Cross-Discipline Team Leader Review

Date	August 5, 2022
From	Melisse Baylor, MD
Subject	Combined Clinical/Statistical, Cross-Discipline Team Leader and Division Director Review
NDA # and Supplement#	214410/Original 2 210854/S-05, 09
Applicant	Genentech, Inc.
Date of Submission	2/16/2022
PDUFA Goal Date	8/16/2022
Proprietary Name	Xofluza®
Established or Proper Name	Baloxavir marboxil
Dosage Form(s)	Oral granules for suspension (NDA 214410) Tablets (NDA 210854)
Applicant Proposed Indication(s)/Population(s)	Treatment of acute, uncomplicated influenza in otherwise healthy patients ≥ 5 years of age to <12 years of age and postexposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza
Applicant Proposed Dosing Regimen(s)	Granules and tablet dosing in patients 5 years of age and older: Weight: 20 kg to <80 kg: single oral dose of 40 mg Weight: At least 80 kg: single oral dose of 80 mg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	XOFLUZA is indicated for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours and who are: • otherwise healthy adults and pediatric patients 5 years of age and older [see Clinical Studies (14.1)], OR • adults and pediatric patients 12 years of age and older who are at high-risk of developing influenza-related complications1 [see Clinical Studies (14.2)]. XOFLUZA is indicated for post-exposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza [see Clinical Studies (14.3)].
Recommended Dosing Regimen(s) (if applicable)	Granules and tablet dosing in patients 5 years of age and older: Weight: 20 kg to <80 kg: single oral dose of 40 mg Weight: At least 80 kg: single oral dose of 80 mg

1. Executive Summary

This combined Clinical/Statistical, Cross Discipline Team Leader (CDTL), and Division Director Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment for the use of baloxavir marboxil for the treatment of acute, uncomplicated influenza and for the postexposure prophylaxis of influenza in pediatric patients ≥ 5 years to < 12 years of age. Please also see the Dr. Ince's Clinical Virology review and Dr. Zhao's Clinical Pharmacology review. The data support extension of the baloxavir marboxil indications for treatment and post-exposure prophylaxis of influenza to include patients from 5 years to <12 years of age.

The Applicant has submitted a response to a Complete Response Letter and has included data to support the use of baloxavir marboxil in pediatric patients ≥ 5 years to < 12 years of age for the treatment of acute, uncomplicated influenza and for the postexposure prophylaxis of influenza. This submission includes an amended Clinical Study Report for CP40563, a Phase 3 safety, pharmacokinetic (PK) and effectiveness trial of the treatment of influenza in pediatric patients ≥ 5 to <12 years of age. In Study CP40563, subjects were randomized to receive either a single oral dose of baloxavir marboxil or to receive the recommended dose of the active control, oseltamivir. The results for the time to alleviation of symptoms (TTAS), a key secondary endpoint, were similar in pediatric subjects ≥ 5 to <12 years old who received baloxavir marboxil to the TTAS in the subjects who received oseltamivir. However, as with previous pediatric approvals for influenza, efficacy of baloxavir marboxil in the treatment of influenza in pediatric patients was demonstrated by extrapolation, because baloxavir exposures in pediatric subjects were similar to those of adults and adolescents in the pivotal treatment trials of baloxavir.

The results of Trial T0834, a Phase 3 post-exposure prophylaxis trial which evaluated PK, safety and efficacy in subjects 5 years of age and older who were household contacts of influenza-infected individuals were also included in this submission. Household contacts (study subjects) received a single dose of baloxavir marboxil or placebo and were followed for 10 days for the development of RT-PCR-positive, symptomatic influenza. The efficacy of baloxavir marboxil for postexposure prophylaxis in patients ≥ 5 to < 12 years of age was demonstrated by extrapolation, because baloxavir exposures in pediatric subjects in T0834 were similar to those of adults in Trial T0834. In addition, only 2% of subjects ≥ 5 to < 12 years of age who received baloxavir developed symptomatic influenza compared to 13% of subjects who received placebo.

No new safety signals were identified in either Trial CP40563 or in Trial 0834. There were no serious adverse events in either trial, and no Grade 3 or Grade 4 adverse events were reported in subjects ≥ 5 to < 12 years of age. In Trial CP40563, the proportion of subjects ≥ 5 to < 12 years of age with any adverse event was similar in the

baloxavir marboxil arm and the oseltamivir control arm. The most commonly reported AEs in the baloxavir arm were vomiting and diarrhea, which were both reported in 5% of subjects. The most frequently reported AE in Trial T0834 was nasopharyngitis, which was reported in 5% of subjects ≥ 5 to < 12 years of age and in 6% of adults and adolescents. Nasopharyngitis was also the most commonly reported AE in the placebo arm (6%). Treatment-emergent resistance to baloxavir marboxil was observed in 16% of pediatric subjects ≥ 5 to < 12 years of age, which is higher than the frequency of resistance in adults and adolescents (7%). The frequency of treatment-emergent resistance reported in pediatric patients ≥5 to < 12 years of age who received baloxavir marboxil will be described in the package insert, including in a new subsection of the Warnings and Precautions section. Overall, the benefits of the use of baloxavir marboxil in the treatment and postexposure prophylaxis of influenza outweigh the risks in patients ≥ 5 years to < 12 years of age, and the risks will be described in labeling. Therefore, the baloxavir marboxil indications for treatment of influenza and postexposure prophylaxis of influenza will be extended to include patients 5 years of age and older. Baloxavir marboxil will not be approved for treatment or for postexposure prophylaxis in pediatric patients younger than 5 years of age because of the higher incidence of treatment emergent resistance in this age group (40%). The increased incidence of resistance to baloxavir marboxil in patients < 5 years of age is described in the package insert (Warnings and Precautions section, (b) (4) and Microbiology section).

2. Benefit-Risk Assessment

Although influenza is often a mild, self-limited disease, infection may result in serious disease or death. In addition to baloxavir marboxil, which is currently approved for treatment of acute, uncomplicated influenza and for the postexposure prophylaxis of influenza in adults and adolescents, drugs from two classes, neuraminidase inhibitors (NAIs) and adamantanes, are available for the treatment and prevention of influenza. However, only one of the NAIs is available in an oral formulation, and the use of adamantanes is not recommended by the Centers for Disease Control and Prevention because of widespread resistance in circulating influenza viruses. Therefore, there is a need for additional oral drugs to treat and to prevent influenza infection in pediatric patients.

The Applicant submitted a response to a Complete Response Letter from the Division of Antivirals. This submission includes an amended Clinical Study Report for a Phase 3 safety, pharmacokinetic (PK) and effectiveness trial (CP40563) to support the use of baloxavir marboxil for the treatment of acute, uncomplicated influenza in pediatric patients ≥ 5 to <12 years of age. Safety data from three single arm, open-label studies of baloxavir marboxil in pediatric patients were also reviewed; the Clinical Study Reports and corresponding datasets were previously submitted to the NDA. As with previous pediatric approvals for influenza, efficacy of baloxavir marboxil in the treatment of influenza in pediatric patients was demonstrated by extrapolation because baloxavir

exposures in pediatric subjects were similar to those of adults and adolescents in the pivotal treatment trials of baloxavir. The time to alleviation of symptoms (TTAS) was a key secondary endpoint in Trial CP40563, the TTAS in pediatric subjects (≥ 5 to <12 years old) who received baloxavir marboxil was similar to that for those who received an active control (oseltamivir) in Trial CP40563.

No new safety signal was identified in pediatric subjects ≥ 5 to <12 years old treated with baloxavir marboxil. The percentage of subjects with adverse events was low and all adverse events were Grade 1 or 2 in intensity with no serious adverse events reported. The frequency of treatment-emergent resistance (TE-RAS) to baloxavir was higher in pediatric subjects (≥ 5 to <12 years old) than in adults and adolescents. However, the frequency of TE-RAS was similar to that reported with oseltamivir in the Tamiflu® package insert. The risk of resistance is described in multiple sections of the Xofluza package insert, including a new description of TE-RAS in the WARNINGS AND PRECAUTION section and detailed description of the risk of TE-RAS by age in Section 12.4. Overall, the benefits of baloxavir marboxil for the treatment of influenza outweigh the risks, and the risks are well described in labeling.

Amended results for subjects ≥ 5 years to < 12 years of age in a Phase 3 trial (T0834) were also submitted in the Applicant's response to the Complete Response Letter to support the use of baloxavir marboxil for the postexposure prophylaxis of influenza in pediatric subjects from 5 to < 12 years of age. Subjects in this study were household contacts of influenza-infected individuals and received a single dose of baloxavir marboxil or placebo for prevention of influenza. The efficacy of baloxavir marboxil for postexposure prophylaxis in patients ≥ 5 to < 12 years of age was demonstrated by extrapolation because baloxavir exposures in pediatric subjects in T0834 were similar to those of adults in Trial T0834. In addition, only 2% of subjects ≥ 5 to < 12 years of age who received baloxavir developed symptomatic influenza compared to 13% of subjects who received placebo. Adverse events in pediatric subjects were uncommon and were consistent with breakthrough influenza infection in both arms. There were no Grade 3 or 4 adverse events or serious adverse events in pediatric subjects ≥ 5 to < 12 years of age.

Efficacy was demonstrated in pediatric patients by extrapolation of efficacy for both the treatment of acute, uncomplicated influenza and for the postexposure prophylaxis of influenza. In addition, trends toward efficacy for treatment and for postexposure prophylaxis in pediatric patients from 5 to < 12 years of age were observed in two Phase 3 trials. The sizes of the safety databases for treatment and for postexposure prophylaxis were adequate. Adverse drug reactions were uncommon. In the treatment trial, diarrhea and vomiting were reported in pediatric patients ≥5 to <12 years of age more commonly than in adults/adolescents. Nasopharyngitis was the most commonly reported adverse event in the postexposure prophylaxis trial and was reported at a similar incidence in pediatric patients, and adults/adolescents who received baloxavir marboxil, as well as in in the placebo arm. No serious adverse events were reported, and no new safety signals were detected. The frequency of treatment-emergent

resistance is higher in pediatric patients ≥ 5 years to < 12 years of age, however, an increased frequency of TE-RAS in pediatric patients has also been observed with oseltamivir. This may be due to an immature immune system resulting in higher viral loads or more prolonged viral shedding. The risk of treatment-resistance in pediatric patients ≥5 to < 12 years of age who receive baloxavir marboxil will be described in the Warnings and Precautions, (b) (4) and Microbiology sections of the Xofluza package insert. Overall, the benefits of the use of baloxavir marboxil in the treatment and postexposure prophylaxis outweigh the risks in patients ≥ 5 years to < 12 years of age, and the risks will be described in labeling. Therefore, the baloxavir marboxil indications for treatment of influenza and postexposure prophylaxis of influenza will be extended to include patients 5 years of age and older.

Baloxavir marboxil will not be approved for treatment or for postexposure prophylaxis in pediatric patients younger than 5 years of age at this time because of the higher incidence of treatment emergent resistance observed in clinical trials in this age group. The higher incidence of resistance to baloxavir marboxil in patients < 5 years of age is described in the package insert (Warnings and Precautions section, (b) (4) and Microbiology section).

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza occurs in annual outbreaks each fall and winter in the United States. In spite of the availability of influenza vaccines, it is estimated that 5% to 20% of the U.S. population gets influenza each year, and the Centers for Disease Control and Prevention (CDC) estimate that there are between 9.2 and 35.6 million influenza illnesses each year in the United States. Influenza typically causes a self-limited respiratory illness with fever that lasts from 3 to 7 days. However, influenza can cause severe disease and result in death. • The severity of influenza varies by season. While the CDC estimated that there were between 140,000 and 170,000 hospitalizations each influenza seasons from 2010 through 2016; the 2017–18 influenza season in the United States was a very severe influenza season with approximately 900,000 influenza-related hospitalizations. Healthcare providers are not required to report deaths associated with influenza in adults, so the number of deaths related to influenza is estimated. • The CDC estimated that there were 12,000 to 56,000 deaths each year due to influenza in the six influenza seasons from 2010 through 2016 and approximately 80,000 deaths in the 2017–18 influenza season.	The efficacy of baloxavir marboxil has been demonstrated in two pivotal trials for treatment of acute, uncomplicated influenza in otherwise healthy and high-risk adults and adolescents. The primary endpoint in both trials was the median time to alleviation of influenza symptoms.
Analysis of Condition (cont'd.)	**Influenza in pediatric patients** • Influenza is typically more severe in the very young and the elderly. Approximately 7,000 to 26,000 patients <5 years of age with influenza-related conditions have been hospitalized yearly since 2010. The CDC	The efficacy of baloxavir marboxil for treatment of acute, uncomplicated influenza in pediatric patients 1 to <12 years of age has been demonstrated in a single randomized, active-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	monitors deaths due to influenza in children through the Influenza-Associated Pediatric Mortality System. The 2017–18 influenza season was particularly severe with 183 pediatric deaths due to laboratory-confirmed influenza reported to CDC. This was the highest number of pediatric deaths due to influenza since the 2009 influenza pandemic in which there were 358 pediatric deaths. • The 2019–2020 influenza season was also severe with 166 pediatric deaths due to influenza. In addition, the rate of hospitalization due to influenza in pediatric patients ≤4 years of age in the 2019–2020 season was higher than in the 2009 influenza pandemic, while the rate of hospitalization due to influenza in patients from 5 to 17 years of age was higher than any influenza season except for the 2009–2010 pandemic. **Prevention of influenza** • While chemoprophylaxis is available for individuals who have been exposed to influenza or are at high risk of influenza complications, vaccination against influenza is the best way to prevent influenza. The CDC recommends annual influenza vaccination for all persons 6 months of age and older. However, only approximately one-half of Americans receive the influenza vaccine each year. The CDC estimated that influenza vaccine coverage in the United States during the 2018–19 season was 62.6% among children 6 months through 17 years and 45.3% in adults ≥18 years of age. • Influenza vaccine efficacy can be lower than expected if the influenza vaccine strains differ from the influenza strains that circulate in a community. When that occurs even more persons in the United States are vulnerable to influenza.	controlled trial. Efficacy was based on pharmacokinetic (PK) extrapolation from adults and adolescents as well as similar time to alleviation of symptoms to the oseltamivir comparator. This indication will be approved for children ≥ 5 to < 12 years of age, but not in pediatric patients < 5 years of age because of the higher frequency of baloxavir resistance in pediatric patients < 5 years of age (40%) compared to pediatric patients ≥ 5 to < 12 years of age (16%) and to adults and adolescents (7%). The efficacy of baloxavir marboxil for postexposure prophylaxis of influenza has been demonstrated in a single, randomized, placebo-controlled trial in adults and adolescents; and baloxavir marboxil is indicated for post-exposure prophylaxis in individuals ≥ 12 years of age. Efficacy for the prevention of influenza was also demonstrated in pediatric patients from 1 to <12 years of age. However, the prevention indication will not be approved in pediatric patients 1 to < 5 years of age due to the high frequency of treatment emergent resistance to baloxavir in that population.
Current Treatment Options	**Treatment of influenza in pediatric patients <12 years of age** • There are two classes of influenza drugs available in the United States for treatment of pediatric patients younger than 12 years of age. Oseltamivir, zanamivir, and peramivir are viral neuraminidase inhibitors (NAIs) preventing virus release from infected cells. Oseltamivir is the only NAI available for oral administration; zanamivir is administered through oral inhalation; and peramivir is administered intravenously. Oseltamivir and zanamivir are taken twice daily for 5 days and peramivir is administered as a single dose. All three NAIs are indicated for use in children: oseltamivir for pediatric patients ≥2	There is a need for additional antiviral drugs for treatment of influenza that are effective and available in an oral formulation, particularly in the pediatric population. There is also a need for additional oral influenza drugs for postexposure prophylaxis. In addition, the use of a drug available as a single dose may increase compliance, particularly in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weeks of age; zanamivir for patients ≥7 years of age; and peramivir for patients ≥2 years of age. • The other class of anti-influenza drugs is the adamantanes. Use of the adamantanes is not recommended because of widespread adamantine resistance among influenza virus strains. **Prevention of influenza** • Vaccination against influenza is the best way to prevent influenza, but chemoprophylaxis can be administered as postexposure prophylaxis, e.g., in persons who have been exposed to a person with influenza, or as preexposure prophylaxis, e.g., in institutional outbreaks or in persons who are at high risk of influenza complications. Oseltamivir and zanamivir are the only two NAIs indicated for prevention of influenza in pediatric patients younger than 12 years of age; oseltamivir is indicated for patients ≥1 year of age and zanamivir for patients ≥5 years of age. • Oseltamivir and zanamivir are both administered once daily for 10 days for postexposure prophylaxis. Oseltamivir can be administered daily for up to 6 weeks for pre-exposure prophylaxis; zanamivir may be administered daily for up to 28 days for pre-exposure prophylaxis.	
Benefit	**Treatment of acute, uncomplicated influenza in pediatric patients > 1 year to <12 years of age** • In the previous submission, the efficacy of baloxavir marboxil in pediatric patients >1 year to <12 years was extrapolated from the efficacy in adults and adolescents after similar PK exposures of baloxavir were demonstrated in pediatric patients and adults and adolescents as well as a demonstration of trend toward efficacy in a Phase 3 pediatric trial, CP40563. • In this response to the CR Letter, baloxavir exposures in pediatric subjects ≥5 years to <12 years of age who participated in Trial CP40563, a Phase 3, safety, PK, and efficacy trial of pediatric patients were compared to baloxavir exposures in the pivotal Phase 3 safety, PK, and efficacy trial (Trial T0831) of subjects ≥12 years of age with acute, uncomplicated influenza. Based on similar exposures in pediatric patients and adults/adolescents, the efficacy from adults and adolescents can be extrapolated to pediatric patients ≥ 5 years to < 12 years of age.	Baloxavir marboxil efficacy in pediatric patients ≥5 to <12 years of age was extrapolated from adults and adolescents based on similar baloxavir exposures in pediatric subjects in a Phase 3 trial and in adults and adolescents in a Phase 3 pivotal trial for the treatment of acute, uncomplicated influenza. Efficacy was further supported by the results of the Phase 3 pediatric trial in which the median time to alleviation of symptoms was similar in subjects who received baloxavir marboxil and in subjects who received an FDA-approved active control, oseltamivir. Therefore, baloxavir marboxil will be approved for use in pediatric patients ≥ 5 years of age but will not be approved for treatment in pediatric patients < 5 years of age. Baloxavir marboxil will not be

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	• Efficacy was further supported by the results of the Phase 3 trial in pediatric patients. Trial CP40563 was a Phase 3, randomized, double-blind, active-controlled (oseltamivir) safety, efficacy, and PK trial. Efficacy was evaluated as a secondary endpoint and the study was not powered for efficacy. The key efficacy endpoint was the time to alleviation of symptoms. The median time to alleviation of symptoms was 138 hours (95% CI of 116.7, 163.4) in the baloxavir marboxil arm and 126 hours (95% CI of 95.9, 165.7) in the oseltamivir arm. **Postexposure prophylaxis in persons >1 year of age who have had contact with an influenza-infected person** • Baloxavir was approved in November 2020 for the prevention of influenza in persons 12 years of age and older following contact with an individual who has influenza. The efficacy for post-exposure prophylaxis was based on results from a Phase 3, randomized, double-blind, placebo-controlled trial (Trial T0834) in which subjects ≥1 years of age were enrolled. • Efficacy data from subjects ≥ 5 years of age to < 12 years of age who participated in Trial T0834 were submitted in the Applicant's response to the CR Letter. Trial T0834 was a Phase 3, randomized, double-blind, placebo-controlled trial (Trial T0834) in which subjects who had been exposed to a person with influenza (the index case) were randomized to baloxavir marboxil (N=57) or placebo (N=51) and followed for 10 days for symptoms of influenza. The primary endpoint was the proportion of subjects who were influenza RT-PCR positive with fever and at least one respiratory symptom through Day 10. Although the study was not powered to demonstrate efficacy in this age group, a trend toward efficacy was observed. In the subgroup of pediatric patients ≥ 5 years of age, the proportion of subjects ≥ 5 years to < 12 years of age who were RT-PCR-positive with symptomatic influenza in the baloxavir arm was 3.5% compared to 14% in the placebo arm. • When the trial results were analyzed for all subjects 5 years of age and older (pediatric patients, adolescents, and adults), a total of 360 subjects were randomized to receive a single dose of baloxavir marboxil and 355 to receive placebo. The proportion of subjects who were RT-PCR-positive with symptomatic influenza in the baloxavir arm was 2% compared to 13%	approved for use in pediatric patients younger than 5 years of age at this time because of the higher incidence of treatment-emergent resistance observed in that age group. The frequency of TE-RAS observed in clinical trials of baloxavir marboxil was 40% in pediatric patients <5 years of age, 16% in pediatric patients from 5 years to < 12 years, and 7% in subjects 12 years of age and older. Baloxavir marboxil was highly effective in the postexposure prophylaxis of influenza from an index case to a household contact in patients 5 years of age and older. The indication for postexposure prophylaxis will be extended to persons ≥5 years of age who have been exposed to an individual with influenza.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in the placebo arm (p<0.0001).	
Risk and Risk Management	• Pediatric subjects with acute, uncomplicated influenza The safety database for pediatric subjects with acute, uncomplicated influenza ≥ 5 years to <12 year of age included 183 pediatric subjects exposed to baloxavir marboxil. This included subjects from Trial CP40563 and subjects from three open-label, single-arm trials in Japanese pediatric subjects. There were no deaths and no serious adverse events. Two subjects discontinued a study prematurely due to an adverse event: one due to a rash on Day 3 that resolved without treatment and one due to an adverse event of "overdose" of the oseltamivir placebo, but no adverse events associated with the "overdose" were reported. The most commonly reported adverse event was vomiting, which was reported in 5% of subjects ≥ 5 years of age who received baloxavir marboxil in Trial CP40563, compared to 18% of subjects who received the active control (oseltamivir). In the three open-label trials, vomiting was reported in 9% (8/32 subjects) of subjects in Study T0822, and in 3 of 14 subjects (21%) in the two smaller studies. Diarrhea was reported in 5% of pediatric subjects who received baloxavir marboxil in Trial CP40563 compared to none of the subjects who received oseltamivir. Vomiting was reported in 1% of adult and adolescent subjects and diarrhea in 3% of adults and adolescents in trials of acute, uncomplicated influenza. Rash was reported in two pediatric subjects (3%) who received baloxavir marboxil; both rashes were judged as Grade 1 or 2 in severity. All other adverse events reported in at least 2% of pediatric subjects were related to conditions observed with influenza or to common infections of childhood: otitis media, streptococcal pharyngitis, rhinitis, headache, and upper respiratory tract infections, or with medication errors, which were primarily reported at a single site. • Postexposure prophylaxis A total of 57 subjects ≥ 5 to < 12 years of age received baloxavir marboxil as prophylaxis against influenza in Trial T0834. Unlike in other studies of baloxavir marboxil, subjects who received baloxavir marboxil in Trial T0834 did not have signs or symptoms of influenza at enrollment. There were no	The size of the safety database (N=183) for pediatric subjects ≥5 years of age to <12 years who received baloxavir marboxil for treatment of influenza of age was adequate. Adverse drug reactions were uncommon. Diarrhea and vomiting were reported in pediatric patients <12 years of age more commonly than in adults/adolescents. The size of the safety database (N=57) for subjects ≥5 to < 12 years of age who received baloxavir marboxil as postexposure prophylaxis was adequate. There was no safety signal, and adverse drug reactions were uncommon. The frequency of treatment-emergent resistance to antivirals is often higher in younger children than in adolescents or adults. This may be due to an immature immune system resulting in a higher viral load. The frequencies of treatment-emergent resistance with oseltamivir are also higher in children than in adults. The incidence of oseltamivir resistance to influenza A viruses has been detected at rates ranging from 3% to 37% (Tamiflu® package insert). The risk of treatment-resistance in pediatric patients ≥5 to < 12 years of age who receive baloxavir marboxil will be described in the Warnings and Precautions, (b) (4) and Microbiology sections of the Xofluza package

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	deaths and no serious adverse events. The most commonly reported adverse Event in pediatric subjects was nasopharyngitis, which was reported in 8% (N=3) of subjects who received baloxavir marboxil and 4% (N=2) of subjects who received placebo. The only other adverse events reported in >2% of subjects were cough and headache, which were each reported in 4% of subjects. • Treatment-emergent resistance to baloxavir marboxil The frequency of treatment-emergent resistance to baloxavir in the pivotal adult/adolescent treatment trials ranged from 3% to 11% of subjects. The frequency of treatment-emergent resistance-associated substitutions (RAS) in pediatric subjects ≥5 to <12 years of age was assessed in the four pediatric trials included in this submission. Treatment-emergent resistance was observed in 16% of subjects (19/117) in subjects ≥5 to <12 years of age . Resistance was similar in influenza subtypes A/H1N1 (2/12, 17%) and A/H3N2 (17/93, 18%), although the numbers for A/H1N1 were small; resistant variants were not reported for the 15 subjects who were infected with influenza B. Treatment–emergent resistance to baloxavir marboxil was observed at a higher frequency in pediatric patients < 5 years than in pediatric patients ≥ 5 to < 12 years of age or in adolescents and adults. Treatment-emergent resistance substitutions were observed in 40% of pediatric subjects < 5 years of age (37/93) who received baloxavir marboxil in a clinical study. In subjects < 5 years of age, resistance to influenza A/H3N2 (60% or 32/53) occurred at a higher rate than resistance to influenza A/H1N1 (23% or 5/22) or influenza B (0/19). The frequency of resistance varies by influenza type/subtype, by season, by year, and by patient age.	insert. Information regarding the increased incidence of treatment-emergent resistance to baloxavir marboxil in pediatric patients younger than 5 years of age is also described in the Warnings and Precautions, (b) (4) and Microbiology sections of the package insert.

3. Background

Baloxavir marboxil was approved for the treatment of acute, uncomplicated influenza in otherwise healthy adults and adolescents 12 years of age and older on November 15, 2018. Baloxavir was subsequently approved for the treatment of influenza in adults and adolescents ≥ 12 years of age who are at high risk of influenza complications in October 2019. On January 23, 2020, the Applicant submitted NDA 210854 to support the use of baloxavir marboxil 2% granules in solution (b) (4) to support the safety and efficacy of baloxavir marboxil for the treatment of influenza in pediatric patients 1 year of age and older and to support the safety and efficacy of baloxavir marboxil for the prevention of influenza in individuals 1 year of age and older. After DAV review, the baloxavir marboxil 2% granules for solution formulation was approved for use in individuals 12 years of age and older who could not swallow tablets, and baloxavir marboxil was approved for the prevention of influenza in individuals 12 years of age and older. Baloxavir marboxil was not approved for the treatment or the prevention of influenza in pediatric patients from 1 to < 12 years of age because of the increased frequency of treatment-emergent resistance-associated substitutions (TE-RAS) observed in pediatric patients. A Complete Response Letter was issued on November 23, 2020, for the use of baloxavir for the treatment of influenza in patients from 1 year to < 12 years of age and for the use of baloxavir for the prevention of influenza in individuals 1 year of age to < 12 years of age. The application numbering was revised prior to the CR Letter being issued. The contents of the original application and regulatory review decisions are shown in the following table.

Table 1: Applications and FDA Decisions for Baloxavir Marboxil 2% Granules, Pediatric Use of Baloxavir Marboxil, and Use of Baloxavir Marboxil for the Prevention of Influenza

Original Application		**Formulation**	**Proposed Indication**	**Revised Application Numbers**	**Regulatory Outcome**
NDA 214410	01	2% Granules	Treatment and prevention of influenza in pediatric patients ≥ 1 year of age	01	Approved for treatment and prevention in patients ≥ 12 years of age
				02	CR Letter issued for treatment and prevention in patients 1 to < 12 years of age
sNDA 210854	S-04	Tablet	Prevention of influenza in children and adults ≥ 1 year of age	S-04	Approved for treatment and prevention in patients ≥ 12 years of age
				S-09	CR Letter issued for prevention in individuals 1 to < 12 years of age

sNDA 210854	S-05	Tablet	Treatment of influenza in pediatric patients ≥ 1 year of age	S-05	CR Letter issued for treatment of influenza in patients 1 to < 12 years of age
				S-10	Labeling updated with resistance data from pediatric trials

Source: Table created by clinical reviewer and Christine Kim, regulatory project manager.

Previous Review of the Original Applications for Pediatrics (NDA 214410/S-01 and NDA 210854/S-04)

- Treatment of Influenza in Pediatric Patients ≥ 1 to < 12 years of age

The Applicant had included the results of three studies to support the use of baloxavir marboxil for the treatment of influenza in pediatric patients (sNDA 210854, S-05) in the January 23, 2020 sNDA submission. These included one Phase 3 trial and two single arm, open-label trials. The Phase 3 trial, CP40563, was a randomized, double-blind, active-controlled (oseltamivir), PK, safety and effectiveness study in subjects from ≥1 to 12 years of age. The primary endpoints for the trial were safety and pharmacokinetic parameters. The most commonly reported adverse events in pediatric subjects ≥1 year to < 12 years of age who received baloxavir marboxil were vomiting (7%) and diarrhea (5%); vomiting was reported in 16% of subjects who received oseltamivir and diarrhea in 2% of subjects. The efficacy of baloxavir marboxil in pediatric patients was extrapolated from the efficacy in adults and adolescents after similar exposures of baloxavir were demonstrated in pediatric patients and adults and adolescents. Baloxavir exposures in pediatric patients in Trial CP40563 were compared to baloxavir exposures in the pivotal Phase 3 safety, PK, and efficacy trial (Trial T0831) of subjects ≥12 years of age with acute, uncomplicated influenza. Based on overlapping exposures in pediatric patients and adults/adolescents, the efficacy from adults and adolescents can be extrapolated to pediatric patients. In addition, a trend toward efficacy was observed in subjects in Trial CP40563. The median time to alleviation of symptoms was 138 hours in subjects who received baloxavir marboxil and 150 hours in subjects who received oseltamivir. Additional safety data were provided in the two uncontrolled, open-label, pediatric studies, which were both conducted in subjects < 12 years of age. In these studies, the most commonly reported adverse event was vomiting. There were no serious adverse events or Grade 3 or 4 AEs reported in any of the pediatric treatment trials.

- Post exposure Prophylaxis in Pediatric Patients 1 to < 12 years of age

In the original application (NDA 210854/S-04), the Applicant submitted the results of a Phase 3 trial, T0834, to support the safety and efficacy of baloxavir marboxil for the prevention of influenza in individual exposed to a person with influenza. This Phase 3 trial was a randomized, double-blind, placebo-controlled trial conducted in adult, adolescent, and pediatric subjects from birth to < 18 years of age. However, only subjects > 1 year of age were enrolled in the trial. Household contacts (subjects),

who had been exposed to a person (index case) with influenza in the past 48 hours or less, were randomized to receive a single dose of baloxavir marboxil or placebo. Subjects were followed for 10 days for symptoms of influenza. The primary endpoint was the percentage of subjects who were influenza RT-PCR positive with fever and at least one respiratory symptom at Day 10. The proportion of subjects who were RT-PCR-positive with symptomatic influenza in the baloxavir arm was 2% compared to 14% in the placebo arm ($p<0.0001$). Efficacy in pediatric patients for the prevention of influenza was extrapolated from the adult population in T0834 based on similar PK exposures for pediatric and adult subjects. In addition, there was a trend toward efficacy in the pediatric subjects younger than 12 years of age. There were 4 pediatric subjects (1%) with RT-PCR positive symptomatic influenza compared to 40 pediatric subjects (13%) with symptomatic, PCR-positive influenza in the placebo arm. The most commonly reported adverse event was nasopharyngitis, which was reported in 6% of subjects who received baloxavir marboxil and in 7% of placebo subjects. There were no serious adverse events or Grade 3 or 4 AEs reported. Nasopharyngitis was the only AE reported in > 5% of subjects in both the subgroup of subjects 12 years of age and older and in subjects < 12 years of age, and no new safety concerns were identified.

After review of the Clinical Study Report and datasets for Trial T0834, DAV reviewers concluded that baloxavir marboxil was efficacious in the prevention of influenza in individuals 12 years of age and younger. Baloxavir PK exposures were comparable in adults and in pediatric patients; therefore, DAV reviewers concluded that the efficacy of baloxavir marboxil for the post-exposure prophylaxis of influenza could be extrapolated from adult trials to the pediatric population (1 year to < 12 years).

Treatment-emergent resistance-associated substitutions (TE-RAS)
On review of the virology data from Trial CP40563, the Phase 3 pediatric treatment trial, a higher frequency of TE-RAS was observed in subjects who received baloxavir marboxil (19%) compared to those who received oseltamivir (0%). The frequency of TE-RAS in patients < 12 years of age who received baloxavir was also higher than the frequency in trials of adults and adolescents in which resistance ranged from 3% to 11%. Late in the review cycle, the Applicant submitted the preliminary, top-line results from a third single arm, uncontrolled study, performed in Japan, of baloxavir marboxil in pediatric subjects < 12 years of age. In this study, T0835, the frequency of TE-RAS was 41%. In the four pediatric trials (CP40563, T0822, T0833, and T0835), the overall frequency of TE-RAS ranged from 19% to 41% with the higher frequency of TE-RAS observed with influenza A/H3N2 (21% to 70%). Because of the high frequency of treatment-emergent resistance in these pediatric studies, a Complete Response Letter was issued on November 23, 2020, for baloxavir marboxil treatment of acute, uncomplicated influenza and for postexposure prophylaxis in pediatric patients younger than 12 years of age. Baloxavir marboxil was approved for the postexposure prophylaxis of influenza in persons 12 years of age and older, and the 2% granule formulation was also approved for use in adults and adolescents who were unable to swallow tablets.

Focus of current review

The Applicant submitted a response to the Complete Response Letter on February 16, 2022. The Applicant conducted analyses of treatment emergent resistance in pediatric patients and has provided data to support use of baloxavir marboxil in patients 5 years of age and older because the highest incidence of TE-RAS was observed in patients < 5 years of age. In this submission, the Applicant has provided revised Clinical Study Reports for CP40563 and T0834, datasets, and additional analyses to support extension of the indications for the treatment of acute, uncomplicated influenza and for postexposure prophylaxis to include patients 5 years of age and older. This clinical and statistical review will focus on safety, effectiveness/efficacy in pediatric patients 5 years of age to < 12 years of age. Please see the previous Integrated Review for a detailed description of study design and for a discussion of the complete study results *all* subjects enrolled in Trial CP40563 and in Trial T0834. For a comprehensive discussion of treatment-emergent resistance, please see Dr. Ince's virology review.

Table 2: Clinical Trials Submitted in Support of Efficacy and/or Safety of Baloxavir Marboxil*.

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
CP40563 NCT # 03629184	Subjects <1 year of age to <12 years of age with acute, uncomplicated influenza	Phase 3, R, DB, active-controlled, safety, PK, and efficacy trial of baloxavir marboxil for the treatment of acute, uncomplicated influenza in pediatric subjects >1 to <12 years of age Control type: Active (oseltamivir) (dose per package insert) Randomization: 2:1 Blinding: Double-blind	Drug: Baloxavir marboxil Dosage: 2 mg/kg for subjects <20 kg and single 40-mg dose for subjects 20 kg or greater Number treated: 173 Duration: (quantity and units) Single dose orally on Day 1	Primary: Adverse events, SAEs, clinical laboratory Secondary: Baloxavir PKs, Time to alleviation of influenza signs and symptoms	120; 176	10 countries, 81 centers
T0834	Household contacts (>1 year of age) of influenza infected index cases Must be afebrile and not have symptoms of influenza	Phase 3, R, DB, PC, safety, PK, and efficacy trial of baloxavir marboxil for postexposure prophylaxis of influenza in subjects exposed to a household member with influenza Control type: Placebo Randomization: 1:1 Blinding: Double-blind	Drug: Baloxavir marboxil Dosage: Subjects 12 years of age or older: weight <80 kg: 40 mg and weight 80 kg or more: 80 mg. Subjects >1 year and <12 years of age: weight <10 kg: 1 mg/kg, weight 10 to <20 kg: 10 mg, weight 20 to 40 kg: 20 mg, and weight >40 kg: 40 mg Number treated: 748 Duration: (quantity and units) Single dose orally on Day 1	Primary: Proportion of subjects influenza virus RT-PCR+ and symptomatic for influenza Secondary: Proportion of subjects influenza virus RT-PCR+ Proportion of subjects influenza virus PCR+ and asymptomatic Time from study treatment until reach primary endpoint	750;752	1 country (Japan); 52 centers

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Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
T0822	Japanese pediatric subjects with acute, uncomplicated influenza <12 years of age	Single-arm, OL study of baloxavir marboxil for the treatment of acute, uncomplicated influenza in Japanese pediatric patients <12 years of age Control type: None Randomization: None Blinding: None	Drug: Baloxavir marboxil tablet Dosage: Subjects weighing 5 to <10 kg: 5 mg; 10 to <20 kg: 10 mg; 20 to <40 kg: 20 mg; and 40 kg or higher: 40 mg Number treated: 107 Duration: (quantity and units) Single dose orally on Day 1	Primary: Time to alleviation of influenza symptoms Secondary: Change in influenza virus titer from baseline Time to cessation of viral shedding Time to resolution of fever	100; 108	1 country (Japan), 41 centers
T0833	Japanese pediatric subjects with acute, uncomplicated influenza <12 years of age and <20 kg	Single-arm, OL study of baloxavir marboxil for the treatment of acute, uncomplicated influenza in Japanese pediatric patients <12 years of age and <20 kg Control type: None Randomization: None Blinding: None	Drug: Baloxavir marboxil 2% granules Dosage: Weight <10 kg: 1 mg/kg and weight 10 to <20 kg: 10 mg Number treated: 33 Duration: (quantity and units) Single dose orally on Day 1	Primary: Time to alleviation of influenza symptoms Secondary: Change in influenza virus titer from baseline Time to cessation of viral shedding Time to resolution of fever	30; 33	1 country (Japan); 20 centers
T0835	Japanese pediatric subjects with acute, uncomplicated influenza <12 years of age and <20 kg	Single-arm, OL study of baloxavir marboxil for the treatment of acute, uncomplicated influenza in Japanese pediatric patients <12 years of age and <20 kg Control type: None Randomization: None Blinding: None	Drug: Baloxavir marboxil Dosage: <3 months of age: 1 mg/kg; 3 months of age or older and <10 kg: 2 mg/kg; 10 kg to <20 kg: 20 mg Number treated: 43 Duration: (quantity and units) Single dose orally on Day 1	Primary: Time to alleviation of influenza symptoms Secondary: Change in influenza virus titer from baseline Time to cessation of viral shedding Time to resolution of fever	Not provided/43	1 country (Japan)/ Information on sites not provided

Source: Dr. Fraser Smith, Integrated Review NDA 214410 and NDA 210854/S-05 and S-05, Baloxavir marboxil, January 23, 2020.
*Note that for CP40563, trial population was ≥ 1 to <12 years of age rather than <1 to < 12 as shown in table above.

4. List of Review Issues Related to Benefit

There are no new issues related to benefit. Efficacy was demonstrated for pediatric patients ≥ 5 years to < 12 years for the treatment of acute, uncomplicated influenza and for the postexposure prophylaxis of influenza. Efficacy in pediatric patients was extrapolated from the efficacy of adults and adolescents in Phase 3 trials of baloxavir marboxil because of similar PK exposures in pediatric and adult/adolescent populations. Please see Section 10 for a complete discussion of efficacy.

This submission was in response to a Complete Response letter. The CR letter was issued due to the increased frequency of treatment-emergent resistance in pediatric subjects. Please see Sections 3 and 12 in this summary review, and Dr. Ince's virology review.

5. List of Review Issues Related to Risk

1. **Increased frequency of baloxavir resistance in pediatric patients ≥ 5 years to < 12 years compared to adults and adolescents.**

6. Product Quality

Please see Dr. Guerrieri's CMC review. All CMC information included in the response to the CR Letter was identical to that submitted in the original review. As part of the review from January 2020, the CMC reviewers determined that the information submitted was sufficient to ensure the identity, strength, purity, and quality of the baloxavir marboxil drug product. This included the tablet and the 2% granule formulation. The manufacturing and testing facilities were inspected and also were determined to be acceptable. There were no new findings during this review period.

7. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology data were included in this submission. Please see Dr Digg's review for the first submission to NDA 210854.

8. Clinical Pharmacology

Please see the Clinical Pharmacology review for the original submission from January 2020. No new analyses were conducted by the clinical pharmacology reviewer for the response to the Complete Response Letter; however, the reviewer, Dr. Zhao, did provide labeling recommendations for Section 12.3 Pharmacokinetics of the package

insert. Pharmacokinetic parameters for baloxavir in pediatric patients from 5 to < 12 years of age were added to the label, and the label states that baloxavir exposures are similar in pediatric subjects 5 to < 12 years of age and in adults and adolescents.

9. Clinical Microbiology

Please see Dr. Ince's virology review. Please see Section 12 of this review for a discussion of treatment-emergent resistance with baloxavir marboxil.

10. Clinical/Statistical- Efficacy

10.1 Trial CP40563: Treatment of Acute, Uncomplicated Influenza in Otherwise Healthy Pediatric Patients ≥ 5 to < 12 years of age

10.1.1 Study Design:

Trial CP40563 was a randomized, double-blind, active-controlled safety, pharmacokinetic, and effectiveness trial in otherwise healthy pediatric subjects ≥ 1 < 12 years of age. The trial enrolled pediatric patients with influenza-like symptoms (fever ≥38°C plus either cough or nasal congestion) who presented within 48 hours of symptom onset. After enrollment, subjects had a nasopharyngeal swab for influenza diagnosis by RT-PCR, which was performed at a central study laboratory. After the nasopharyngeal swab was obtained, subjects were randomized in a 2:1 ratio to receive baloxavir marboxil or oseltamivir. Oseltamivir is approved for the treatment of influenza in patients 2 weeks of age and older. Oseltamivir was administered twice daily for 5 days, subjects in the oseltamivir arm received the weight-based dose as recommended in the package insert. Baloxavir marboxil was administered as 2% granules in solution. Subjects received a single oral dose of baloxavir marboxil at the study site. Baloxavir marboxil dosing was based on weight; subjects weighing less than 20 kg received a 2 mg/kg dose and subjects weighing ≥ 20 kg received a single 40 mg dose. Both treatment arms received matching placebo for the other study drug.

Diary cards were distributed to parents/caregivers on Day 1. Parents/caregivers were instructed to record daily temperature and influenza symptoms in the diary cards until Day 15. The Canadian Acute Respiratory Illness and Flu Scale (CARIFS) was used to monitor influenza symptoms. Although the CARIFS includes 18 questions regarding symptoms only three were used as part of as part of the measurement of efficacy: cough, nasal symptoms, and return to daycare/school or to normal daily activity. Each question was answered using a 4-point Likert response from 0 for no problem to 4 for major problem).

10.1.2 Eligibility Criteria

Trial CP40563 enrolled patients with a clinical diagnosis of influenza defined as fever ≥ 38° C plus either cough or nasal congestion. Patients had to be symptomatic for ≤

48 hours. This review will describe results for study subjects from 5 to < 12 years of age.

Patients were excluded from study participation for any of the following:

- Severe influenza requiring inpatient hospital treatment
- Concurrent infection requiring systemic antiviral therapy
- Treatment with peramivir, laninamivir, oseltamivir, zanamivir, or amantadine within the 2 weeks prior to randomization and
- Immunization with live/attenuated influenza vaccine in the 2 weeks prior to randomization

10.1.3 Statistical Analysis

The primary endpoint was safety as measured by the incidence, severity, and timing of adverse events (AEs), serious adverse events (SAEs), vital sign measurements, and clinical laboratory test results. The safety analysis was conducted on the safety population, defined as all subjects who received a single dose of study drug.

Trial CP40563 was not powered to demonstrate efficacy or to statistically compare the two drugs. The efficacy of baloxavir marboxil in pediatric patients was demonstrated by extrapolation from the efficacy observed in Phase 3 trials of adults and adolescents after comparable PK exposures were observed in pediatric subjects in CP40563 and adult and adolescents in Phase 3 trials. See Dr. Zhou's Clinical Pharmacology review for the response to the CR Letter and the Integrated Review for the original submission for a complete discussion of extrapolation.

Efficacy was assessed in Trial CP40563 as the key secondary objective. The key secondary efficacy endpoint was time to alleviation of influenza signs and symptoms (TTAS), defined as length of time from the start of treatment until all of the following were met and remained as shown for at least 21.5 hours:

- A score of 0 or 1 for cough and for nasal symptoms on the CARIFS,
- An answer of "yes" on CARIFS in response to "Since the last assessment has the subject been able to return to day care/school or resume his or her normal daily activity in the same way as performed prior to developing the flu," and
- First return to afebrile state (tympanic temperature ≤ 37.2° C).

Efficacy was analyzed for the intent-to-treat-infected (ITTI) population, defined as subjects who received a single dose of study drug and who were RT-PCR positive for influenza.

10.1.4 Efficacy Results of Trial CP40563

Demographics and Baseline Characteristics:

Overall, 118 subjects ≥ 5 to < 12 years of age received at least one dose of study drug. The characteristics of the study population are shown in the following table.

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Table 3: Demographics of Subjects ≥ 5 Years to < 12 Years of Age in CP40563 (Safety Population)

	Baloxavir Marboxil N=79	**Oseltamivir N=39**
Mean Age (years)	7.7	7.8
Sex		
Female	44 (56%)	22 (56%)
Male	35 (44%)	17 (44%)
Race		
White	71 (90%)	34 (87%)
Black or African American	1 (1%)	3 (8%)
Other race, multiple races, or unknown	7 (9%)	2 (5%)
Hispanic or Latino	38 (48%)	17 (44%)

Source: NDA 214410, Response to CR, CSR CP40563, Table 5, page 22.

The mean age of study participants was 7.7 years. and most subjects were female (56%). The majority of subjects in both treatment arms were White (89%); almost one-half of study subjects were of Hispanic/Latino ethnicity. As shown in the Table 3, the demographic characteristics were very similar between the two arms.

Almost one-half of subjects (49%) in each treatment arm were previously vaccinated against influenza. More subjects in the baloxavir marboxil arm had been vaccinated (52%) than in the oseltamivir arm (44%). Although the study enrolled subjects who already had influenza, it is possible that prior vaccination could have shortened the time to alleviation of symptoms. If this were the case, it would have biased by shortening TTAS in the baloxavir marboxil arm more than in the oseltamivir arm.

Table 4: Time to Alleviation of Influenza Signs and Symptoms (TTAS) in Subjects ≥ 5 Years to < 12 Years of Age in Trial CP40563 by Vaccination Status (Safety Population)

Vaccination Status	**Alleviation of Symptoms**	**Baloxavir Marboxil Arm N=79***	**Oseltamivir Arm N=39**
Yes	Number (%) of subjects with event	33/41 (82%)	13/17 (76%)
	Median time to event in hours (95% CI)	163 (116, 191)	122 (68, 166)
No	Number (%) of subjects with event	38/38 (100%)	19/22 (86%)
	Median time to event in hours (95% CI)	119 (92, 139)	115 (71, 166)

*Subject (b) (6) (baloxavir marboxil arm, vaccinated) does not have TTAS values.
Source: NDA 214410, Statistical Analysis, Yifan (Katie) Wang

As shown in Table 4, previous vaccination did not reduce the time to alleviation of symptoms in either arm. The reasons for longer TTAS with vaccination, particularly in the baloxavir marboxil arm, are unclear. However, this is a subset analysis with small numbers of subjects; therefore, it is difficult to reach any conclusions regarding these data.

The infecting influenza types and subtypes are shown in Table 5 for subjects in whom influenza type and subtype were available.

Table 5: Influenza Type and Subtype in Subjects ≥ 5 Years to < 12 Years of Age in CP40563

	Baloxavir Marboxil N=57	**Oseltamivir N=31**
A/H1N1	10 (18%)	7 (23%)
A/H3N2	37 (65%)	22 (71%)
B	5 (9%)	2 (7%)
Mixed	1 (2%)	0
Unknown	4 (7%)	0

Source: NDA 214410, Response to CR, CSR CP40563, Table 5, page 22.

The predominant influenza subtype identified in the trial was influenza A/H3N2, which was observed in 65% of subjects in the baloxavir marboxil arm and in 71% of subjects in the oseltamivir arm. In adult clinical trial, resistance was most observed in subjects infected with influenza A/H3N2 (Ince WL, et. al. Journal of Infectious Diseases. 2020:222:957-961). However, treatment-associated resistance to oseltamivir is most commonly associated with influenza A/H1N1 strains. (Roosenhoff R et.al. Clinical Infectious Diseases. 2020;71:1186-94). Therefore, the predominance of influenza A/H3N2 observed in Trial CP40563 may have resulted in bias towards an increase in resistance to baloxavir marboxil compared to oseltamivir.

Subject Disposition:

Five percent of subjects in each treatment arm discontinued prematurely. In the oseltamivir arm, two subjects 5% discontinued due to withdrawn consent. In the baloxavir marboxil arm, one subject withdrew due to withdrawn consent and one due to poor compliance. Another two subjects in the baloxavir marboxil arm withdrew prematurely due to adverse events and will be discussed in the safety section of this review. Overall, the premature discontinuation of only 5% of subjects indicates that the study was well conducted.

Efficacy Results:

The key efficacy endpoint was the time to alleviation of influenza signs and symptoms. The results in the ITTI population are shown in the following table.

Table 65: Time to Alleviation of Influenza Signs and Symptoms (TTAS) in Subjects ≥ 5 Years to < 12 Years of Age in Trial CP40563 (ITTI Population)

	Baloxavir Marboxil Arm N=61	**Oseltamivir Arm N=33**
Number (%) of subjects with event	56 (93%)	27 (82%)
Median time to event in hours (95% CI)	138 (117, 163)	126 (95, 166)

Source: NDA 214410, Response to CR, CSR CP40563, Table 9, page 36.

As shown in the preceding table, the median TTAS was 138 hours in the baloxavir marboxil arm and 126 hours in the oseltamivir arm. The study used an active control, oseltamivir, which is indicated to treat influenza in pediatric patients 2 weeks of age and older. Therefore, the similar point estimates and overlapping confidence intervals support a trend toward efficacy for baloxavir marboxil. It should be noted that the results should be interpreted with caution since the sample size is small which leads to a wide 95% confidence interval and the study was not sufficiently powered to compare the efficacy of the two drugs. The actual efficacy of baloxavir marboxil in pediatric patients ≥ 5 years to < 12 years of age was demonstrated by extrapolation of efficacy from Phase 3 trials in adults and adolescents to pediatric subjects.

Second efficacy analyses included measurement of the duration of fever. The median duration of fever was 41 hours (23.5, 51.4) in the baloxavir marboxil arm and 51 hours (30.7, 56.8) in the oseltamivir arm. This further supports the trend toward efficacy in the baloxavir marboxil arm. Only one subject in each arm required antibiotics; therefore, no conclusions can be reached regarding the ability of either antiviral to either prevent bacterial infections or prevent indiscriminate use of antibiotics in patients with viral infections.

A post-hoc analysis was conducted to analyze the primary endpoint without the criteria for “return to normal activity”. In this analysis TTAS was defined as the return of afebrile state and cough/nasal congestion graded as 0 or 1. This analysis is similar to the definition of TTAS used in the Phase 3 trials of baloxavir marboxil in adults, in which TTAS was based on the resolution of influenza signs and symptoms and of fever. The criterion of “return to normal activity” was not used in influenza treatment trials in adults and adolescents. In this analysis the median TTAS (without return to normal activity) was 70 hours in the baloxavir marboxil arm and 71 hours in the oseltamivir arm. This analysis results in median TTAS in pediatric subjects that is more similar to those reported in adult subjects and may be a more appropriate endpoint for use in future influenza trials.

10.1.5 Conclusions regarding Efficacy for the Treatment of Acute, Uncomplicated Influenza

The efficacy of baloxavir marboxil in the treatment of acute, uncomplicated influenza in otherwise healthy pediatric patients ≥ 5 years to < 12 years was demonstrated by extrapolation because baloxavir exposures in pediatric subjects were similar to those of adults and adolescents in the pivotal treatment trials of baloxavir marboxil. This demonstration of efficacy was further supported by the results of Trial CP40563, in which the median time to alleviation of symptoms was 138 hours in the baloxavir marboxil arm and 126 hours in the active control (oseltamivir) arm. In addition, the analyses of other secondary efficacy endpoints, such as duration of fever, further supporting the effectiveness of baloxavir marboxil.

10.2 Trial T0834: Post-Exposure Prophylaxis of Influenza in Household Contacts

10.2.1 Study Design

Trial T0834 was a randomized, double-blind, placebo-controlled safety and efficacy trial of baloxavir marboxil for the prevention of influenza virus infection in household contacts of influenza-infected index patients. Index patients were treated for influenza according to the local standard of care. Household contacts (study subjects) of each index patient were enrolled in Trial T0834. Subjects (household contacts) were randomized in a 1:1 ratio to receive a single oral dose of baloxavir marboxil or matching placebo, which were administered at the study site. Subjects 12 years of age and older, received baloxavir marboxil at the dose recommended in the U.S. package insert for treatment of acute uncomplicated influenza. This trial was conducted in Japan, and the baloxavir marboxil doses used in subjects < 12 years of age were those recommended by the Japanese Regulatory Authorities. Baloxavir marboxil dosing and formulation for subjects ≥ 5 years to < 12 years of age in Trial 0834 are shown in the following table. In Trial CP40563, which was conducted under IND and included U.S. sites, the baloxavir marboxil dose was 2 mg/kg for subjects who weighed < 20 kg and 40 mg for subjects who weighed 20 kg or more.

Table 7: Dosage and Formulation of Baloxavir Marboxil in Subjects ≥ 5 Years to < 12 Years of Age in Trial T0834

Subject Weight	Baloxavir Marboxil Dose	Baloxavir Marboxil Formulation
10 to < 20 kg	10 mg	2% granules in solution
20 to < 40 kg	20 mg	Tablet
≥ 40 kg	40 mg	Tablet

Source: NDA 214410, Response to CR, CSR T0834, Table 1, page 13.

Household contacts or their parent/caregiver were given an electronic subject diary on Day 1 and trained on its use. Subjects or parents/caregivers were to complete the subject diary twice daily for the 10 days following study drug administration. Axillary temperature was taken twice daily and entered into the dairy. The presence or absence of influenza signs and symptoms were also entered into the diary twice daily. Subjects ≥12 years of age were to self-assess their signs and symptoms of influenza

(cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) on a 4-point rating scale (0 or absent, 1 or mild, 2 or moderate, 3 or severe). Parents/caregivers of subjects <12 years of age were to complete the diary card. Influenza symptoms recorded in subjects <12 years of age were fever, cough, and nasal discharge/nasal congestion.

All study subjects (household contacts) had nasopharyngeal swabs obtained on Day 1 for influenza RT-PCR. Subjects received a single dose of baloxavir marboxil or placebo at the study site prior to discharge. Study subjects were instructed to return to the study clinic if they had an axillary temperature ≥ 37.5° C and had moderate or severe influenza symptoms on their subject diary. At the study visit, a physical examination was performed and nasopharyngeal swabs for influenza RT-PCR were obtained. All asymptomatic subjects had nasopharyngeal swabs for influenza RT-PCR obtained on Days 5 and 11.

10.2.2 Eligibility Criteria
The study had different entry criteria for the index patients and the household contacts; however, the household contacts were the study subjects.

Index patients:
Index patients were patients of any age who weighed at least 10 kg and who had been diagnosed with influenza by a rapid influenza diagnostic test. Index patients' symptoms must have started ≤ 48 hours before study entry. The index patient must have been the first person in the family with influenza during that influenza season.

Household contacts:
Household contacts were individuals who lived with the index case for at least 48 hours prior to study entry. Household contacts had to be able to live with the index case for the 10 days post-dose. Household contacts could not be febrile or have any influenza-like symptoms. Although this study enrolled household contacts one year of age and older; this review will focus on the study results for household contacts 5 years of age and older.

Household contacts would be excluded from study participation if they had already had influenza during that influenza season or if another household member, other than the index case, had been diagnosed with influenza or was strongly suspected of having influenza. Household contacts would also be excluded from participation if they had received an anti-influenza antiviral within the previous 30 days.

10.2.3 Statistical Analysis
The primary efficacy endpoint was the proportion of subjects who were influenza RT-PCR positive, febrile (axillary temperature ≥37.5°C) and had at least one respiratory symptom (cough and/or nasal discharge/nasal congestion) in the period from Day 1 to Day 10. The respiratory symptom had to have a severity of 2 (moderate) or 3 (severe). The primary efficacy analysis was conducted on the modified intent-to-treat (mITT) population, defined as all randomized subjects who received the study drug

and had postbaseline efficacy data available. Secondary efficacy endpoints included proportion of subjects who were RT-PCR positive for influenza but asymptomatic by the study criteria for symptomatic influenza and proportion of subjects who were RT-PCR positive for influenza regardless of symptoms.

The assessment of safety was a secondary objective. The safety analysis population included all randomized subjects who received at least one dose of the study drug.

10.2.4 Efficacy Results of Trial CP40563

Demographics and Baseline Characteristics
The demographic characteristics of household contacts 5 years of age and older in Trial T0834 are shown in the following table.

Table 8: Demographics of Subjects (Household Contacts) ≥ 5 Years to Age in Trial T0834 (Safety Population)

	Baloxavir Marboxil N=360	**Oseltamivir N=355**
Mean Age and Age Range (years)	35 (5-87)	42 (5-85)
Median Age (years)	38	38
Number (%) Subjects ≥5 to < 12 Years of Age	57 (16%)	51 (14%)
Sex		
Female	292 (81%)	278 (78%)
Male	68 (19%)	77 (22%)
Race		
Asian	360 (100%)	355 (100%)

Source: NDA 214410, SN 001, Trial T0834, Demographics dataset.

The mean age of subjects in the baloxavir arm was 35 years and the mean age of subjects in the placebo arm was 42 years. Although the mean age of subjects in the placebo arm was slightly older than for the baloxavir arm, the median age for both treatment arms was identical and the age range of the two arms were very similar. Therefore, the difference in mean age was unlikely to affect the safety or efficacy results. The percentage of subjects from 5 years to < 12 years of age was similar in the two arms: 16% in the baloxavir marboxil arm and 14% in the placebo arm. The majority of subjects in the study population were female and were mothers of the index patients. Most index patients were younger than 10 years of age; 67% of index patients for subjects in the baloxavir marboxil arm and 60% of index patients for subjects in the placebo arm were < 10 years of age. In the subgroup of subjects ≥ 5 years to < 12 years, the percentage of female subjects was 55% and the percentage of male subjects was 45%. Subjects in the ≥ 5 years to < 12 years age group were mostly siblings (>90%) of index patients. The trial was conducted in Japan and enrolled only Asian subjects. See the Integrated Review of the original submission for a discussion of issues regarding conducting this study solely in Japan.

The percentage of subjects 5 years of age and older who had been vaccinated against influenza in the previous 6 months was similar in the two arms: 34% in the baloxavir marboxil arm and 32% in the placebo arm. In the subgroup of pediatric patients ≥ 5 years to < 12 years of age, 28% of subjects in the baloxavir marboxil arm had received an influenza vaccine compared to 22% in the placebo arm.

The influenza types and subtypes for the index patients at baseline are shown in the following table.

Table 9: Trial T0834 – Influenza Type and Subtype for Index Patients of Subjects ≥ 5 Years to Age (Safety Population)

Influenza Type/Subtype	Baloxavir Marboxil N=360	Oseltamivir N=355
A/H1N1	171 (48%)	170 (48%)
A/H3N2	172 (48%)	173 (49%)
B	2 (0.6%)	3 (0.8%)
Mix of influenza A subtypes or influenza A subtype not identified	8 (2%)	3 (0.8%)
Mix of influenza A and B	2 (0.6%)	3 (0.8%)
PCR negative	5 (1%)	3 (0.8%)

Source: NDA 214410, SN 001, Trial T0834 ADSL dataset.

The infection influenza type or subtype for index patients at enrollment was almost evenly split between influenza A/H1N1 and A/H3N2. Only 5 index patients were infected with influenza B. A small percentage of index patients were infected with a mix of influenza types/subtypes or were PCR negative. The results were very similar between the two treatment arms. In the subgroup of household contacts ≥ 5 to < 12 years of age, the percentage of corresponding index patients infected with A/H3N2 was slightly higher in the baloxavir marboxil arm (51%); while in the index patients for placebo subjects, the percentage of index patients with A/H1N1 was slightly higher (59%). As shown in the effectiveness discussion for this study, the number of subjects in the ≥ 5 to < 12 years age group who were diagnosed with influenza during the study was too small to analyze prevention of influenza by type/subtype.

Subject Disposition

All subjects except for one subject in each arm (>99% in each arm) completed the study. Consent was withdrawn for one 6-year-old in the baloxavir marboxil arm on Day 6. A 41-year-old prematurely withdrew from the placebo arm on Day 46 due to an adverse event (psychotic disorder).

Efficacy Results

The primary efficacy endpoint was the proportion of subjects who were influenza RT-PCR positive, febrile (axillary temperature ≥37.5°C) and had at least one respiratory symptom (cough and/or nasal discharge/nasal congestion) in the period from Day 1 to Day 10. The results of Trial T0834 were reviewed with the original submission, and baloxavir marboxil is currently approved for the prevention of influenza in individuals

12 years of age and older. The results for the primary efficacy endpoint in subjects ≥ 5 years of age is shown in the following table.

Table 10: Trial T0834: Proportion of Household Contacts 5 Years of Age and Older who were RT-PCR Positive and Symptomatic for Influenza

	Baloxavir Marboxil N=360	**Placebo N=355**
Number of subjects with influenza (%)	6 (2%)	47 (13%)
95% confidence interval	(1%, 4%)	(10%, 17%)

Source: NDA 214410, Sponsor provided in proposed package insert

Two percent of household contacts in the baloxavir marboxil arm compared to 13% in the placebo arm were diagnosed with symptomatic influenza during the 10-day follow-up after prophylaxis. The reduction in the risk ratio was statistically significant (p-value < 0.0001). Efficacy was clearly demonstrated for the entire study population of subjects 5 years of age and older. In the subgroup of subjects ≥ 5 years to < 12 years of age, there were 2 cases of influenza in the baloxavir marboxil arm (3.5%) and 7 (14%) in the placebo arm for a adjusted risk ratio of 0.28 (95% CI: 0.006, 0.124) and a p-value of 0.0934. A trend toward efficacy was demonstrated for the ≥ 5 years to < 12 years age group. However, the trial was not powered to demonstrate efficacy in this age group, and efficacy in subjects ≥ 5 years to < 12 years of age, was extrapolated from efficacy in adults in the postexposure prophylaxis trial after demonstration of similar PK exposures in the pediatric and adult populations. Please see Dr. Zhao's clinical pharmacology review for a discussion of extrapolation by exposure.

The primary endpoint was analyzed for the subgroup of household contacts who had a negative PCR at baseline. The percentage of household contacts ≥ 5 years to < 12 years of age who were RT-PCR negative at baseline and were symptomatic and RT-PCR-positive for influenza was 4% in the baloxavir marboxil group and 14% in the placebo group. These results for this subgroup analysis were almost identical to those for the primary endpoint.

Secondary efficacy analyses included the percent of household contacts who were RT-PCR positive at follow-up and asymptomatic, and the percentage of household contacts who were RT-PCR positive at follow-up, regardless of symptoms.

The percentage of subjects ≥ 5 years to < 12 years who were RT-PCR positive during follow-up, with or without symptoms was 21% in the baloxavir marboxil arm (N=12) and 33% (N=17) in the placebo arm for an adjusted risk ratio of 0.64 (95% CI of 0.23, 1.19). This is consistent with the overall study efficacy results.

The percentage of household contacts ≥ 5 years to < 12 years who were RT-PCR positive during follow-up but were asymptomatic for influenza was 12% in the baloxavir arm (N=7) and 3% (N=3) in the placebo arm. The reason for the higher proportion of asymptomatic RT-PCR positive subjects in the baloxavir arm is unclear,

but it is difficult to reach any conclusion regarding this analysis given the small number of study subjects in this subgroup. The results of this secondary endpoint in the entire study population of household contacts 5 years of age and older are shown in the following table.

Table 11: Trial T0834 - Proportion of Household Contacts 5 Years of Age and Older who were RT-PCR Positive and Asymptomatic (mITT Population)

	Baloxavir Marboxil N=360	**Placebo N=355**
Number of subjects RT-PCR+ and asymptomatic (%)	25/360 (7%)	29/355 (8%)
Clopper-Pearson exact 95% confidence interval (%)	(5%, 10%)	(6%, 12%)

Source: NDA 214410, Analysis provided by Dr. Wang

As shown in Table 11, the proportion of subjects in the entire study population (≥ 5 years of age and older) who were RT-PCR positive and asymptomatic was similar in the baloxavir marboxil and placebo arms. It is unclear why there was a larger difference between treatment arms observed in pediatric subjects ≥ 5 years to < 12 years only. However, it is difficult to reach any conclusions about the analysis in pediatric patients because of the small study number of pediatric subjects.

10.2.5 Conclusions regarding Efficacy for the Postexposure Prophylaxis of Influenza

Baloxavir marboxil is currently indicated for the post-exposure prophylaxis of influenza in individuals 12 years of age and older. The Applicant has submitted these data to support the extension of the age for this indication to 5 years of age and older. Trial T0834 was not powered to demonstrate efficacy in the subgroup of household contacts ≥ 5 years to < 12 years of age. Efficacy in this age subgroup can be extrapolated from efficacy in adults because of similar PK exposures in the ≥ 5 years to < 12-year age group and in adults in T0834. In addition, there was a trend toward efficacy in the subgroup of subjects ≥ 5 years to < 12 years of age, with two cases of influenza in the baloxavir marboxil arm (3.5%) and seven (14%) in the placebo arm. Therefore, the results of this study support the efficacy of baloxavir marboxil in the prevention of influenza in pediatric patients ≥ 5 years to < 12-years of age.

10. Safety

Baloxavir marboxil is currently indicated for the treatment of acute, uncomplicated influenza in patients 12 years of age and older and for the prevention of influenza in individuals 12 years of age and older. This section addresses safety in subjects ≥ 5 years to < 12-years of age. Safety findings differ in subjects with influenza who receive an antiviral for treatment and in healthy individuals who received an antiviral for prevention of influenza; therefore, the safety data for these indications were not pooled and will be presented separately. In addition, safety results from open-label, single arm studies in pediatric patients will be presented briefly to support the safety of treatment with baloxavir marboxil.

11.1 Trial CP40563: Safety of Baloxavir Marboxil in the Treatment of Influenza in Subjects ≥ 5 Years to < 12 Years of Age

11.1.1 Overall Treatment-Emergent Adverse Event Summary for Subjects ≥ 5 to < 12 Years of Age in Trial CP40563

In the subgroup of subjects ≥ 5 to < 12 years of age in Trial CP40563, treatment-emergent adverse events were reported at in 44% of subjects in each treatment arm as shown in Table 38. Two subjects in the baloxavir marboxil arm had adverse events leading to premature study discontinuations; no subjects in the oseltamivir arm prematurely discontinued the study due to an AE. There were no Grade 3 or 4 AEs, SAEs, or deaths in either treatment arm.

Table 12: Overview of Treatment-Emergent Adverse Event Summary in Subjects ≥ 5 to < 12 Years of Age, Days 1 to 29, Trial CP40563

	Baloxavir Marboxil N=79	**Oseltamivir N=39**
Total number (%) of subjects with ≥ 1 AE	35 (44%)	17 (44%)
Grade 3 or 4 AEs	0	0
SAEs	0	0
AEs leading to premature discontinuation of study drug	2 (3%)	0

Source: NDA 214410, Response to CR, CSR CP40563, Table 6, page 25.

11.1.2 Discontinuations Due to Adverse Events in Subjects ≥ 5 to < 12 Years of Age, Trial CP40563

Two subjects in the baloxavir marboxil arm prematurely discontinued the study due to an adverse event. One subject was a 7-year-old white female who developed a rash on Day 3. The rash was graded as mild and resolved on Day 4 without treatment. The second subject discontinued the trial after an adverse event reported as a placebo overdose; this subject received “16.5 mg” of oseltamivir placebo instead of “6 mg”. There were no premature discontinuations due to adverse events in the oseltamivir arm.

11.1.3 Treatment-Emergent Adverse Events in Subjects ≥ 5 to < 12 Years of Age, Trial CP40563

Treatment-emergent AEs that were reported in at least 2% of subjects in the baloxavir marboxil arm are shown in Table 13.

Table 13: Treatment-Emergent Adverse Event Reported in ≥ 2% of Subjects in the Baloxavir Marboxil Arm (Subjects ≥ 5 to < 12 Years of Age), Trial CP40563

	Baloxavir Marboxil N=79	**Oseltamivir N=39**
Any TEAE	35 (44%)	17 (44%)
Vomiting	4 (5%)	7 (18%)
Diarrhea	4 (5%)	0
Medication error	4 (5%)	1 (3%)
Rhinorrhea	3 (4%)	1 (3%)
Allergic rhinitis	2 (3%)	0
Upper respiratory tract infection	2 (3%)	1 (3%)
Accidental overdose	2 (3%)	1 (3%)

Source: NDA 214410, Response to CR, CSR CP40563, Table 8, page 29.

The percentage of subjects with TEAEs was identical in the two treatment arms. The most commonly reported AE in the trial was vomiting which was reported in 11 or 9% of study subjects. However, vomiting was reported more frequently in the oseltamivir arm (18%) than in the baloxavir marboxil arm (5%). The only AEs reported in a higher percentage of subjects ≥ 5 years to < 12 years of age who received baloxavir marboxil compared to those who received oseltamivir, with a difference of > 2% were diarrhea and allergic rhinitis. Diarrhea was reported in four subjects (5%) in the baloxavir arm compared to no subjects in the oseltamivir arm. Allergic rhinitis was reported in two subjects (3%) in the baloxavir marboxil arm compared to none in the oseltamivir arm. Of note, there were four AEs of medication error and 2 of accidental overdose in the baloxavir marboxil arm. All four of the medication errors occurred at the same study site. That site administered 2 mL of baloxavir marboxil instead of 2 mg/mL, so the four subjects at this site received only 4 mg of baloxavir marboxil before the dosing error was discovered. Two subjects were "overdosed" with the oseltamivir placebo; they did not receive an overdose of baloxavir.

There were two treatment-related adverse events (3%) in the baloxavir marboxil arm. Both resulted in premature study discontinuation and are described in Section 11.1.2. There was one treatment-related AE, vomiting, reported in the oseltamivir arm (3%).

11.1.4 Laboratory Findings in Subjects ≥ 5 to < 12 Years of Age, Trial CP40563

Safety laboratory tests were obtained on Days 1 and 6. There were no laboratory abnormalities reported as adverse events. There were no Grade 3 or 4 laboratory values reported in subjects from 5 to < 12 years of age.

11.2 Supportive Pediatric Safety Data for Subjects ≥ 5 to < 12 Years of Age from Other Studies

The safety results of three open-label, single arm, uncontrolled studies (T0822, T0833, and T0833) were reviewed to support the safety of baloxavir marboxil in pediatric patients. The study design and safety results of T0822 and T0833 were described in the review of the original submission. This review will focus on the safety

results for subjects ≥ 5 years to < 12 years of age who participated in the three studies. All three studies were conducted in Japan; lower doses of baloxavir were used in T0822 and T0833 than in Trial CP40563.

Studies T0833 and T0835 both enrolled pediatric patients < 12 years of age who weighed < 20 kg; however, the dose of baloxavir used in Study T0835 was higher than that used in T0833. Baloxavir marboxil exposures are higher in Asians compared to non-Asians, so the safety results for these trials are applicable to the U.S. population. The baloxavir doses used in each of the three studies are shown in the table below. Because no subjects in the ≥ 5 to < 12-year age group weighed < 10 kg, dosing for < 10 kg is not included in the table. Only subjects weighing < 20 kg were enrolled in Studies T0833 and T0835.

Table 14: Baloxavir Marboxil Dosing in the Open-Label, Single Arm Studies Conducted in Japan

	Baloxavir Dose		
Subject Weight	**Study T0822**	**Study T0833**	**Study T0835**
≥ 10 kg to < 20 kg	10 mg	10 mg	20 mg
≥ 20 kg to < 40 kg	20 mg	--	--
≥ 40 kg	40 mg	--	--

Source: NDA 214410, SN01, CSRs for T0822 and T0833; SDN 089, CSR for T0835.

In all three studies, subjects received a single oral dose of baloxavir and were followed for safety for 20 days post dose. There were 90 subjects in the ≥ 5 to < 12-year-old age group who participated in Study T0822. The mean age was 8.16 years; 46 subjects or 51% were male; and all subjects were Asian. A total of 42 AEs were reported in 32 subjects (36%). Adverse events reported in at least 2% of subjects were vomiting in 8 subjects (9%), diarrhea in 4 subjects (4%), and in 2 subjects (2%) each: pharyngitis, sinusitis, headache, and herpes labialis. All AEs were Grade 1 or Grade 2. Four AEs were judged as drug related: diarrhea in 3 subjects and Grade 1 increased ALT in one subject. One subject experienced urticaria on Day 1 and one subject reported nightmares. Neither AE was judged as drug-related. (b) (4) urticaria (b) (4) included in the baloxavir marboxil package insert.

Studies T0833 and T0835 only enrolled subjects weighing < 20 kg, so there were fewer subjects in the ≥ 5 to < 12-year age group in these studies. Three of the five subjects from 5 years to < 12 years of age in Study T0833 reported AEs. The five AEs in these 3 subjects were vomiting in all three subjects, conjunctivitis in one subject, and bacterial infection in one subject. All AEs were Grade 1 or 2 in severity, and all were judged as not related to study drug. There were nine subjects in the ≥ 5 to < 12-year age range in Study T0835. In this study, 6 AEs were reported in four subjects. Two subjects had nasopharyngitis and one subject each had cough, abdominal pain, diarrhea, and constipation. All six AEs were Grade 1 or Grade 2 in intensity, and all were judged as not related to study drug.

The TEAEs observed in the three open-label, single arm studies were similar to those observed in Trial CP40563. Gastrointestinal AEs, particularly vomiting and diarrhea. were observed in all of the studies in pediatric patients. Other AEs were those observed with influenza or were typical infections observed in children. In addition, no Grade 3 or 4 AEs and no SAEs were reported in any of the pediatric studies confirming that the majority of TEAEs observed with baloxavir marboxil are mild in intensity.

11.3 Trial T0834: Safety of Baloxavir Marboxil in the Postexposure Prophylaxis of Influenza in Household Contacts ≥ 5 Years to < 12 Years of Age

11.3.1 Overall Treatment-Emergent Adverse Event Summary for Subjects ≥ 5 to < 12 Years of Age in Trial T0834

An overview of treatment-emergent adverse events in subjects ≥ 5 years to < 12 years of age in Trial T0834 are shown in the following table.

Table 15: Overview of Treatment-Emergent Adverse Event Summary in Subjects ≥ 5 to < 12 Years of Age, Trial T0834

	Baloxavir Marboxil N=57	**Placebo N=51**
Total number (%) of subjects with ≥ 1 AE	12 (21%)	8 (16%)
Grade 3 or 4 AEs	0	0
SAEs	0	0
AEs leading to premature discontinuation of study drug	0	0

Source: NDA 214410, Response to CR, CSR T0834, text, page 34.

TEAEs were reported slightly more often in the baloxavir marboxil arm than in the placebo arm. However, none of the adverse events were Grade 3 or 4 in severity and there were no serious adverse events. In addition, there were no AEs leading to premature study discontinuation.

11.3.2 Treatment-Emergent Adverse Events in Subjects ≥ 5 to < 12 Years of Age, Trial T0834

Treatment-emergent AEs that were reported in at least 2% of subjects in the baloxavir marboxil arm are shown in Table 16.

Table 16: Treatment-Emergent Adverse Event Reported in ≥ 2% of Subjects in the Baloxavir Marboxil Arm (Subjects ≥ 5 to < 12 Years of Age), Trial T0834

	Baloxavir Marboxil N=57	**Oseltamivir N=51**
Any TEAE	12 (21%)	8 (16%)
Nasopharyngitis	3 (5%)	2 (4%)
Headache	2 (4%)	0
Cough	2 (4%)	0

Source: NDA 214410, Response to CR, CSR T0834, Table 18, page 35.

The numbers of subjects in both treatment arms with individual AEs in low and represents the otherwise healthy population enrolled in this study. The only TEAEs reported in at least 2% of subjects in the baloxavir marboxil arm were nasopharyngitis (5%), headache (4%), and cough (4%). These are all symptoms of influenza and are consistent with household contacts who were infected with influenza. Of note, nasopharyngitis was also the most commonly reported TEAE in subjects ≥ 12 years of age in Trial T0834 and was reported in 6% of adolescent and adult subjects.

All of the TEAEs were Grade 1 or 2 in intensity. There were no Grade 3 or 4 AEs in subjects from 5 to < 12 years of age.

No TEAEs in the ≥ 5 to < 12 year old age group was judged as drug-related.

11.3.3 Treatment-Emergent Adverse Events in Subjects ≥ 5 to < 12 Years of Age, Trial T0834

Safety laboratory testing was obtained on Study Day 1 (predose) and on Days 5 and 15. Laboratory findings could be included as a TEAE if they were new in onset or were aggravated in severity from baseline. The decision of whether to classify a laboratory abnormality as an AE was the responsibility of the investigator. Two subjects (4%) in the baloxavir marboxil arm had a laboratory abnormality reported as an adverse event. One subject had hematuria and proteinuria; a second subject had an increased ALT and neutropenia. One subject in the placebo arm (2%) had a laboratory abnormality reported as an TEAE; this subject had an increased uric acid. All of the laboratory abnormalities were Grade 1, and none were judged as drug-related.

Trial T0834 was not conducted under U.S. IND and only hepatic enzyme tests values were evaluated by toxicity grading. One subject, a 7 year old male, had a Grade 1 increase in ALT on Day 15 that had resolved on repeat testing on Day 44.

Although the evaluation of safety laboratory testing was limited due to the lack of grading for laboratory values besides liver function tests, few laboratory abnormalities were classified as adverse events. Also, the types of laboratory abnormalities varied with no clear single abnormality. This suggests that few laboratory abnormalities were considered clinically significant.

11.4. 4 Conclusions Regarding Baloxavir Marboxil Safety in Patients ≥ 5 Years to < 12 Years of Age

Baloxavir marboxil was studied in a Phase 3, randomized, double-blind, oseltamivir-controlled trial for treatment of acute, uncomplicated influenza. The most commonly reported treatment-emergent adverse events in subjects ≥ 5 to < 12 years of age who received baloxavir marboxil were vomiting and diarrhea, which were both reported in 5% of study subjects. Vomiting was reported more often in subjects who received oseltamivir (18%), but diarrhea was not observed in subjects who received oseltamivir. Vomiting and diarrhea were also reported in the open-label, single arm

studies of baloxavir marboxil. Other TEAEs reported in subjects ≥ 5 to < 12 years of age who received baloxavir marboxil were consistent with underlying influenza and were reported in a small number of subjects. For example, rhinorrhea was reported in 3 subjects in the baloxavir marboxil arm, headache in 2, and upper respiratory tract infection in 2. Similar findings were observed in the oseltamivir arm and in the supporting single arm, open-label studies.

When baloxavir marboxil was administered to otherwise healthy children to prevent influenza, the most commonly reported TEAEs were nasopharyngitis, cough, and headache, which suggest breakthrough influenza infection. Similar results were observed in the placebo group. Nasopharyngitis was also the most commonly reported TEAE in adults and adolescents who received baloxavir marboxil in Trial T0834.

Overall, no new safety signal was identified in pediatric subjects ≥ 5 to < 12 years of age, and the percentage of subjects with adverse events was low. In addition, all TEAEs were judged as Grade 1 or 2 in severity and no serious AEs were reported in this age subgroup.

12. Review Issues Related to Risk

Increased frequency of baloxavir resistance in pediatric patients ≥ 5 years to < 12 years compared to adults and adolescents.

12.1 Applicant Proposal

A Complete Response Letter was issued after review of the pediatric data in the original submission to support the use of baloxavir marboxil in patients from 1 year of age to < 12 years of age because of the high frequency of treatment-emergent resistance-associated substitutions (TE-RAS) to baloxavir in that age group. The Applicant has responded to the CR Letter and proposed extending the indication for the treatment of and the postexposure prophylaxis of influenza to patients 5 years of age and older. The Applicant has provided information to support that the frequency of TE-RAS is lower in patients < 5 years of age than in those 5 years of age to < 12 years of age. The overall incidence of TE-RAS and the incidence of TE-RAS by influenza type/subtype is shown by age group in the table below. These data are from the Applicant's studies of baloxavir marboxil in pediatric patients, adolescents, and adults

Table 17. Incidence of Subjects with Treatment-Emergent Resistance Substitutions by Influenza Type/Subtype and by Age Group

	Total [a]	**A/H1N1 [a]**	**A/H3N2 [a]**	**B [a]**
Key Age Categories – TE RAS % (subjects with TE RAS/total evaluated)				
<5 years	40% (37/93)	23% (5/22)	62% (32/52)	0 (0/19)
5 - 11 years	16% (19/117)	17% (2/12)	18% (17/93)	0 (0/13)
≥12 years	7% (60/842)	5% (6/134)	11% (53/485)	1% (2/224)

Source: FDA analysis of pooled data from trials CP40559, CP40563, T0822, T0831, T0832, T0821, T0833, T0835.

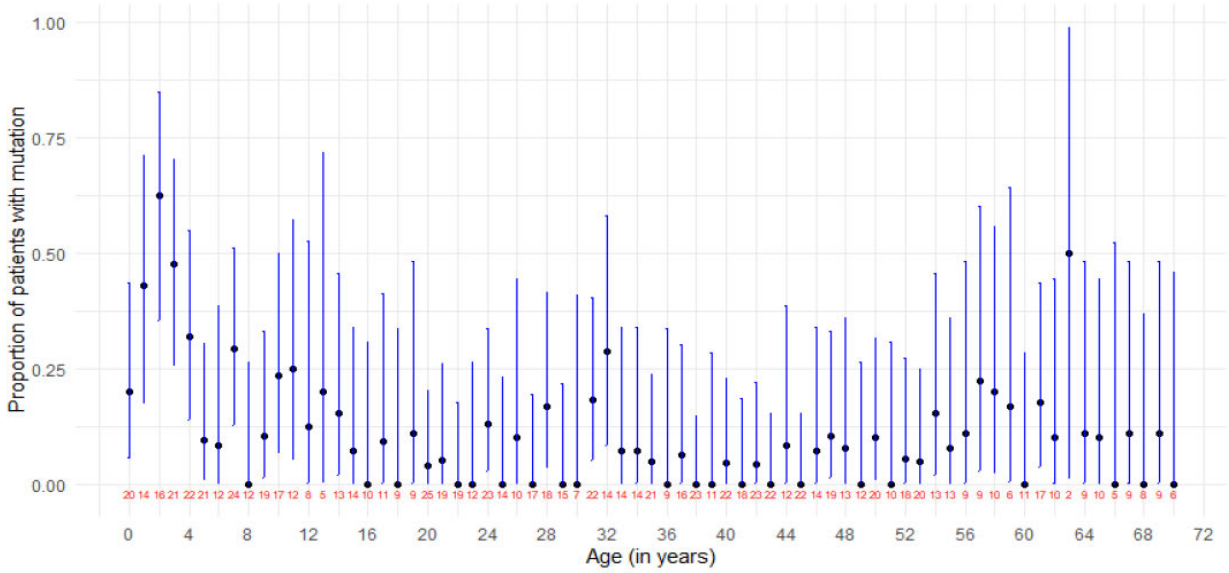
a. For mixed infections, only successfully sequenced virus type/subtype were included in total and in the respective type/subtype subsets.

As shown in Table 17, the overall frequency of TE-RAS to all influenza types/subtypes is much higher in pediatric subjects < 5 years of age (40%) than those ≥ 5 to < 12 years of age (16%) or in adults and adolescents ≥ 12 years of age (7%). The frequency of TE-RAS in pediatric subjects < 5 years of age is particularly high in subjects with influenza A/H3N2 virus infections, but the frequency of TE-RAS is higher in the < 5-year age group than in the 5 to < 12-year age group for both A/H1N1 and A/H3N2 virus infections. While the frequency of TE-RAS for the two respective influenza A virus subtypes is 23% and 62% for pediatric patients < 5 years of age, it is 17% and 18% in pediatric patients ≥ 5 to < 12 years of age. As shown in Table 16, the frequency of TE-RAS in both the < 5 years of age cohort and the frequency of TE-RAS in the ≥ 5 years to < 12 years of age cohort are higher than that observed in adolescents and adults. However, the number of subjects with resistance data is much higher in adolescents and adults than in pediatric patients < 12 years of age.

12.2 Is the Age Group ≥ 5 Years the Appropriate Lower Limit to Minimize the Frequency of TE-RAS in Pediatric Patients?

Although the number of pediatric patients with resistance data is relatively smaller than the number of adolescents and adults with available data, the frequency of TE-RAS was examined by year of age. As shown in Figure 1, TE-RAS frequency is variable across ages, which is not surprising, given the small number of data points and the differences in virus type/subtype across age bands.

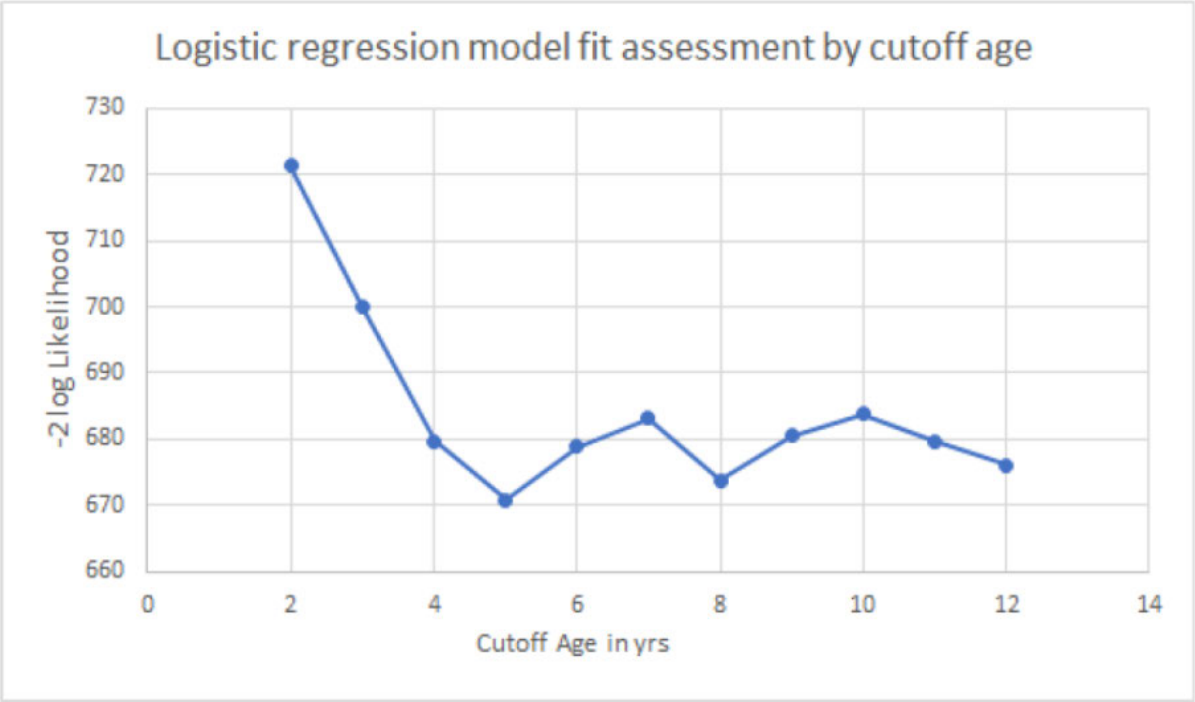
Figure 1: Proportion of Patients with Substitutions (95% Confidence Intervals) by Age up to 70 Years.



Includes data from the following studies: CP40559, CP40563, T0822, T0831, T0832, T0821, T0833, T0835. Clopper Pearson CI have been presented. Numbers in red denote the total number of patients in each individual age group.

A clear increase in frequency is observed in pediatric patients 2 years to 4 years of age. However, there are multiple “blips” of increased frequency of TE-RAS throughout all age groups. A logistic regression model was constructed to examine the frequency by age in subjects < 12 years of age. This model is shown in Figure 2.

Figure 2: Logistic Regression Model Fit Assessment of Treatment-Emergent Substitutions by Cutoff Age



Source: NDA 214410, Report 1113741, Figure 64.

Figure 2 focuses only on data from pediatric patients < 12 years of age. In this figure, it is clearly demonstrated that the frequency of TE-RAS is highest in pediatric patients < 5 years of age. While there are minor increases in the frequency of TE-RAS at 7 years of age and 10 years of age; the frequency of TE-RAS is much higher in subjects younger than 5 years of age. The data shown in these figures are consistent with the data shown in Table 17 and support limiting the indication for baloxavir marboxil to 5 years of age and older for both treatment and postexposure prophylaxis of influenza.

12.3 Comparison of TE-RAS in Pediatric Patients who Receive Oseltamivir and Those who Receive Baloxavir Marboxil

The data in Table 17 show that the frequency of baloxavir TE-RAS is higher in pediatric patients than in adults and adolescents. However, the frequency of resistance is also higher in pediatric patients who have been treated with oseltamivir than in adults who have been treated with oseltamivir. According to the Tamiflu® package insert, the incidence of oseltamivir TE-RAS in pediatric treatment studies has been detected at frequencies as high as 27% to 37% for influenza A/H1N1 and 3% to 18% for influenza A/H3N2.

At the time of the original FDA approval of oseltamivir for use in pediatric patients, oseltamivir TE-RAS were thought to be very uncommon. Multiple studies have been published with variable frequencies of TE-RAS to oseltamivir. The frequency of oseltamivir TE-RAS is reported to be more common in influenza A/H1N1 virus

infections, with reports of TE-RAS up to 26% (Rath et.al. 2017). TE-RAS is less common with influenza A/H3N2 virus; the frequency of TE-RAS in pediatric patients who received the appropriate dose of oseltamivir has been reported as high as 10% (Tamura et.al. 2011). As with baloxavir marboxil, TE-RAS in influenza B viruses is very uncommon.

In the 2007/2008 influenza season, an H275Y substitution in neuraminidase emerged in circulating influenza A/H1N1 viruses that conferred significantly reduced susceptibility to oseltamivir. By the 2008/2009 influenza season, A/H1N1 virus with the H275Y substitution had become the dominant influenza strain in the U.S. One response to the emergence of circulating, oseltamivir-resistant virus, was the initiation of a global observational network, The Influenza Resistance Information Study (IRIS), to monitor neuraminidase inhibitor resistance (Whitley et al. 2012). Prior to IRIS, the studies of oseltamivir resistance in pediatric patients had been relatively small, enrolling 10-50 subjects for each influenza type or subtype [Rath (2015) and Kiso (2004)]. In 2020, seven years of TE-RAS data for oseltamivir from 2131 children ≤ 13 years of age enrolled in IRIS were published (Roosenhoff et al. 2020). The overall frequency of oseltamivir TE-RAS was 5.0% for influenza A/H1N1 (34/683) and 1.3% for A/H3N2 (15/825). No resistance substitutions were detected in influenza B viruses. The IRIS confirmed that oseltamivir resistance substitutions were most commonly found in A/H1N1 viruses. The IRIS also demonstrated that the frequency of oseltamivir TE-RAS for A/H1N1 was higher in children < 5 years compared to those > 5 years. The frequency of TE-RAS by age is shown in the following table.

Table 18: Frequency of Substitutions in Influenza A/H1N1 Conferring Resistance to Oseltamivir by Age Group in the Influenza Resistance Information Study (IRIS)

< 6 Months	6 Months to 1 Year	1 to 3 Years	3 to 5 Years	5 to 10 Years	10 to 13 Years
2/4 (50%)	2/7 (29%)	15/151 (10%)	9/158 (6%)	6/270 (2%)	0/93 (0%)

Source: Roosenhoff et al. Clinical Infectious Diseases. 2019:71(5);1186-94.

Prior to the IRIS study, estimates of TE-RAS to oseltamivir ranged from 0 (Kimberlin et al. 2013) to 26% (Rath et.al. 2017). The results of the IRIS demonstrate that it requires a large international trial conducted across multiple seasons to accurately describe treatment-emergent resistance substitutions. The IRIS is also the only large study with subjects across the age ranges from birth to 13 years of age. The results show that the frequency of TE-RAS to oseltamivir is highest in subjects younger than 5 years of age.

In contrast to oseltamivir, for which TE-RAS have occurred most frequently in A/H1N1 virus, the highest frequency of TE-RAS to baloxavir has been observed in influenza A/H3N2 viruses in the studies conducted to date. The frequency of TE-RAS in pediatric patients is higher with baloxavir marboxil compared to what has been reported in the IRIS for oseltamivir. However, it is important to note that the studies of

TE-RAS to baloxavir marboxil thus far have been small and may not be reflective of the overall TE-RAS frequency across multiple seasons and evolving influenza virus type/subtypes. The Applicant has agreed to monitor resistance as a postmarketing commitment.

12.4 Reasons for Increased Treatment-Emergent Resistance Substitutions in Pediatric Patients < 5 Years of Age

The reasons that TE-RAS have been observed in pediatric patients < 5 years of age more often than in older children and adults is thought to be due to differences in viral shedding and due to the immature immune response in young children.

The overwhelming majority of clinical studies have shown that that viral shedding is prolonged in pediatric patients. However, results vary by influenza type and subtype. In Rosenhoff's study of 2,131 children < 13 years of age with influenza, influenza viral RNA was cleared faster in children 10 to 13 years of age than in those < 10 years of age (Roosenhoff, 2020). In analyses of influenza viral RNA AUCs or mean viral load over time course, pediatric patients from 1 to 5 years of age had a significantly higher viral AUC than those older than 5 years of age. The median time to viral non-detection was longest in patients < 5 years of age in patients infected with A/H1N1 and influenza B. In a clinical trial by Lau et al, (2013) the influenza A viral AUC was higher, and the duration of shedding was longer in pediatric patients ≤ 18 years of age compared to adults. Ng et al (2016), demonstrated longer duration of shedding in patients < 16 years of age than in those older; but duration varied and was shortest in A/H3N2 infections.

In a study by van der Vries et al (2013), 11 immunocompromised patients had prolonged shedding (>14 days) of A/H1N1pdm09, and 5 (45%) developed TE-RAS to NAIs. The authors then infected immunocompromised ferrets with influenza A/H1N1pdm09 and treated the ferrets with oseltamivir. After one week, all 18 ferrets were still shedding influenza and TE-RAS were observed in all 18 ferrets. Multiple case series have been published documenting prolonged influenza viral shedding in immunocompromised patients with the development of treatment-emergent resistance to oseltamivir (Ison et al., 2006) (Baz et al., 2006) (CDC MMWR, 2009). It is possible that the causes of prolonged shedding observed in pediatric patients could also predispose them to the development of TE-RAS.

Prolonged influenza viral shedding in pediatric patients is typically attributed to their immature immune system. The immune system is not fully developed at birth with deficiencies in both the innate and adaptive components. Many young pediatric patients have not been exposed to influenza, and therefore, do not have antibodies to influenza. In a study by Bodewes et al. (2011), the seroprevalence of influenza antibodies was examined in 720 serum samples from children from 0 to 7 years of age. While maternal antibodies were detected in infants from birth to 6 months of age, the percentage of subjects from 7 to 12 months with antibodies to one of the three influenza types/subtypes ranged from 4% to 19%. The percentage of subjects who were seropositive gradually increased until 100% of children had antibodies to all

three strains by 8 years of age. Because of the decreased seroprevalence of antibodies to influenza in children, two doses of influenza vaccine are administered to children ≤ 8 years. In an article describing the immunogenicity of two doses of influenza vaccine in pediatric patients, the authors note that the strongest predictor of antibody response to vaccination is serostatus at baseline (Neuzil et al., JID. 2006). Children are not only more likely to be seronegative, but the antibody response to influenza may vary in children. In an article by Meade et al. (2020) the antibody response to natural influenza A/H1N1 infection resulted in antibodies with a narrower response to fewer locations on hemagglutinin than antibodies in adults. Other researchers have examined juvenile monkeys' immunity to influenza A and observed that there is delayed viral clearance (associated with decreases in IFN-gamma and IFN-12 and to increases in IL-10) and excessive inflammation (associated with increased IL-23, IL06, and IL-1β) (Coates et al., 2016). These immune deficiencies are likely to be, at least part, of the reason for increased influenza virus shedding and could be related to the increased risk of the development of baloxavir-associated TE-RAS in pediatric patients < 5 years of age. Consistent with this theory, the median baseline influenza virus antibody titer was lower in subjects with TE-RAS compared to those without TE-RAS in pooled analyses of baloxavir marboxil clinical trial data.

12.5 Conclusion

In clinical trials of baloxavir marboxil, treatment-emergent resistance to baloxavir marboxil was observed more commonly in pediatric patients younger than 5 years of age (40% overall). The frequency of TE-RAS to oseltamivir is also higher in pediatric patients younger than 5 years of age. The increase in resistance in this age group is likely due to the immature of their immune system and the lack of previous exposure to influenza antigens children < 5 years of age. The frequency of TE-RAS was higher in subjects ≥ 5 years to < 12 years of age (16%) compared to in subjects ≥ 12 years of age (7%), but the frequency of TE-RAS in subjects ≥ 5 years to < 12 years of age is considered acceptable and does not exceed the TE-RAS frequency that has been observed for oseltamivir in populations in which it is approved for use (Tamiflu® package insert).

It is likely that the frequency of baloxavir TE-RAS will be better understood with additional information obtained over multiple influenza seasons. Baloxavir marboxil has been on the market in the U.S. for a relatively short time. In the time since marketing, there has been a global SARS-CoV-2 pandemic, which has resulted in both a decrease in the amount of circulating influenza virus and an increase in infection control practices, such as mask wearing and hand washing, that decrease influenza virus infections. Therefore, the use of baloxavir marboxil has been limited, and information regarding treatment-emergent resistance and the presence of circulating influenza virus with TE-RAS is limited at this time. Under current postmarketing commitments, the Applicant will be collecting global surveillance data on baloxavir resistance patterns in circulating influenza viruses. The Applicant is also conducting a transmission trial in which baloxavir marboxil or placebo is administered to index patients in an attempt to decrease influenza transmission to household

contacts. Data regarding the transmission of influenza virus with resistance-associated substitutions may be obtained in this trial in the future.

13. Advisory Committee Meeting

No Advisory Committee meeting was held for this response to a CR Letter.

14. Pediatrics

The application was taken to the Pediatric Research Committee (PeRC) on July 12, 2022, to provide an updated assessment to the PeRC and to provide an update on the PREA PMRs that had been fulfilled. The PeRC agreed with DAV's decision to approve baloxavir marboxil in pediatric patients ≥ 5 years to < 12 years of age. The PeRC also agreed that baloxavir marboxil had been fully assessed in pediatric patients ≥ 1 year to < 12 years of age based on the previous review.

The following postmarketing requirements and postmarketing committments were fulfilled by submission of the Clinical Study Reports in the original submission and in this response to the CR Letter.

PREA PMR 3502-2 (3961-2): Conduct a randomized active-controlled clinical trial to evaluate the pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from 12 months to less than 12 years of age with acute uncomplicated influenza. Include characterization of baloxavir resistance-associated substitutions in viral isolates from subjects with prolonged viral shedding.

PREA PMR 3503-3: Submit the clinical study report and datasets for the pharmacokinetics, safety, and efficacy trial of baloxavir marboxil in Japanese pediatric subjects who weigh less than 20 kg with acute, uncomplicated influenza. Include characterization of resistance-associated substitutions, including supportive datasets.

PREA PMR 3961-2: Submit the clinical study report including the datasets and pharmacokinetic/pharmacodynamic modeling data for the Phase 3 Trial 1719T0834 conducted in pediatric subjects from 12 months to less than 12 years of age to evaluate the pharmacokinetics, safety, and efficacy of baloxavir marboxil for the prevention of influenza as postexposure prophylaxis in household contacts of an index case. Include characterization of baloxavir resistance-associated substitutions including supporting datasets.

PMR 3961-4: Submit the full clinical study report and datasets for Trial T0835 conducted to evaluate the pharmacokinetics, safety, and effectiveness of baloxavir marboxil for the treatment of acute, uncomplicated influenza in Japanese pediatric subjects <12 years of age and <20 kilograms in weight. The study report should include characterization of the emergence of baloxavir resistant viral variants, including supportive datasets

PMC 3503-8: Conduct a randomized, double-blind, placebo-controlled trial of baloxavir marboxil post-exposure prophylaxis to prevent influenza in household contacts of an index case.

15. Other Relevant Regulatory Issues

The financial disclosures for the trials discussed in this review were reviewed as part of the original review. Please see the Integrated Review (November 21, 2020).

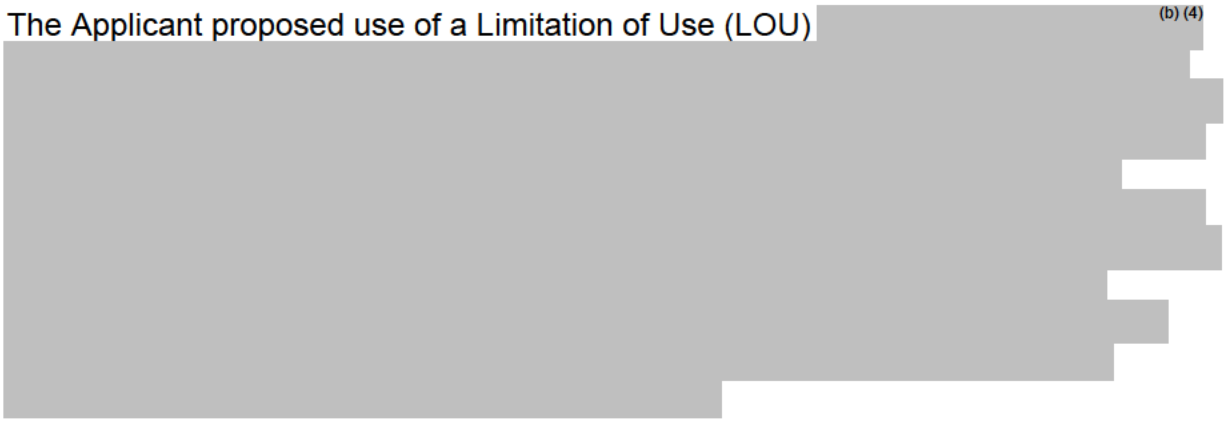
The Applicant states the clinical trials were conducted in accordance with the principles of the "Declaration of Helsinki" and with International Conference on Harmonization good clinical practice requirements. Study sites from the two pivotal trials, CP40563 and T0834 were previously inspected by reviewers from the Office of Scientific Investigations, and no deficiencies that would affect the study results were found.

16. Labeling

The baloxavir marboxil labeling has been updated to reflect changes in the indication, extending the indications for treatment of influenza and for postexposure prophylaxis to patients 5 years of age and older. The changes with this response to the CR Letter primarily affected the following sections.

- INDICATIONS AND USAGE:

The Applicant proposed use of a Limitation of Use (LOU) (b) (4)



The indications for Xofluza will now read as follows:
XOFLUZA is indicated for treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours and who are:

- otherwise healthy adults and pediatric patients 5 years of age and older [see Clinical Studies (14.1)],
  OR

- adults and pediatric patients 12 years of age and older who are at high-risk of developing influenza-related complications [see Clinical Studies (14.2)].

XOFLUZA is indicated for post-exposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza *[see Clinical Studies (14.3)].*

- DOSAGE AND ADMINISTRATION:

This section was revised to include dosing for pediatric patients ≥ 5 to < 12 years of age.

Table 1 Recommended XOFLUZA Tablet Dosage in Adults and Pediatric Patients 5 Years of Age and Older

Patient Body Weight (kg)	**Recommended Single Oral Dose (Tablets)**
20 kg to less than 80 kg	One 40 mg tablet (blister card contains one 40 mg tablet)
At least 80 kg	One 80 mg tablet (blister card contains one 80 mg tablet)

Table 2 Recommended XOFLUZA for Oral Suspension Dosage in Adults and Pediatric Patients 5 Years of Age and Older

Patient Body Weight (kg)	**Recommended Single Oral Dose[a, b] (For Oral Suspension)**
Less than 20 kg	2 mg/kg taken as a single dose
20 kg to less than 80 kg	40 mg (20 mL) taken as a single dose
At least 80 kg	80 mg (40 mL[c]) taken as a single dose

a Recommended XOFLUZA dosage is based on the patient's weight.
b Use a measuring device (oral syringe) to measure the prescribed dose for use.
c Dosage requires two bottles of XOFLUZA for oral suspension

A new WARNINGS AND PRECAUTIONS section was added to describe the increased incidence of treatment emergent resistance substitutions in pediatric patients younger than 5 years of age.

5.2 **Increased Incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age**

XOFLUZA is not indicated in patients less than 5 years of age due to increased risk of treatment-emergent resistance in this age group. In clinical trials, the incidence of virus with treatment-emergent substitutions associated with reduced susceptibility to baloxavir (resistance) was higher in pediatric subjects younger than 5 years of age

(43%, 36/83) than in pediatric subjects ≥ 5 years to < 12 years of age (16%, 19/117) or subjects ≥ 12 years of age (7%, 60/842). The potential for transmission of resistant strains in the community has not been determined. [see Indications and Usage (1), Use in Specific Populations (8.4), and Microbiology (12.4)]

Additional information was added to Section 12.4. Please see Dr. Ince's virology review.

- ADVERSE REACTIONS section:

This section was revised to update the number of subjects treated with baloxavir marboxil and to include information on adverse events reported in pediatric subjects in the treatment and postexposure prophylaxis trials. The following section was added:

Pediatric Subjects (5 to < 12 Years of Age):
In an active-controlled, double-blind trial (Trial CP40563) in otherwise healthy pediatric subjects, a total of 79 subjects 5 to less than 12 years of age, received the recommended weight-based dosage of XOFLUZA, and 39 subjects received oseltamivir. The most frequently reported AEs (≥ 5%) in the XOFLUZA treatment arm were vomiting (5%) and diarrhea (5%). Vomiting was reported in 18% of subjects in the oseltamivir arm [see Clinical Studies (14.1)].

The following sentence was added to the description of safety in the postexposure trial:

The safety profile was similar in pediatric patients ages 5 to < 12 years old as that reported in adults and adolescents 12 years of age and older *[see Clinical Studies (14.3)]*

- USE IN SPECIAL POPULATIONS, Pediatric Use.

The following section was added to the Pediatric Use section:
<u>Treatment of Acute Uncomplicated Influenza in Pediatric Subjects (5 to < 12 Years of Age)</u>
The safety and effectiveness of XOFLUZA in otherwise healthy pediatric subjects 5 to less than 12 years of age is supported by one randomized, double-blind, controlled Trial CP40563 with a primary endpoint of safety. In this trial, 118 otherwise healthy pediatric subjects were randomized and treated in a 2:1 ratio and received either XOFLUZA (N=79) or oseltamivir (N=39). Efficacy was extrapolated from adults and adolescents based on comparable PK exposures in adults, adolescents and pediatric subjects 5 to less than 12 years of age. The median time to alleviation of signs and symptoms in influenza-infected subjects was comparable in the XOFLUZA and oseltamivir arms. Adverse events reported with XOFLUZA in pediatric subjects were similar to those observed in adults and adolescents except for vomiting and diarrhea, which were both more commonly reported in pediatric subjects *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)].*

The number of study subjects in the postexposure trial was updated.

A section was added for pediatric patients < 5 years of age.
Pediatric Subjects (< 5 Years of Age)
The safety and effectiveness of XOFLUZA for treatment and post-exposure prophylaxis of influenza in pediatric subjects less than 5 years of age have not been established *[see Warnings and Precautions (5.2) and Microbiology (12.4)].*

- CLINICAL STUDIES section:

The following section was added to 14.1 Treatment of Acute, Uncomplicated Influenza – Otherwise Healthy Subjects, Pediatrics (5 to < 12 Years of Age). The Division agreed with the presentation of the trial results.

Trial 5 CP40563 (NCT03629184) was a randomized, double-blind, multicenter, active-controlled study, designed to evaluate the safety, efficacy, and pharmacokinetics of a single oral dose of XOFLUZA compared with oseltamivir in otherwise healthy pediatric subjects (including subjects ages 5 to < 12 years of age) with influenza-like symptoms. Eligible subjects had a tympanic temperature of at least 38°C and at least one respiratory symptom of either cough or nasal congestion.
A total of 118 subjects 5 to less than 12 years of age were randomized and received a single one-time oral dose of XOFLUZA (N=79) based on body weight (2 mg/kg for subjects weighing < 20 kg or 40 mg for subjects weighing ≥ 20 kg) or oseltamivir (N=39) for 5 days (dose based on body weight). The primary objective was to compare the safety of a single one-time dose of XOFLUZA with 5 days of oseltamivir administered twice daily. The secondary efficacy endpoint included time to alleviation of influenza signs and symptoms, which was defined as the time when all of the following were met for at least 21.5 hours: cough and nasal symptoms were assessed by the caregiver as no problem or minor problem, subject was able to return to normal daily activity, and subject was afebrile (temperature ≤ 37.2°C). However, the trial was not powered to detect statistically significant differences in this secondary endpoint.
Of the 118 randomized subjects 5 to less than 12 years of age in Trial CP40563, 94 subjects had influenza confirmed by RT-PCR at baseline or during the trial; 89% percent of subjects were White, 3% Black or African American and 8% Other/unknown/multiple races. The mean age was 8 years [SD=1.97]; 56% of subjects were female and 44% male. The predominant influenza virus strain in this study was the A/H3N2 subtype (67%), followed by A/H1N1 (20%) and type B (9%).
The median time to alleviation of influenza signs and symptoms was 138 hours in the XOFLUZA arm (95% CI of 117, 163) and 126 hours in the oseltamivir arm (95% CI of 96, 166).

Section 14.3 Post-Exposure Prophylaxis of Influenza was revised to include information for subjects from 5 to < 12 years of age who participated in the Phase 3 postexposure prophylaxis trial.

17. Postmarketing Recommendations

One Postmarketing Requirement (PMR) and two Postmarketing Commitments (PMCs) were requested:

Number	PMR Description	Timetable
1	Evaluate PA substitution F314S, alone and in combination with A231V, for its impact on baloxavir susceptibility in A/H1N1 virus.	Study Completion: 07/2023 Final Report Submission: 09/2023
Number	PMC Description	Timetable
2	Conduct a prospective, multicenter, observational study in baloxavir marboxil-treated patients over at least five influenza seasons that will capture the susceptibility and genotype of influenza viruses in baseline and on-treatment respiratory samples to determine the frequency of baseline and treatment-emergent baloxavir resistance and the impact on outcomes.	Final Protocol Submission: 01/2023 Study Completion: 04/2027 Final Report Submission: 10/2027
3	Provide a semi-annual (twice-yearly) update on global baloxavir usage and emergence of resistance to baloxavir as an integrated review of information from national and international influenza drug resistance databases and sequence databases, including but not limited to World Health Organization and US Centers for Disease Control and Prevention surveillance, data collected by the sponsor, and information in the published literature. Each update will include information on the methodologies (e.g. viral gene sequencing and phenotypic assay descriptions) used in studies during that reporting period. Substitutions of particular interest include all those listed as resistance-associated in the USPI, as well as substitutions currently identified or identified in the future that reduce susceptibility to baloxavir.	Initial Report Submission 05/2023 Final Report Submission: 05/2026

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