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Baloxavir Marboxil Single-dose Treatment in Influenza-infected Children

A Randomized, Double-blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2)

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Background: Baloxavir marboxil (baloxavir) is a novel, cap-dependent endonuclease inhibitor that has previously demonstrated efficacy in the treatment of influenza in adults and adolescents. We assessed the safety and efficacy of baloxavir in otherwise healthy children with acute influenza.

Methods: MiniSTONE-2 (Clinicaltrials.gov: NCT03629184) was a double-blind, randomized, active controlled trial enrolling children 1–<12 years old with a clinical diagnosis of influenza. Children were randomized 2:1 to receive either a single dose of oral baloxavir or oral oseltamivir twice daily for 5 days. The primary endpoint was incidence, severity and timing of adverse events (AEs); efficacy was a secondary endpoint.

Results: In total, 173 children were randomized and dosed, 115 to the baloxavir group and 58 to the oseltamivir group. Characteristics of participants were similar between treatment groups. Overall, 122 AEs were reported in 84 (48.6%) children. Incidence of AEs was similar between baloxavir and oseltamivir groups (46.1% vs. 53.4%, respectively). The most common AEs were gastrointestinal (vomiting/diarrhea) in both groups [baloxavir: 12 children (10.4%); oseltamivir: 10 children (17.2%)]. No deaths, serious AEs or hospitalizations were reported. Median time (95% confidence interval) to alleviation of signs and symptoms of influenza was similar between groups: 138.1 (116.6–163.2) hours with baloxavir versus 150.0 (115.0–165.7) hours with oseltamivir.

Conclusions: Oral baloxavir is well tolerated and effective at alleviating symptoms in otherwise healthy children with acute influenza. Baloxavir provides a new therapeutic option with a simple oral dosing regimen.

Key Words: baloxavir marboxil, influenza, children, oseltamivir, virology

Annual influenza epidemics are estimated to cause 3–5 million cases of severe illness and up to 650,000 deaths globally among all ages.[1] Influenza infects all childhood age subsets and is associated with substantial morbidity,[2] with the youngest at particular risk of viral injury, secondary bacterial infections and complications.[3,4] Mortality in children varies across seasons and depends on viral subtype, preexisting immunity and presence of underlying disease.[5,6] Recent estimates for children from 92 countries, the majority of whom were <5 years old, are 9000–106,000 (median: 44,888) influenza-associated deaths annually.[7] In addition, children play a central role in influenza dissemination in the community because of their relative susceptibility to infection, high illness attack rates, prolonged viral shedding, and high contact rates between others in the household and community.[2,8]

Annual vaccination is the most effective control measure for prevention of seasonal influenza and related complications.[9,10] Vaccination is recommended in the United States for individuals ≥6 months of age, who have no contraindications.[11] However, the need for vaccine reformulations each year, difficulties in producing these within short timeframes, and variable uptake and efficacy across countries mean that this strategy has limitations,[12,13] and needs to be complemented by the availability of effective antiviral treatments.

In many countries, there are currently only 2 classes of antivirals approved for the treatment of influenza in children: M2 blockers and neuraminidase inhibitors.[3] Widespread, stable and transmissible resistance has rendered M2 blockers essentially ineffective.[14,15] Although neuraminidase inhibitors are effective in the treatment of influenza in children, there are restrictions for some of these based on age and mode of administration. A simplified dosing regimen (ie, single oral dosing), with better overall antiviral activity and favorable safety and tolerability, is considered desirable for the treatment of influenza in children.

Baloxavir marboxil (baloxavir) is a novel, first-in-class, cap-dependent endonuclease inhibitor.[16–18] Baloxavir was first approved in Japan in February 2018, followed by the United States in October 2018. In the United States, the initial indication included single-dose, oral treatment of acute uncomplicated influenza in patients ≥12 years old, who have been symptomatic for ≤48 hours, which was expanded in October 2019 to include those at high risk of developing influenza-related complications.[17] These approvals were based on the clinical efficacy and safety of baloxavir versus placebo and oseltamivir in 2 pivotal phase III trials (CAPSTONE 1 and CAPSTONE 2, respectively).[19,20] In these studies, baloxavir showed significant improvements in time to alleviation of influenza symptoms (CAPSTONE 1) and time to improvement of influenza symptoms (CAPSTONE 2) compared with placebo, and faster reduction in infectious viral titers compared with placebo and oseltamivir in adults and adolescents.[19,20]

We report the safety and efficacy results of single oral dose baloxavir treatment in otherwise healthy children 1–<12 years old with acute influenza from miniSTONE-2 (Clinicaltrials.gov identifier: NCT03629184), a phase III, randomized, active controlled trial.

MATERIALS AND METHODS

Trial Design and Participants

This was a global, multicenter, double-blind, randomized, active controlled trial of the safety, pharmacokinetics and efficacy of a single oral dose of baloxavir versus twice-daily (for 5 days) oral oseltamivir, in otherwise healthy children with influenza. The trial enrolled children 1–<12 years of age with influenza (who were otherwise healthy) during the 2018/2019 Northern Hemisphere influenza season, including sites in the United States, South America and Europe. Enrolled children had a clinical diagnosis of influenza infection consisting of fever (tympanic temperature of ≥38°C) at screening and at least one respiratory symptom (either cough or nasal congestion). The time interval allowed between the onset of symptoms and screening was ≤48 hours. The trial excluded children with severe influenza symptoms requiring inpatient treatment and those with concurrent infections requiring systemic antiviral therapy at screening. Acetaminophen was permitted for severe symptoms. Children were considered "otherwise healthy" if they met none of the following exclusion criteria: any immunosuppressive disorder (including human immunodeficiency virus infection), uncontrolled renal, vascular, neurologic, or metabolic disease, hepatitis, cirrhosis, or pulmonary disease, known chronic renal failure, active cancer at any site, or a history of organ transplantation.

Randomization and Treatment

Children were enrolled in parallel to 2 cohorts: 1–<5 years old (minimum of 20 children) and 5–<12 years old (minimum of 40 children). Using a permuted block randomization method, children were assigned in a 2:1 ratio to receive a single dose of oral baloxavir on day 1 (2 mg/kg for those weighing <20 kg and a single dose of 40 mg for those weighing ≥20 kg), or oral oseltamivir twice daily according to prescribing information (30 mg for patients weighing ≤15 kg, 45 mg for >15–≤23 kg, 60 mg for >23–≤40 kg, and 75 mg for >40 kg) on days 1–5.[21] Doses of baloxavir in this study were chosen based on population pharmacokinetic analyses performed using data from a phase 3 study of children in Japan (JapicCTI-173811), and evaluated with respect to their ability to match adult drug exposure. Children in both groups received a 5-day regimen (baloxavir and a matching oseltamivir placebo or oseltamivir and matching baloxavir placebo). Following randomization, the first dose of the trial regimen was administered under direct observation, and participants were followed until day 29.

Outcomes Measured

The primary endpoint was safety, defined as the incidence, severity and timing of adverse events (AEs) during the 5-day treatment period and a 24-day follow-up period. Vital signs (blood pressure, respiratory rate, heart rate and tympanic temperature) were measured at scheduled visits [days 1, 2, 4, 6, 10, 15 and 29 (if there were abnormal findings or AEs since the previous measurement)]. Blood was collected for hematology and chemistry assessment on day 1 and day 6, and nasopharyngeal swabs were performed for viral quantification (using infectious titer) on days 1, 2, 4, 6, 10, as well as days 15 and 29 if considered appropriate by the treating physician.

Parents completed the Canadian Acute Respiratory Illness and Flu Scale (CARIFS)[22] questionnaire at scheduled visits (day 1–15), and responses were used to measure secondary efficacy endpoints including time to alleviation of signs and symptoms (TTASS) of influenza [defined as when a score of 0 (no problem) or 1 (minor problem) was reported for cough and nasal symptoms on the CARIFS questionnaire, return to normal health and activity, and return to afebrile state (tympanic temperature ≤37.2°C), remaining for at least 21.5 hours]. Subgroup analyses of TTASS based on virus subtype were also performed.

Other secondary efficacy endpoints were duration of fever [defined as time to return to afebrile state (≤37.2°C)], duration of all symptoms, time to return to normal health and activity, frequency of influenza-related complications (all of which were predefined and required investigator confirmation: death, hospitalization, pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures or myositis) and proportion of children requiring antibiotics.

Secondary virologic endpoints included time to cessation of viral shedding by virus titer and change from baseline in influenza virus titer.[23] Exploratory virologic endpoints included frequency of treatment-emergent amino acid substitutions (using Sanger sequencing).[24] Baseline samples from both treatment groups were also tested for coinfections (viral and bacterial pathogens), using the BioFire FilmArray Respiratory Panel 2 assay.[25]

Statistical Analysis

A sample size of 80 children in the baloxavir arm (120 in total) provided a probability of ≥90% that ≥1 child would experience an AE with a background incidence rate of 3%. A sample size of 120 children provided a probability of 80.1% that ≥1 child would experience an AE with an incidence rate of 2%. Because the study was not powered for a statistical comparison between treatments, results are descriptive. The safety population comprised children who received any portion of a single dose. The intent-to-treat influenza-infected (ITTi) population was used for all efficacy analyses and comprised children who had a laboratory reverse transcriptase-polymerase chain reaction confirmation of influenza infection from any swab sample collected at baseline or during the study. The number of children in the ITTi population was continuously monitored to ensure an adequate number of influenza-infected children were recruited. Data were summarized using descriptive statistics and Kaplan–Meier plots where applicable (SAS version 9.4).

Ethics and Consent

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH E6) guidelines, and was approved by all relevant institutional review boards and/or ethic committees at each center. All parents/caregivers of participants gave written informed consent and child consent was obtained where applicable.

RESULTS

Patient Disposition and Characteristics

This study was performed between November 20, 2018 and August 27, 2019 at 36 sites across 6 countries (USA, Poland, Spain, Costa Rica, Mexico and Russia). Of the 176 children enrolled, 117 (66.5%) and 59 (33.5%) patients were randomized into the baloxavir and oseltamivir groups, respectively. In total, 169 children (96%) completed the trial (Fig. 1). The predominant influenza A subtype at baseline assessed by reverse transcriptase-polymerase chain reaction was H3N2 for both groups, followed by H1N1pdm09. Numbers were low for influenza B in both groups (n = 5 for baloxavir and n = 2 for oseltamivir). In the safety population, 49.1% of
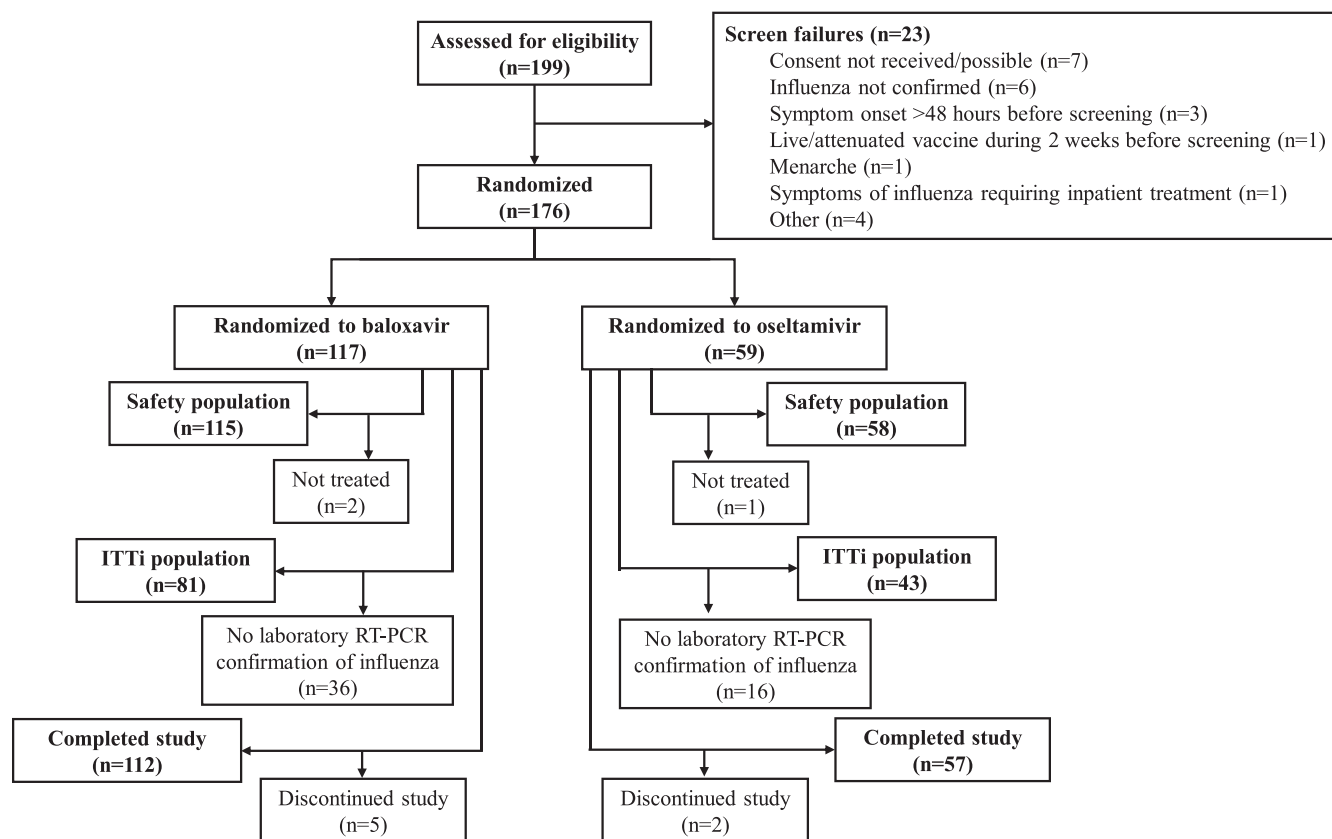
FIGURE 1. Participant disposition. The ITTi population comprised children who had a laboratory reverse transcriptase polymerase chain reaction confirmation of influenza infection from any swab sample collected at baseline or during the study. RT-PCR indicates reverse transcriptase polymerase chain reaction.

children were vaccinated against flu, with similar proportions vaccinated in each treatment group.

Demographics and baseline characteristics were similar between treatment groups (Table 1). There were no notable differences between the treatment groups in the use of concomitant medications during the study; the most frequently reported class in both was analgesics, most commonly acetaminophen. Other concomitant medications were predominantly symptomatic treatments, and were reported in very few children.

Primary Objective: Safety

A total of 122 AEs was reported in 84 children (48.6%) during the study (between day 1 and 29) and most AEs resolved or were resolving by study end (95.1%). The overall incidence of AEs was similar between the baloxavir group (46.1%) and the oseltamivir group (53.4%; Table 2). The incidence of AEs considered related to study drug was low in both groups, 2.6% (3/115) for baloxavir compared with 8.6% (5/58) for oseltamivir. The most common AEs in both groups were gastrointestinal disorders (vomiting or diarrhea), experienced by 12 children (10.4%) for baloxavir and 10 (17.2%) for oseltamivir. No deaths, serious AEs or hospitalizations were reported during the study. Two children experienced AEs which led to withdrawal from treatment in the baloxavir group, including accidental overdose of oseltamivir placebo and grade 2 rash occurring on day 4 that resolved after 24 hours without treatment in a child who received an accidental under-dose of baloxavir

(4 mg instead of 40 mg). No AEs led to withdrawal in the oseltamivir group.

All AEs observed in the study were grade 1 or 2, except for 3 grade 3 AEs. These were abdominal pain on day 8 in the baloxavir group, and severe vitamin D deficiency at baseline (undiagnosed preexisting conditions, determined by raised alkaline phosphatase levels on day 1) in 2 children in the oseltamivir group. There were no clinically meaningful changes from baseline in any laboratory parameters or vital signs.

Secondary Objective: Clinical Efficacy

The TTASS based on the CARIFS questionnaire was similar between treatment groups, with a median of 138.1 [95% confidence interval (CI): 116.6–163.2] hours for baloxavir and 150.0 (95% CI: 115.0–165.7) hours for oseltamivir (Fig. 2 and Table 3). For children infected with H3N2, median TTASS was similar between the baloxavir and oseltamivir groups, while for those infected with H1N1pdm09, TTASS was numerically lower for baloxavir than oseltamivir; Table 3). The number of children with influenza B was too low to allow meaningful interpretation of the data.

The median duration of fever was similar between the baloxavir and oseltamivir groups: 41.2 (95% CI: 24.5–45.7) versus 46.8 (30.0–53.5) hours, respectively (Table 3), as was the duration of all symptoms: 66.4 (95% CI: 43.7–76.4) versus 67.9 (45.8–88.7) hours, respectively. The median time to return to normal health and activity was similar in the baloxavir and oseltamivir groups [116.5

TABLE 1. Baseline Characteristics of the Safety Population

	Baloxavir Marboxil (n = 115)	Oseltamivir (n = 58)	All (N = 173)
Age (years)			
Mean (SD)	6.1 (2.9)	6.0 (3.2)	6.1 (3.0)
Median	6.0	6.0	6.0
1 to <5, n (%)	36 (31.3)	19 (32.8)	55 (31.8)
5 to <12, n (%)	79 (68.7)	39 (67.2)	118 (68.2)
Sex, n (%)			
Female	60 (52.2)	32 (55.2)	92 (53.2)
Race, n (%)			
Black or African American	6 (5.2)	5 (8.6)	11 (6.4)
White	98 (85.2)	51 (87.9)	149 (86.1)
Other/unknown*	11 (9.6)	2 (3.4)	13 (7.5)
Weight (kg)			
Mean (SD)	26.1 (12.3)	28.1 (16.0)	26.8 (13.6)
Median	23.30	23.78	23.60
Vaccinated (yes), n (%)	59 (51.3)	26 (44.8)	85 (49.1)
Virus subtype, n (%)†			
N	76	40	116
A/H1N1pdm09	18 (23.7)	10 (25.0)	28 (24.1)
A/H3N2	48 (63.2)	28 (70.0)	76 (65.5)
B	5 (6.6)	2 (5.0)	7 (6.0)
Mixed‡	1 (1.3)	–	1 (0.9)
Unknown	4 (5.3)	–	4 (3.4)
Coinfection with another infectious pathogen, n (%)†§	25 (30.9)	7 (16.3)	32 (25.8)

The safety population comprised children who received any portion of a single dose of treatment.

*Including American Indian or Alaska Native (n = 1 for baloxavir), Asian (n = 1 for baloxavir), Native Hawaiian or other Pacific Islander (n = 1 for oseltamivir), multiple (n = 4 for baloxavir) and unknown (n = 5 for baloxavir, n = 1 for oseltamivir).

†Taken from the ITTi population.

‡One child had influenza A/H1N1pdm09 and influenza B coinfection.

§In the baloxavir marboxil group, 23 children with influenza A had viral coinfections: coronavirus (11), rhinovirus/enterovirus (8) and respiratory syncytial virus (4). In the oseltamivir group, 5 children with influenza A had viral coinfections: rhinovirus/enterovirus (3) and coronavirus (2). In the baloxavir marboxil group, 2 children with influenza B had viral coinfections: rhino/enterovirus (1), and both adenovirus and rhinovirus/enterovirus (1). In the oseltamivir group, 1 child with influenza B had a coinfection: rhinovirus/enterovirus. No results for coinfections after baseline are available.

(95% CI: 94.9–138.0) hours vs. 111.6 (80.8–138.3) hours, respectively].

The overall incidence of influenza-related complications meeting predefined diagnostic criteria was low overall: 6 (7.4%) children in the baloxavir group and 3 (7.0%) in the oseltamivir group. The most frequent complication was otitis media in both groups [3 (2.6%) for baloxavir, 4 (6.9%) for oseltamivir], with single cases of bronchitis, pneumonia and sinusitis (baloxavir) and febrile seizure (oseltamivir). The proportion of children requiring antibiotics was low in both groups: 2 children in each group received antibiotics for otitis media and 2 children in the baloxavir group received antibiotics for pneumonia and sinusitis.

Secondary Objective: Virology

As previously observed in phase II and phase III studies,[19,20] baloxavir was associated with a more rapid decline in infectious viral titer compared with oseltamivir. The mean reduction from baseline in influenza virus titer on day 2 (24 hours posttreatment) was considerably greater for baloxavir than oseltamivir [−3.59 (standard deviation = 1.34) vs. −1.79 (1.54) $\log_{10}$ median tissue culture infectious dose/mL, respectively]. Thereafter, the mean change from baseline was similar in the 2 treatment groups, plateauing on day 2 for baloxavir and from day 4 for oseltamivir. The median time to cessation of viral shedding by virus titer was shorter

TABLE 2. Overview of AEs Experienced by >2% of Children in at Least One Treatment Group (Safety Population)

	Baloxavir Marboxil (n = 115)	Oseltamivir (n = 58)	All (N = 173)
Vomiting	7 (6.1)	9 (15.5)	16 (9.2)
Diarrhea	6 (5.2)	1 (1.7)	7 (4.0)
Otitis media	3 (2.6)	4 (6.9)	7 (4.0)
Upper respiratory tract infection	5 (4.3)	2 (3.4)	7 (4.0)
Bronchitis	3 (2.6)	1 (1.7)	4 (2.3)
Medication error	5 (4.3)	2 (3.4)	7 (4.0)
Accidental overdose	3 (2.6)	1 (1.7)	4 (2.3)
Rhinorrhea	4 (3.5)	1 (1.7)	5 (2.9)
Cough	3 (2.6)	1 (1.7)	4 (2.3)
Ear pain	1 (0.9)	2 (3.4)	3 (1.7)

The safety population comprised children who received any portion of a single dose of treatment.

for baloxavir than oseltamivir by 51.6 hours [24.2 hours (95% CI: 23.5–24.6) vs. 75.8 hours (68.9–97.8); Table 3].

In total, 32 (25.8%) children in the ITTi population had a coinfection with another infectious pathogen at baseline [25/81 (30.9%) in the baloxavir group and 7/43 (16.3%) in the oseltamivir group; Table 1]. For baloxavir, most children with a coinfection had a subtype of coronavirus, followed by rhinovirus/enterovirus and respiratory syncytial virus. For oseltamivir, most children had rhinovirus/enterovirus. No results for coinfections after baseline are available.

In an exploratory genotyping analysis of the polymerase acidic (PA) gene using Sanger sequencing in the 81 influenza-positive children (ITTi) treated with baloxavir, none of the children had preexisting PA/I38X mutations in baseline samples; PA/I38X mutations have previously been shown to be the most common determinant of reduced susceptibility to baloxavir.[26] In 57 of the 81 children, sequencing was possible for both baseline and post-treatment samples, whereas 24 children had no detectable virus after treatment, or such low levels that sequencing was not possible. Treatment-emergent PA/I38X substitutions were detected in 11 of 57 children (19.3%); 9 had influenza A subtype H3N2 and 2 had subtype H1N1pdm09. However, when the 24 children with no detectable virus or such low levels that sequencing was not possible (suggesting no PA/I38X substitutions) are also included in this calculation, the rate of PA/I38X substitutions is 13.5% (11/81). The prevalence of PA/I38X substitutions was higher in children 1–<5 years old [5/16 (31.3%)] than in children 5–<12 years old [6/41 (14.6%)].

DISCUSSION

Baloxavir has a novel mechanism of action, preventing the formation of new virions by blocking replication early in the influenza life cycle.[16,17] Two previous Japanese studies evaluating the use of baloxavir in children <12 years old have been completed; however, both were small, open-label studies (JapicCTI-163417[24] and JapicCTI-173811). MiniSTONE-2 is the first global, phase III, randomized active controlled study designed to investigate the safety and efficacy of a single dose of baloxavir in children.

Baloxavir safety was the primary objective of this study, and the overall findings were unremarkable, with no new safety signals identified, confirming that baloxavir is well tolerated in children. Rates of AEs were generally similar between groups and there were no serious AEs or deaths reported. The most common AEs in both groups were gastrointestinal related (diarrhea/vomiting).
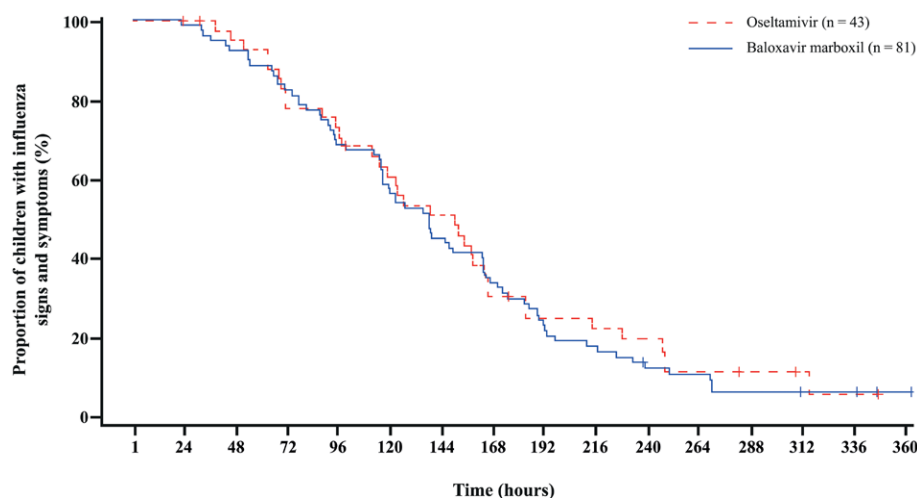
FIGURE 2. Kaplan–Meier plot of TTASS in the ITTi population, by treatment group. Solid line, baloxavir marboxil-treated children (n = 81); dashed line, oseltamivir-treated children (n = 43). The ITTi population comprised children who had a laboratory reverse transcriptase-polymerase chain reaction confirmation of influenza infection from any swab sample collected at baseline or during the study. Numbers of children remaining at risk shown beneath relevant timepoints. Children without alleviation of signs and symptoms were censored from the analysis (n = 7 in each group). NE indicates not evaluable.

TABLE 3. Overview of Secondary Efficacy and Virologic Endpoints in the ITTi Population

	Baloxavir Marboxil (N = 81)	Oseltamivir (N = 43)
Efficacy		
Evaluable children (n)	80	43
Median TTASS*, hours (95% CI)	138.1 (116.6–163.2)	150.0 (115.0–165.7)
Evaluable children (n)	47	28
In patients with H3N2 infection	126.9 (112.3–163.0)	118.4 (95.9–158.1)
Evaluable children (n)	18	10
In patients with H1N1pdm09 infection	115.8 (86.9–166.1)	206.9 (122.5–314.7)
Evaluable children (n)	80*	43
Median duration of fever, hours (95% CI)	41.2 (24.5–45.7)	46.8 (30.0–53.5)
Virology		
Patients with a post-baseline virology assessment (n)†	67	37
Evaluable children (n)‡	67	36
Time to cessation of viral shedding, hours (95% CI)	24.2 (23.5–24.6)	75.8 (68.9–97.8)

The ITTi population comprised children who had a laboratory reverse transcriptase-polymerase chain reaction confirmation of influenza infection from any swab sample collected at baseline or during the study.

*The number of children with influenza B was too low to allow meaningful interpretation of the data.

†Children with a positive virus titer on day 1 were included in this analysis.

‡Children whose virus titers did not reach the limit by the last observation time point were censored.

Treatment-related AEs were less frequent in the baloxavir group than the oseltamivir group. Most AEs were considered by investigators to be related to influenza infection. In both treatment groups, most AEs were either mild or moderate in severity and most resolved or were resolving by the end of the study.

The data showed that TTASS, a key efficacy endpoint for the study, were similar between the baloxavir and oseltamivir treatment groups. All other secondary efficacy endpoints were similar between treatment groups, and there were no differences in the incidence of influenza-related complications or the use of antibiotics.

As in previous studies,[19,20] the antiviral activity of baloxavir was shown to be favorable compared with oseltamivir. The rapid decline of infectious virus titer after 24 hours and reduced time to viral shedding are consistent with those seen previously in completed phase II and phase III studies, confirming the marked virologic effects achieved with a single dose of baloxavir.[19,20] The further potential clinical value of an antiviral with such favorable virologic properties has been recently demonstrated in a postexposure prophylaxis study.[27] Moreover, further studies are being conducted to determine whether transmission from infected individuals is reduced by baloxavir,[28] and whether, in combination with a neuraminidase inhibitor, baloxavir can offer benefit in patients hospitalized with severe influenza (Clinicaltrial.gov identifier: NCT03684044).

Multiple viral infections are frequent in hospitalized children with respiratory tract disease, and may be linked to greater severity in symptoms and longer lengths of hospital stays.[29,30] In contrast, although respiratory tract infections are commonly diagnosed and treated in the community, few studies report on the frequency of coinfection in this setting. A quarter of the ITTi population had a coinfection with another respiratory viral pathogen at baseline. Given that no data are available after baseline, there is a possibility that both baseline coinfections and later-onset coinfections contributed to a longer TTASS than may have been observed in the absence of coinfections.

In this study, there were no bacterial coinfections at baseline, and only 3 cases of otitis media (2 requiring antibiotics) observed in the baloxavir arm following treatment; therefore, these results may potentially indicate a reduction in acute otitis media complications following baloxavir treatment, compared with the 1 in 4 children in whom this usually develops without antiviral treatment.[31] This could contribute to a reduction of the overuse of antibiotics for prevention of this complication,[32] particularly in younger children, similar to the effect observed with oseltamivir.[33] However, these speculative results should be interpreted with caution in the absence of a specific analysis of the reduction in acute otitis media complications following baloxavir treatment.

All influenza antivirals can lead to the emergence of resistant variants with reduced susceptibility;[34] however, in acute infections such as influenza, these variants are usually transient. An amino acid substitution at position 38 in the RNA polymerase (PA/I38X) has been shown to be the most common determinant of reduced susceptibility to baloxavir.[35] The rate of PA/I38X viral variants in this study was consistent with that observed in 2 previous

completed Japanese studies in children (JapicCTI-163417[24] and JapicCTI-173811) including higher prevalence rates in children <5 years old, which has also been documented for oseltamivir.[35] In this study, clinical benefit was observed regardless of I38X variants. However, the approach taken to calculate resistance rates is conservative, generally including patients in whom virus is detectable after a certain time (usually days 3–5), but excluding those who have cleared the virus before sampling. Potent antivirals would be expected to clear the virus more rapidly, leaving fewer patients with samples for resistance analysis. This can potentially lead to an overestimation of resistance rates.

In conclusion, this study showed that a single oral dose of baloxavir is well-tolerated, effective at alleviating influenza signs and symptoms, and results in rapid elimination of the virus in children with uncomplicated, acute influenza. Importantly, it presents a new therapeutic option with a simplified and convenient single-dose oral regimen, of particular value for children.

Data Sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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