Day 9

End point title	Percentage of Households With Any Symptomatic Infection at HH Level by Day 9

End point description:

Percentage of HHs with at least one HHC who meets the endpoint of any symptomatic infection by Day 9 are reported. HHCs ≥12 years were symptomatic if they had (1) a temperature ≥38.0°C and one respiratory symptom (cough, sore throat, nasal congestion) or (2) one respiratory & one systemic symptom (headache, chills, muscle/joint pain, fatigue), with/without fever. HHCs ≥2 & <12 years were symptomatic with a temperature ≥38.0°C &upper respiratory symptoms (cough, nasal congestion, rhinorrhea). PAS-HH included all households of randomized IPs that were PCR+ at screening and with at least one HHC enrolled for the full study. The IPs should be a part of the PAS-IP which includes all randomized IPs with at least one HHC in the PAS-HC. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B, received the study drug, and where all contacts were PCR negative at baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 9

End point values	Placebo: Household	Baloxavir Marboxil: Household		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	544[12]	548[13]		
Units: percentage of HHs				
number (not applicable)	12.9	9.5		

Notes:

[12] - Number analyzed represents the number of households analyzed for this endpoint.

[13] - Number analyzed represents the number of households analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Placebo vs Baloxavir Marboxil

Statistical analysis description:

The OR shown represents the odds of BMX versus the odds of Placebo.

Comparison groups	Placebo: Household v Baloxavir Marboxil: Household
Number of subjects included in analysis	1092
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds Ratio (BMX vs Placebo)
Point estimate	0.71
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.48
upper limit	1.04

Secondary: Percentage of HHCs With Any Symptomatic Infection by Day 9

End point title	Percentage of HHCs With Any Symptomatic Infection by Day

End point description:

Percentage of HHCs who tested PCR+ for influenza by Day 9 post IP randomization and develop symptoms at any time during the study are reported. HHCs ≥12 years were symptomatic if they had (1) a temperature ≥38.0°C and one respiratory symptom (cough, sore throat, nasal congestion) or (2) one respiratory & one systemic symptom (headache, chills, muscle/joint pain, fatigue), with/without fever. HHCs ≥2 and <12 years were symptomatic with a temperature ≥38.0°C and upper respiratory symptoms (cough, nasal congestion, rhinorrhea). Symptoms must be either new, or have worsened versus baseline in HHC with baseline symptoms due to a preexisting comorbidity. PAS-HC included unvaccinated HHCs who were linked to households where the IP was baseline PCR+ for influenza A or B and received study drug and where all contacts were PCR negative at baseline. Overall number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Day 9

Notes:

[14] - 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: This endpoint was planned to only evaluate the HHCs associated with the IPs.

End point values	Placebo: HHCs	Baloxavir Marboxil: HHCs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1039	1069		
Units: percentage of HHCs				
number (confidence interval 95.38%)	8.71 (6.49 to 11.60)	6.43 (4.61 to 8.91)		

Statistical analyses

Statistical analysis title	Baloxavir Marboxil vs Placebo

Statistical analysis description:

The OR shown represents the odds of BMX versus the odds of Placebo.

Comparison groups	Placebo: HHCs v Baloxavir Marboxil: HHCs
Number of subjects included in analysis	2108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted OR (BMX vs Placebo)
Point estimate	0.72
Confidence interval	
level	95.38 %
sides	2-sided
lower limit	0.49
upper limit	1.07

Secondary: Number of IPs With Adverse Events (AEs)

End point title	Number of IPs With Adverse Events (AEs)[15]

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and regardless of 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. Safety IP Set included all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Day 9 (for IPs ≥12 years old) and Day 21 (for IPs <12 years old)

Notes:

[15] - 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: Safety data was collected only for the IPs enrolled in the study.

End point values	Placebo: IPs	Baloxavir Marboxil: IPs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	726	723		
Units: participants	51	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of IPs With Serious Adverse Events (SAEs)

End point title	Number of IPs With Serious Adverse Events (SAEs)[16]

End point description:

A 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 or incapacity, is a congenital anomaly or birth defect, is medically significant or requires intervention to prevent one or other of the outcomes listed above. Safety IP Set included all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Day 9 (for IPs ≥12 years old) and Day 21 (for IPs <12 years old)

Notes:

[16] - 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: Safety data was collected only for the IPs enrolled in the study.

End point values	Placebo: IPs	Baloxavir Marboxil: IPs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	726	723		
Units: participants	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Baseline up to Day 9 (IPs ≥12 years old)
Baseline up to Day 21 (IPs <12 years old)

Adverse event reporting additional description:

Safety IP Set included all randomized participants who received at least one dose of study treatment. Safety data was collected only for IPs as no treatment was administered to the HHCs in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Placebo: IPs

Reporting group description:

IPs were randomized in this arm to receive a single dose of matching placebo orally as a tablet or oral suspension based on their weight and age.

Reporting group title	Baloxavir Marboxil: IPs

Reporting group description:

IPs received a single dose of baloxavir marboxil orally based on their weight and age.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no Non-serious adverse events at a 5% threshold in this study.

Serious adverse events	Placebo: IPs	Baloxavir Marboxil: IPs	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 726 (0.28%)	1 / 723 (0.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 726 (0.00%)	1 / 723 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 726 (0.14%)	0 / 723 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 726 (0.14%)	0 / 723 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 726 (0.14%)	0 / 723 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo: IPs	Baloxavir Marboxil: IPs	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 726 (0.00%)	0 / 723 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2019	Protocol amended primarily to update safety information.
10 August 2020	Protocol amended primarily to expand the pediatric IP population to include IPs 5 to 11 years old, to add SARS-CoV-2 testing at screening and during the study as applicable, and to exclude and/or withdraw IPs and households who test positive for SARS-CoV-2 during the study.
29 March 2022	Protocol amended to reduce the requirement from 2 or more HHCs to 1 or more HHCs to participate in the entire duration of the study and who had not received the influenza vaccine within 6 months prior to screening. In addition, IPs who are <12 years old who had received the oral suspension were asked to answer a questionnaire regarding the palatability and acceptability of the study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported