Integrated Review

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Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214410/Original 1, 210854/S-04, 10 214410/Original 2, 210854/S-05, 09
Priority or standard	Standard
Submit date(s)	1/23/2020
Received date(s)	1/23/2020
PDUFA goal date	11/23/2020
Division/office	Division of Antivirals (DAV)
Review completion date	11/23/2020
Established/proper name	Baloxavir marboxil
(Proposed) proprietary name	Xofluza
Pharmacologic class	Influenza virus polymerase acidic endonuclease inhibitor
Code name	S-033188
Applicant	Genentech, Inc.
Dosage form(s)/formulation(s)	Granules for oral suspension, 2 mg/mL; 20-mg and 40-mg tablets
Dosing regimen	Granules and tablet dosing in patients 12 years of age and older: (b) (4) <80 kg: single oral dose of 40 mg At least 80 kg: single oral dose of 80 mg
Applicant proposed indication(s)/ population(s)	Treatment of acute, uncomplicated influenza in otherwise healthy patients >1 year of age to <12 years of age and postexposure prophylaxis of influenza in persons 1 year of age and older following contact with an individual who has influenza
Proposed SNOMED indication	6142004 |Influenza (disorder)|
Regulatory action for NDA 214410/ Original 1	Approval
Regulatory action for NDA 214410/ Original 2	Complete response
Regulatory action for NDA 210854/S-04	Approval
Regulatory action for NDA 210854/S-09	Complete response
Regulatory action for NDA 210854/S-05	Complete response
Regulatory action for NDA 210854/S-10	Approval
Approved dosage (if applicable)	Tablet dosing in patients 12 years of age and older: (b) (4) <80 kg: single oral dose of 40 mg At least 80 kg: single oral dose of 80 mg
Approved indication(s)/ population(s) (if applicable)	Treatment of acute, uncomplicated influenza in patients 12 years of age and older who are otherwise healthy or at high risk for developing influenza-related complications
Approved SNOMED term for indication (if applicable)	6142005 | Influenza (disorder)

Table of Contents

Table of Tables

Table of Figures

Glossary

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CARIFS	Canadian Acute Respiratory Illness and Flu Scale
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CSR	clinical study report
DAV	Division of Antivirals
EC_{50}	half maximal effective concentration
FDA	Food and Drug Administration
GEE	generalized estimating equations
HI	hemagglutination inhibition
IND	investigational new drug
IRIS	Influenza Resistance Information Study
ITT	intent-to-treat
ITTI	intent-to-treat-infected
K_a	absorption rate constant
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NAI	neuraminidase inhibitor
NDA	new drug application
OSI	Office of Scientific Investigations
PA	polymerase acidic
PEP	postexposure prophylaxis
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	prothrombin time
Q/F	intercompartmental clearance
RAS	resistance-associated substitution
RMST	restricted mean survival time
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SOC	System Organ Class
sNDA	supplemental new drug application
SUR	safety update report

TEAE	treatment-emergent adverse event
TQT	thorough QT
TTAS	time to alleviation of influenza signs and symptoms
ULN	upper limit of normal
Vc/F	apparent central volume of distribution
Vp/F	apparent peripheral volume of distribution

I. Executive Summary

1. Summary of Regulatory Action

Baloxavir marboxil is a polymerase acid endonuclease inhibitor approved for the treatment of acute, uncomplicated influenza in otherwise healthy and high risk adults and adolescents 12 years of age and older. This new drug application (NDA) and these supplemental NDAs (sNDAs) for baloxavir marboxil are submitted by Genentech (the Applicant) to support the treatment of (1) influenza in pediatric patients >1 year to <12 years of age, (2) the postexposure prophylaxis of influenza in patients >1 year of age following household contact with an individual who has influenza, and (3) the use of a baloxavir marboxil 2% granules (2 mg/mL when constituted in drinking water or sterile water for oral and enteral use. These NDA/sNDAs were reviewed by the multidisciplinary review team. Each discipline has recommended approval of baloxavir marboxil for postexposure prophylaxis of influenza in patients ≥12 years of age and approval of the oral baloxavir marboxil 2% granules. Baloxavir marboxil will not be approved for the treatment of or postexposure prophylaxis of influenza in pediatric patients <12 years of age due to the increased frequency of baloxavir resistance-associated amino acid substitutions observed during treatment in this population, and I, the signatory authority for this application, concur with those recommendations.

The Applicant has submitted one Phase 3 safety, pharmacokinetic (PK) and effectiveness trial (CP40563) and two single-arm trials (T0822, T0833) to support the use of baloxavir marboxil for treatment of acute, uncomplicated influenza in pediatric patients 1 to <12 years of age. Preliminary results on baloxavir resistance from a fourth pediatric treatment trial (T0835) were submitted late in the review cycle, but were also reviewed. 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 was also similar for pediatric subjects (1 to <12 years old) who received baloxavir marboxil and for those who received an active control (oseltamivir) in Trial CP40563.

Notably, no new safety signal was identified in pediatric subjects (1 to <12 years old), and the percentage of subjects with adverse events was low, with no serious adverse events reported in pediatric subjects in this age group. However, the frequency of treatment-emergent resistance to baloxavir was substantially higher in pediatric subjects (1 to <12 years old) than in adults and adolescents, with the proportion of subjects with baloxavir resistance-associated amino acid substitutions ranging from 22% to 44%, overall, and even higher based on subtype in the four pediatric trials. Because of concerns for decreased efficacy and increased viral shedding and the possibility of increased influenza transmission associated with the high frequency of baloxavir-resistance, the risks associated with baloxavir marboxil use in pediatrics outweigh the benefits. Thus, baloxavir marboxil will not be approved for the treatment of acute, uncomplicated influenza in patients 1 to <12 years of age.

The results of a single Phase 3 trial (T0834) also provide evidence of efficacy and safety of baloxavir marboxil in the postexposure prophylaxis of influenza in subjects ≥12 years of age

who were household contacts of influenza-infected individuals. The large, randomized, placebo-controlled Phase 3 trial showed statistically robust efficacy with a p-value <0.001. Efficacy was also demonstrated in the subgroup of pediatric subject <12 years of age in this trial (n=142). Adverse events were uncommon and there were no serious adverse events or premature discontinuations due to adverse events in this population. The overall benefit-risk for use of baloxavir marboxil for postexposure prophylaxis of influenza is favorable for adults and adolescents (≥12 years old), as described in the benefit-risk assessment in Table 2. However, baloxavir marboxil will also not be approved for postexposure prophylaxis in pediatric patients 1 to <12 years old due to the high frequency of treatment-emergent baloxavir resistance in this age group, as described above.

For detailed information supporting the approval of baloxavir marboxil for patients ≥12 years of age, but not approving for treatment or postexposure prophylaxis in those 12 years old and younger, please refer to the detailed reviews included in this interdisciplinary assessment document. For additional information regarding the 2% granules formulation, please refer to the product quality review.

In summary, NDA 21440/Original 1 for treatment and postexposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older will be approved; while NDA 21440/Original 2 for treatment and postexposure prophylaxis of influenza in pediatric <12 years of age will receive a complete response.

In addition, NDA 210854/S-04 for postexposure prophylaxis of influenza in adults and pediatric patients 12 years of age and older will be approved, while NDA 210854/S-09 for postexposure prophylaxis in pediatric patients <12 years of age will receive a complete response. NDA 210854/S-05 for treatment of influenza in pediatric patients 1 to <12 years of age will also receive a complete response, while NDA 210854/S-10 to update labeling with information on baloxavir resistance in pediatric patients 1 to <12 years of age will be approved.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Influenza** • 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 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 esitmated 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.	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-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 not be approved, however, due to the emergence of baloxavir resistance at high frequencies in this pediatric population. The efficacy of baloxavir marboxil for postexposure prophylaxis of influenza has been demonstrated in a single, randomized, placebo-controlled trial in adults and adolescents, as well as in pediatric patients 1 to <12 years of age. The primary endpoint was reverse transcription-polymerase chain reaction (RT-PCR)-confirmed influenza with fever and at least one respiratory symptom. This indication will be approved in adults and adolescents ≥12 years of age, but will not be approved in pediatric patients 1 to <12 years of age due to the high frequencies of treatment-emergent resistance to baloxavir in that population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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. 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 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 pre-exposure 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; 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.	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.

Benefit	**Treatment of acute, uncomplicated influenza in pediatric patients >1 year to <12 years of age** • 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 as well as a trend toward efficacy in a Phase 3 pediatric trial. Baloxavir exposures in pediatric patients in Trial CP40563, a Phase 3, safety, PK, and efficacy trial of pediatric patients >1 year to <12 years of age 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. • 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 in the baloxavir marboxil arm and 150 hours in the oseltamivir arm. Treatment-emergent virus variants with baloxavir resistance-associated amino acid substitutions were identified in 13/58 (22.4%) subjects evaluated who received baloxavir marboxil, and treatment-emergent virus variants with oseltamivir resistance-associated substitutions were identified in 0/36 subjects evaluated who received oseltamivir in this trial (see Section 7.7.2). **Postexposure prophylaxis in persons >1 year of age who have had contact with an influenza-infected person** • The efficacy of baloxavir marboxil for the prevention of influenza in household contacts of index cases was demonstrated in a Phase 3, randomized, double-blind, placebo-controlled trial (Trial T0834) in subjects >1 year of age. In Trial T0834, subjects who had been exposed to a person (index case) with influenza were randomized to baloxavir marboxil (N=374) or placebo (N=375) 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 at Day 10. The proportion of subjects who were RT-PCR-positive with symptomatic influenza in the baloxavir arm was 1.9% compared to 13.6% in the placebo arm (p<0.0001). Overall virus variants with resistance-associated substitutions were identifed in 15/31 (48.4%) subjects who were influenza	Baloxavir marboxil efficacy in pediatric patients >1 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 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. However, the relatively high incidence of treatment-emergent baloxavir resistance in CP40563 and the supportive trials, T0822 and T0833, in this pediatric population in comparison to that observed in adults and adolescents, raised concerns about prolonged shedding of resistant virus and widespread transmission of baloxavir resistance. Thus, baloxavir marboxil will not be approved for treatment in pediatric patients >1 to <12 years of age at this time. Baloxavir marboxil was highly effective in the postexposure prophylaxis of influenza from an index case to a household contact in patients 1 year of age and older. Baloxavir marboxil will be approved in adults and adolescents ≥12 years of age for postexposure prophylaxis. However, as noted above, because of the high incidence of treatment-emergent baloxavir resistance in younger pediatric patients (1 to <12 years of age), baloxavir marboxil will not be approved at this time for postexposure prophylaxis in this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	virus RT-PCR-positive postbaseline and evaluated for resistance (see Section 7.7.1). Given the high frequency of resistance observed in pediatric treatment trials overall in subjects <12 years of age, postexposure porphylaxis will not be approved for subjects <12 years of age.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	**Safety/Adverse events** • Pediatric subjects with acute, uncomplicated influenza The safety database for pediatric subjects with acute, uncomplicated influenza >1 year to <12 year of age included 255 pediatric subjects exposed to baloxavir marboxil. This included subjects from Trial CP40563 and subjects from two 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 6% of subjects who received baloxavir marboxil in Trial CP40563, compared to 16% of subjects who received the active control. In the two open-label trials, vomiting was reported in 8% of subjects in one trial and 18% in the other trial. Diarrhea was reported in 5% of subjects who received baloxavir marboxil in Trial CP40563 compared to 2% who received placebo. Vomiting was reported in 1% of adult and adolescent subjects and diarrhea in 3% of adults and adolescents in trials of acute, uncomplicated influenza. All other adverse events reported in at least 2% of subjects were related to conditions observed with influenza: otitis media (rhinitis, bronchitis, and cough) or with medication errors, which were primarily reported at a single site. • Postexposure prophylaxis A total of 374 subjects 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 deaths and no serious adverse events. No adverse event that was judged as drug-related was reported in >1% of subjects. The most commonly reported adverse event was nasopharyngitis, which was reported in 6% of subjects who received baloxavir marboxil and 7% of subjects who received placebo. No other adverse event (AE) was reported in >2% of subjects.	The size of the safety database for pediatric subjects >1 year of age to <12 years 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 for subjects 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 baloxavir was substantially higher in pediatric subjects compared to frequencies reported in trials of adults and adolescents. The frequency of resistance to baloxavir (22.4%) was substantially higher than to the active control, oseltamivir (0%) in the pivotal pediatric trial. The frequency of baloxavir resistance was observed in 44% subjects overall in one of the Japanese single-arm trials in pediatric patients weighing <20 kg. Resistance to anti-influenza drugs may result in prolonged shedding of resistant influenza virus, increased risk of transmission, and decreased drug efficacy. Because of the high frequency of treatment-emergent resistance to baloxavir marboxil in pediatric subjects and the potential consequences associated with drug resistance, baloxavir marboxil will not be approved at this time for use in pediatric patients <12 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management (cont'd)	• 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 was assessed in the three pediatric trials included in these submissions. In addition, late in the review cycle, resistance data from a fourth trial, T0835, became available. All four trials enrolled pediatric patients <12 years of age and used weight-based dosing of baloxavir marboxil. Trial CP40563 was the pivotal trial to support pediatric efficacy and safety of baloxavir marboxil for treatment of acute, uncomplicated influenza, and was the only controlled pediatric trial submitted. In Trial CP40563, the frequency of treatment-emergent resistance to baloxavir marboxil was 22.4%; the frequency of RAS was highest in influenza A/H3N2 subtypes (25%). No treatment-emergent RAS were observed in the subjects who received oseltamivir. The proportion of subjects with treatment-emergent resistance to baloxavir marboxil in two open-label, single-arm studies in Japan, T0822 and T0833, were 26% and 23% respectively. T0835 was also an open-label, single-arm study conducted in Japan; the design for T0835 was identical to that of T0833, but a higher dose of baloxavir marboxil was used in T0835. Preliminary results from T0835 showed an overall frequency of treatment-emergent RAS of 44% with a 75% frequency of resistance in influenza A/H3N2 virus subtypes. Treatment-emergent RAS were more commonly observed in patients weighing 10 to 20 kg compared to those weighing <10 kg or those weighing >20 kg; however, there was no clear weight or age threshold in subjects <12 years of age demarcating significantly increased frequencies of resistance.	A Complete Response letter will be issued to the Applicant for baloxavir treatment of acute, uncomplicated influenza and for postexposure prophylaxis in patients 1 to <12 years of age because of the relatively high frequency of baloxavir resistance in this age group. Baloxavir resistance is relatively lower in adults and adolescents >12 years of age and will be appproved for postexposure prophylaxis in that population. Additional data will be obtained from two ongoing trials: a pharmacokinetic, safety, and effiectiveness trial in pediatric subjects <1 year of age and a safety and efficacy trial assessing the use of baloxavir marboxil to prevent transmission of influenza virus in pediatric and adult subjects. Analyses of the data included in the current submissions along with review of the data from the two additional trials may identify a means for the safe use of baloxavir marboxil in all pediatric patients or in a subgroup of pediatric patients. Review of the data may also aid in the design of another clinical trial to address the high frequency of baloxavir marboxil resistance in pediatric patients (e.g., by use of a different baloxavir dosing regimen or use of combination antiviral therapy).

2.2. Conclusions Regarding Benefit-Risk

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 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 prevent influenza infection.

The Applicant submitted two supplemental NDAs to support treatment of influenza in pediatric patients and postexposure prophylaxis of influenza in patients following household contact with infected individuals. A Phase 3, randomized, double-blind, placebo-controlled trial was submitted to support the efficacy of baloxavir marboxil for the treatment of acute, uncomplicated influenza in pediatric subjects from 1 to <12 years of age. The efficacy of baloxavir marboxil in pediatric patients was extrapolated from adults and adolescents by demonstration of similar baloxavir exposures in the Phase 3 pediatric trial and the pivotal adult/adolescent trials of baloxavir marboxil. The results for the primary efficacy endpoint in the pediatric Phase 3 trial, time to alleviation of influenza symptoms, were similar in the baloxavir marboxil arm and the active control arm. However, treatment-emergent baloxavir resistance associated amino acid substitutions were identified in 22.4% of pediatric patients 1 to <12 years of age in Trial CP40563. A randomized, double-blind, placebo-controlled Phase 3 trial supports the efficacy of baloxavir marboxil for the postexposure prophylaxis of influenza in patients ≥1 year of age. The primary efficacy analysis comparing baloxavir marboxil to placebo in this prophylaxis trial was highly statistically significant ($p<0.0001$). In addition, see discussion on baloxavir treatment-emergent resistance in pediatric patients 1 to <12 years of age (see Section 7.7.2).

The sizes of the safety database for pediatrics and for postexposure prophylaxis were adequate. Adverse drug reactions were uncommon and reported in 3% of pediatric patients in the Phase 3 trial and 2% of subjects in the Phase 3 postexposure prophylaxis trial. There were no serious adverse events in the Phase 3 trial in pediatric subjects or in two open-label Japanese trials submitted to support safety. No serious adverse events were reported in subjects who received baloxavir marboxil in the Phase 3 trial for postexposure prophylaxis. No safety signals were identified.

Treatment-emergent resistance to baloxavir has been reported in 3% to 11% of adult and adolescent subjects who received baloxavir marboxil in Phase 3 trials. Resistance was evaluated in the Phase 3 pediatric trial, the two open-label Japanese studies, and in an additional Japanese study. The frequency of treatment-emergent resistance to baloxavir was 22.4% in the Phase 3 trial and ranged from 22% to 44% in the Japanese studies, including T0835. The frequency of treatment-emergent resistance was higher in the subgroup of subjects infected with influenza A/H3N2 and ranged from 25% to 75%. The frequency of resistance-associated amino acid substitutions did not clearly correlate with any specific age or weight subgroup; therefore, no subgroup in which there was an acceptable frequency of baloxavir resistance, could be identified. Treatment-emergent resistance to baloxavir in baloxavir marboxil-treated subjects is associated with a trend toward longer time to alleviation of influenza symptoms compared to treated

subjects without treatment-emergent resistance. In addition to potentially decreased efficacy, drug resistance is associated with increased duration of viral shedding and possible increased transmission of resistant influenza virus. The risks associated with baloxavir resistance do not outweigh the benefits for pediatric patients 1 to <12 years of age for influenza treatment or postexposure prophylaxis until there is more information on transmission of baloxavir resistant influenza virus. See virology review and comments related to emergence of resistance (see Section 7.7.2).

With all factors considered, the benefits of baloxavir marboxil in the postexposure prophylaxis of influenza for patients ≥12 years of age who are exposed to influenza-infected persons clearly outweigh the risks. The availability of baloxavir marboxil for postexposure prophylaxis in adults and adolescents will provide an additional option for the prevention of influenza and will also provide the convenience of a single oral dose. However, the risks associated with baloxavir marboxil resistance do not outweigh the potential benefits for pediatric patients 1 to <12 years of age, and a complete response letter will be issued to the Applicant for that age group. Additional data from an ongoing transmission study in adults and pediatrics, as well as ongoing studies in pediatric patients are expected to be submitted and will be reviewed to further understand the risks and consequences of baloxavir resistance in pediatric patients.

II. Interdisciplinary Assessment

3. Introduction

The Applicant submitted new drug application (NDA) 214410 for baloxavir marboxil and two new supplemental NDAs (210854, S-004 and S-005). The NDA was submitted for the use of baloxavir marboxil granules for oral suspension (2mg/mL) for pediatric use and in patients unable to or have difficulty swallowing tablets and for patients who require enteral administration. The supplemental NDAs (sNDAs) are seeking to expand the indication of acute, uncomplicated influenza in otherwise healthy patients to include patients >1 year of age to <12 years of age and to add the indication for postexposure prophylaxis of influenza in persons >1 year of age following contact with an individual who has influenza.

Baloxavir marboxil is the only U.S. Food and Drug Administration (FDA)–approved anti-influenza drug that is an influenza virus polymerase acidic endonuclease inhibitor. Baloxavir marboxil is a prodrug that is hydrolyzed to baloxavir, the active form of the drug. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral ribonucleic acid (RNA) polymerase complex required for viral gene transcription. Baloxavir marboxil was approved for use in the United States in October 2018. The regulatory history is summarized in Section 12 of this review.

Baloxavir marboxil is the only influenza virus polymerase acidic endonuclease inhibitor approved for treatment of influenza and is the only anti-influenza drug administered as a single oral dose. There are two classes of anti-influenza drugs available in the United States. Oseltamivir, zanamivir, and peramivir act by inhibiting viral neuraminidase preventing virus release from infected cells. Oseltamivir is available for oral administration, while 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 weeks of, 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.

Vaccination against influenza is the best way to prevent influenza, but chemoprophylaxis can be considered in individuals who have been exposed to a person with influenza (postexposure prophylaxis), in institutional outbreaks (pre-exposure prophylaxis), or in persons who are at high risk of influenza complications (pre-exposure prophylaxis). Oseltamivir and zanamivir are currently the only two NAIs indicated for prevention of influenza; 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.

Section 6 and Section 7 of this review summarize the key review issues relating to evaluation of (1) benefit and (2) risk and risk management, respectively. The key review issues were addressed by an interdisciplinary review team approach and each applicable discipline contributed to the overall team assessment and conclusions.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Baloxavir Marboxil Dosing in Pediatric Patients 1 to <12 Years of Age for Treatment and Postexposure Prophylaxis of Influenza

3.1.1.2. Design of Postexposure Prophylaxis Trial (T0834)

3.1.1.3. Insufficient Information to Evaluate PEP Efficacy Against for Influenza Type B Virus Infection

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Potential Transmission of Baloxavir Resistance in PEP Trial

3.1.2.2. Increased Frequency of Baloxavir Resistance in Pediatric Patients Compared to Adults and Adolescents

3.1.2.3. Potential for Medication Errors With Baloxavir Marboxil Granule Formulation in Pediatric Patients 1 to <12 Years of Age

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials important to the review of baloxavir marboxil for (1) treatment of acute, uncomplicated influenza in pediatric patients from >1 year of age to <12 years of age, (2) the postexposure prophylaxis of influenza in persons >1 year of age who were household contacts of persons with influenza, and (3) the use of the new 2% granule formulation.

Trial CP40563, was a Phase 3, randomized, double-blind, active-controlled trial in pediatric patients with acute, uncomplicated influenza. The results of this pivotal trial were the primary support for the safety, pharmacokinetics, and efficacy of baloxavir marboxil in pediatric patients. Additional data from three Japanese trials (1618T0822, 1705T0833, and 1813T0835) were submitted to support the evaluation of safety, resistance, and pharmacokinetics of baloxavir marboxil in pediatric patients. The Clinical Study Report and datasets were submitted for Trials T0822 and T0833. Trial T0822 was a single-arm, open-label trial of baloxavir marboxil tablets in

Japanese subjects 12 years of age and under. Trial T0833 was a single-arm, open-label trial of baloxavir marboxil 2% granules in Japanese subjects who were <12 years of age and who weighed <20 kg. Preliminary virology results for Trial T0835 were provided late in the review cycle after the study was completed but prior to completion of the Clinical Study Report. The study design of T0835 was similar to that of Trial T0833 (open-label study of baloxavir marboxil in Japanese subjects <12 years of age and who <20 kg), but higher doses of baloxavir marboxil were administered in Trial T0835 than in Trial T0833.

Trial 1703T081G (or Trial T081G) was a randomized, two-sequence, two-period crossover, open-label Phase 1 study to evaluate the bioequivalence of baloxavir marboxil (S-033188) 20-mg tablet and S-033188 granules, 2%. This trial was conducted in healthy adults. Bioequivalence of baloxavir marboxil granules for oral suspension to baloxavir marboxil tablets was evaluated in Trial T081G, and the granules were deemed bioequivalent to tablets.

Trial 1719T0834/XV41428 (Trial T0834) was a Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy of baloxavir marboxil in prevention of influenza infection in household contacts of influenza-infected index cases. The trial enrolled pediatric subjects >1 year of age as well as adults and adolescents. The safety, pharmacokinetic, and efficacy data from this trial was submitted to support the new indication for influenza postexposure prophylaxis.

The statistical reviewer reviewed the study designs and efficacy results for Trial CP40563 and Trial T0834. The clinical reviewer reviewed the study designs and safety results from Trial CP40563, Trial T0834, and the three supportive Japanese pediatric studies. The clinical reviewer worked with the clinical data scientist to identify and perform pertinent safety analyses and to present these analyses in this review. The virology reviewer reviewed data from Trials CP40563 and T0834 and the three Japanese pediatric studies, with a particular focus on amino acid substitutions conferring resistance. The clinical pharmacology reviewers reviewed data from Trials CP40563 and T0834, from the supportive Japanese trials, and from Trial T081G, the bioequivalence study.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for [Drug]

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

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

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
T081G	Healthy Japanese adult males	Phase 1 bioequivalence study comparing baloxavir marboxil tablet and 2% granule formulations Control type: None Randomization: Randomized to formulation sequence Blinding: None	Drug: Baloxavir marboxil Dosage: one 20-mg tablet or 1 gram of 2% granules Number treated: 28 Duration: (quantity and units) One dose of each formulation:	Primary: Bioequivalence between tablet and 2% granules (geometric least square ratios of C_{max} and AUC) Secondary: Safety of each formulation	28; 28	1 country (Japan); 1 center

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum plasma concentration; DB, double-blind; OL, open-label; PC, placebo-controlled; PCR, polymerase chain reaction; PK, pharmacokinetic; R, randomized; SAE, serious adverse event

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		Section 6.2, Design of Clinical Trials Intended to Demonstrate Benefit to Patients
☒	Patient-reported outcome	
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5 summarizes the pharmacologic activity, pharmacokinetics, and clinical pharmacology of baloxavir.

Table 5. General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Baloxavir is an influenza virus polymerase acidic (PA) endonuclease inhibitor.
Mechanism of action	Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity. Baloxavir inhibits the endonuclease activity of the PA protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication. The 50% inhibitory concentration (IC_{50}) values of baloxavir ranged from 1.4 to 3.1nM (n=4) for influenza A viruses and 4.5 to 8.9nM (n=3) for influenza B viruses in a PA endonuclease assay. Viruses with reduced susceptibility to baloxavir have amino acid substitutions in the PA protein.
Active moieties	Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity.
QT prolongation	At twice the expected exposure from recommended dosing, Xofluza did not prolong the QTc interval.
	General Information
Bioanalysis	A bioanalytical LC/MS/MS method was employed for quantification of baloxavir marboxil and baloxavir in human plasma samples. The method was validated according to the FDA guidance for industry, *Bioanalytical Method Validation* (May 2018). The method is deemed acceptable by the review team.
Healthy subjects versus patients	No PK differences were observed in healthy adults subjects versus influenza virus infected adult patients.

Characteristic	Drug Information
Drug exposure after a single dosage	

Table 6. Baloxavir Pharmacokinetic Parameters in Adults and Adolescents

Pharmacokinetic Parameters of Plasma Baloxavir in Adults and Adolescents[a]	Xofluza Dose 40 mg n (%)	Xofluza Dose 80 mg n (%)
AUC (ng·h/mL)	5520 (46.3)	6930 (48.6)
C_{max} (ng/mL)	68.9 (44.9)	82.5 (43.0)
C_{24} (ng/mL)	50.9 (45.8)	62.6 (45.9)
C_{72} (ng/mL)	24.2 (45.5)	30.8 (47.0)

[a] Trial T0831 summary data, mean (%CV)
Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum plasma concentration; C_{24}, concentration at 24 hours; C_{72}, concentration at 72 hours

Table 7. Baloxavir Pharmacokinetic Parameters in Pediatric Subjects Aged 1 Year to < 12 Years

Parameter [a]	Xofluza Dose for Subjects Weighing <20 kg 2 mg/kg	Xofluza Dose for Subjects Weighing 20 to 40 kg 40 mg
AUC_{inf} (ng·h/mL)	4050 (51.4)	4430 (47.1)
C_{max} (ng/mL)	109 (50.9)	83.6 (43.4)
T_{max} (h) [b]	4.12 (1-11)	5.55 (2-23.5)
C_{24} (ng/mL)	55.7 (50.4)	53.6 (41.8)
C_{72} (ng/mL)	13.2 (54.1)	18.1 (49.5)

[a] Trial CP40563 summary data, mean (%CV)
[b] Median (range)
Abbreviations: AUC_{inf}, area under the concentration time curve across the total time; C_{max}, maximum plasma concentration; C_{24}, concentration at 24 hours; C_{72}, concentration at 72 hours; T_{max}, time to maximum concentration

Maximally tolerated dosage or exposure	Not identified.
Dosage proportionality	Dose proportionality assessment indicated that baloxavir exposure increases in a dose proportional manner over the proposed dose range of 40 – 80 mg (refer to Clinical Pharmacology review of NDA 210854).
Accumulation	NA. Drug is administered as a single dose.
Bridge between to-be-marketed and clinical trial formulations	Baloxavir marboxil tablets have already been approved (October 2018). Baloxavir marboxil granules for oral suspension were used in Trial CP40563. Bioequivalence of baloxavir marboxil granules for oral suspension to baloxavir marboxil tablets was evaluated in Trial T081G. The granules were deemed bioequivalent to tablets.

Characteristic	Drug Information
	Absorption
T_{max} (median)	4 hr
Food effect (fed/fasted)	C_{max}: ↓48%, $AUC_{0\text{-}inf}$: ↓36% Meal: approximately 400 to 500 kcal including 150 kcal from fat.
	Distribution
Volume of distribution (mean, CV%)	1180 (20.8%) L
Plasma protein binding	92.9-93.9%
Drug as substrate of transporters	Both baloxavir marboxil and baloxavir are substrates of P-glycoprotein (P-gp).
	Elimination
Mass balance results (% of dosage)	Urine: 14.7 (total radioactivity); 3.3 (Baloxavir) Feces: 80.1 (total radioactivity)
Clearance (mean, CV%)	10.3 (22.5%) L/hr
Half-life (mean, CV%)	79.1 (22.4%) hr
Metabolic pathway(s)	Primary: UGT1A3. Secondary: CYP3A4
	Intrinsic Factors and Specific Populations
Body weight	Baloxavir exposure decreases as body weight increases. No clinically significant difference in exposure was observed between body weight groups following the approved recommended dosage.
Age	No clinically significant differences in the pharmacokinetics of baloxavir were observed based on age
Renal impairment	No clinically significant differences in the pharmacokinetics of baloxavir were observed in subjects with moderate hepatic impairment (Child-Pugh class B). The effect of severe hepatic impairment on baloxavir pharmacokinetics has not been evaluated.
Hepatic impairment	No clinically significant differences in the pharmacokinetics of baloxavir were observed in subjects with creatinine clearance of ≥50 mL/min. The effect of severe renal impairment on baloxavir pharmacokinetics has not been evaluated.
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	Cytochrome P450 (CYP) enzymes: Both baloxavir marboxil and baloxavir do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 and do not induce CYP1A2, CYP2B6, or CYP3A4. Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes: Both baloxavir marboxil and baloxavir do not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.
Inhibition/induction of transporter systems	Baloxavir does not inhibit organic anion transporting polypeptides (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT) 1, OAT3, multidrug and toxin extrusion (MATE) 1, or MATE2K.

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration time curve across the total time; C_{max}, maximum plasma concentration; LC/MS/MS, liquid chromatography-mass spectrometry; PK, pharmacokinetic; T_{max}, time to maximum concentration

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Antiviral Activity in Cell Culture

The antiviral activity of baloxavir has been evaluated against temporally and geographically diverse influenza virus strains (see Clinical Virology reviews).[1,2] The median half maximal effective concentration (EC_{50}) values of baloxavir were 0.73nM (n=31; range: 0.20-1.85nM) for subtype A/H1N1 strains, 0.83nM (n=33; range: 0.35-2.63nM) for subtype A/H3N2 strains, and 5.97nM (n=30; range: 2.67-14.23nM) for type B strains. Baloxavir was shown to be nonantagonistic when combined with oseltamivir in cell culture.[1]

5.1.2. Antiviral Activity in Animal Models

The antiviral activity of baloxavir marboxil following oral administration was assessed in several nonclinical therapeutic treatment studies using nonlethal and lethal mouse models of influenza virus infection, in immunocompromised mouse models of influenza virus infection, and in a nonlethal ferret model. Therapeutic treatment with baloxavir marboxil was associated with a significant reduction in lung virus titer and improved survival compared with vehicle control. In some studies, a reduction or prevention of influenza virus-induced weight loss was observed in animals dosed with baloxavir marboxil. In a combination study with oseltamivir, some dose combinations resulted in a statistically significant improvement in survival time and protection from weight loss compared with mice dosed with the individual drugs (see Clinical Virology Review[1] and Table 85 in this review).

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Pediatric Trial CP40563 for Treatment of Pediatric Subjects Aged 1 to <12 Years With Acute Uncomplicated Influenza

Prior to this submission, baloxavir was approved for treatment of acute uncomplicated influenza for patients ≥12 years of age. Prior to the conduct of Trial CP40563, the Applicant performed simulations to predict exposures associated with potential dosing regimens for subjects aged 1 to <12 years. The goal of these simulations was to identify doses for patients aged 1 to <12 years that would match exposures associated with approved doses for adults and adolescents. Based on these results, baloxavir was administered 2 mg/kg for patients weighing <20 kg or 40 mg for patients weighing ≥20 kg) in CP40563.[3] Pharmacokinetic (PK), safety, and efficacy were evaluated in Trial CP40563 and the primary consideration for approval for ages 1 to <12 years was similarity of exposures when compared to patients ≥12 years of age.

[1] See Original NDA 210854 Review(s)

[2] See NDA 210854, Supplement 001

[3] See Trial CP40563 CSR, NDA 214410, Supplement 001

The dosing regimen evaluated in CP40563 (b) (4) was found to result in similar exposures as those observed in adults for the general pediatric population 1 to <12 years of age (see Section 6.3.1).

Trial CP40563 enrolled only one Asian subject. Modeling and simulation was performed using pediatric PK data from CP40563 and Japanese pediatric studies. Administration of the recommended pediatric dosing regimen resulted in higher predicted exposures in Asian versus non-Asian subjects 1 to <12 years of age. However, exposures in Asian subjects 1 to <12 years of age were found to be within the range of safe exposures in adults (see Section 6.3.1). We agree with proposed dosing, which does not include a dose adjustment based on race.

PEP

The postexposure prophylaxis (PEP) trial, Trial T0834,[4] enrolled adults, and pediatric subjects ≥1 year of age and was conducted as a non-investigational new drug (IND) (non-IND) trial. The pediatric dosing evaluated in this study (1 mg/kg if <10 kg, 10 mg for 10 to <20 kg, 20 mg for those 20 to <40 kg, for those <40 kg, 40 mg for those ≥40 kg) differed from that being studied in the ongoing pediatric Trial CP40563. At a meeting on September 20, 2019, FDA requested that the Applicant use the same pediatric dosing in the PEP trial as in CP40563. The Applicant declined to revise the dosing stating that they expected exposures in Asian pediatric subjects who received 1 mg/kg to be comparable to exposures in non-Asians who received 2 mg/kg. FDA informed the Applicant that pediatric dosing would be a review issue.

The primary endpoint of Trial T0834 was the proportion of subjects who were infected with influenza virus (reverse transcription-polymerase chain reaction (RT-PCR) positive) and presented with fever and had at least one respiratory symptom in the period from Day 1 to Day 10. Baloxavir was found to be effective for postexposure prophylaxis when compared to placebo (see Section 6.3.2).

Patients 1 to <12 Years of Age

(b) (4)

Trial T0834 enrolled Asian pediatric and adult subjects. (b) (4) The population PK model we reviewed contained adult and pediatric treatment studies, which included non-Asian and Asian subjects.[5] The review team relied on exposures from pediatric treatment Trial CP40563 (which used the recommended pediatric dosing regimen) (b) (4)

The review team's use of data from treatment trials to predict exposures for the PEP population is supported by comparisons of PK between treatment and PEP studies. In this comparison,

[4] See Trial T0834 CSR, NDA 214410, Supplement 001

[5] See population PK report, NDA 214410, Supplement 001

overlapping exposures were observed between populations, indicating that influenza has no significant effect on the PK of baloxavir (Table 8 and Table 9).

The recommended dosing regimen results in mean C_{72} values of 24.2 ng/mL in adults 40 to 80 kg and 30.8 ng/mL in adults ≥80 kg. Among subjects 1 to <12 years of age, the lowest mean C_{72} values were observed in subjects 10 to <20 kg (11.1 ng/mL) (Table 9). Despite relatively low exposures in pediatric subjects <40 kg versus adults, efficacy was observed for the 1 to <12 years of age subgroup in Trial T0834.

Table 8. Baloxavir Exposures by Study Population in Asian Adult and Asian Adolescent Subjects ≥12 Years of Age

Dose	Study Population	No. of Subjects	AUC_{0-inf} (ng•hr/mL)	C_{24} (ng/mL)	C_{72} (ng/mL)	C_{240} (ng/mL)
40 mg	PEP	280	6060 (1830, 16900)	52.8 (19.5, 98.8)	26.4 (8.55, 51.1)	4.53 (0.92, 19.1)
	OwH	317	6350 (1270, 14900)	57.0 (15.8, 138)	27.8 (5.03, 64.4)	4.4 (0.265, 13.3)
	HR	155	6620 (1110, 14000)	59.7 (10.1, 183)	28.8 (5.39, 70.5)	4.44 (0.792, 9.37)
80 mg	PEP	17	9990 (4960, 16200)	73.6 (36.5, 120)	42.2 (22.4,68.1)	9.18 (2.72, 13.8)
	OwH	37	9730 (4980, 17500)	79.3 (39.5, 124)	42.5 (23.0, 70.1)	7.62 (3.39, 16.0)
	HR	27	9620 (4830, 19100)	77.1 (32.6, 133)	41.8 (20.4, 77.8)	7.64 (2.99, 16.2)

Source: Clinical Pharmacology Summary, NDA 214410 SN 0001, p80.
Mean (minimum-maximum) are presented and reported to 3 significant figures.
Abbreviations: AUC_{0-inf}, area under the concentration time curve over the entire time; C_{max}, maximum plasma concentration; C_{24}, concentration at 24 hours; C_{72}, concentration at 72 hours; C_{240}, concentration at 240 hours; HR, high risk subjects; OwH, otherwise healthy subjects; PEP, postexposure prophylaxis

Table 9. Baloxavir Exposures by Study Population in Asian Pediatric Subjects 1 to <12 Years of Age

Dose (mg)	Study Population	No. of Subjects	AUC_{0-inf} (ng•hr/mL)	C_{24} (ng/mL)	C_{72} (ng/mL)	C_{240} (ng/mL)
10 mg	PEP (T0834)	11	2780 (1160, 6230)	32.4 (16.0, 61.4)	11.1 (3.98, 25.4)	1.42 (0.269, 4.84)
	OwH (T0822)	31	3630 (1420, 8030)	41.5 (17.3, 72.2)	14.8 (6.11, 30.1)	1.98 (0.517, 6.12)
	OwH (T0833)	21	4260 (1200, 6460)	49.7 (12.7, 76.6)	16.9 (5.61, 25.7)	2.31 (0.622, 4.42)
20 mg	PEP (T0834)	43	3680 (2150, 5690)	41.4 (25.2, 65.2)	15.8 (9.22, 24.4)	1.83 (0.894, 3.06)
	OwH (T0822)	66	5120 (1260, 10600)	56.4 (16.1, 95.5)	21.9 (5.20, 43.6)	2.78 (0.362, 8.30)
40 mg	PEP (T0834)	4	7500 (6070, 8760)	71.9 (57.2, 93.5)	33.1 (27.1, 38.8)	4.82 (4.24, 6.25)
	OwH (T0822)	8	7190 (5290, 10500)	76.0 (51.4, 113)	32.4 (24.1, 48.4)	3.87 (2.56, 5.53)

Source: Clinical Pharmacology Summary, NDA 214410 SN 0001, p81. T0822 and T0834 dosing was 10 mg for 10 to <20 kg, 20 mg for 20 to <40 kg, and 40 mg for ≥40 kg.
Mean (minimum-maximum) are presented and reported to 3 significant figures.
Abbreviations: AUC_{0-inf}, area under the concentration time curve over the entire time; C_{max}, maximum plasma concentration; C_{24}, concentration at 24 hours; C_{72}, concentration at 72 hours; C_{240}, concentration at 240 hours; HR, high risk subjects; OwH, otherwise healthy subjects; PEP, postexposure prophylaxis

Use of Baloxavir Granules for Patients ≥12 Years of Age

Proposed labeling allows for use of baloxavir granules for patients unable to swallow tablets. Per labeling, baloxavir marboxil 2% granules are to be reconstituted with 20 mL water to make an oral suspension (2 mg/ml) before administration. In relative bioavailability Trial T081G,[6] baloxavir exposures were shown to be similar when administered as 20 mg of granules or tablets. However, the mode of administration differed compared to labeling as granules were packaged inside a sachet to be administered directly to the mouth of the subject with 200 mL of water. As granules were administered after reconstitution in Trial CP40563, (b) (4) As the biopharmaceutics group concluded that no significant bioavailability difference between the two modes of administration is expected, proposed labeling is also acceptable for use of granules in patients ≥12 years of age.

[6] See Trial T081G CSR, NDA 214410, Supplement 001

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial CP40563 (Treatment of Acute, Uncomplicated Influenza in Pediatric Patients (1 to <12 Years of Age)

6.2.1.1. Design, Trial CP40563

Trial CP40563 was a randomized, double-blind, active-controlled safety, pharmacokinetic, and effectiveness trial in otherwise healthy pediatric subjects from 1 to <12 years of age. Trial CP40563 was designed to enroll a total of 120 subjects with a minimum of 20 subjects from 1 to <5 years of age and a minimum of 40 patients from 5 to <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 provided to study sites as powder for suspension and reconstituted by study pharmacists at each site. 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 provided to study sites as granules for oral suspension; study pharmacists reconstituted the granule formulation with water. Subjects received a single oral dose of baloxavir marboxil at the study site. Baloxavir marboxil dosing was based on weight, as shown in Table 10.

Table 10. Baloxavir Marboxil Dose by Weight and Volume

Subject Weight	Baloxavir Marboxil Dose (Based on Weight)	Baloxavir Marboxil Volume Administrated
<20 kg	2 mg/kg	1 mL/kg
≥20 kg	40 mg	20 mL

Source: sNDA 214410, CSR CP40563, text page 21

Both treatment arms received matching placebos for the other drug. Subjects in the baloxavir marboxil arm received 5 days of oseltamivir placebo, and subjects in the oseltamivir received a single dose of baloxavir marboxil placebo on Day 1.

Diary cards were distributed to parents/caregivers on Day 1. Parents/caregivers were told to take and record the subject's tympanic temperature 4 times a day on Days 1 to 3, twice daily on Days 4 to 9, and once daily on Days 10 to 15. Influenza symptoms were recorded in the diary cards twice daily on Days 1 to 9 and once daily on Days 10 to 15. Influenza symptoms were monitored using the Canadian Acute Respiratory Illness and Flu Scale (CARIFS), which includes 18 total questions in three domains: symptoms (e.g., cough), function (e.g., play), and parental impact (e.g., clinginess). Each question is answered using a 4-point Likert response (no problem, minor problem, moderate problem, major problem, or don't know/NA). The CARIFS was also used in the Phase 3 trial used to support the safety and efficacy of oseltamivir in pediatric patients.

Subjects were allowed to use acetaminophen as rescue medication to treat influenza symptoms. If acetaminophen was used, the parent/caregiver was to record its use in the diary card.

6.2.1.2. Eligibility Criteria, Trial CP40563

Inclusion Criteria

Trial CP40563 enrolled pediatric patients from 1 to <12 years of age with a clinical diagnosis of influenza defined as fever ≥38°C plus either cough or nasal congestion. The time interval between the onset of influenza symptoms and screening must have been ≤48 hours. The onset was the time when body temperature was first known to exceed 37.5°C or the time when the first symptom was noticed by parent/caregiver. The parent/caregiver had to provide informed consent and had to be willing to comply with study requirements.

Exclusion Criteria

Patients who met any of the following criteria were excluded from study participation:

- 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
- Immunization with live/attenuated influenza vaccine in the 2 weeks prior to randomization
- Known HIV infection, presence of an immunosuppressive disorder, or concomitant treatment with steroids or immunosuppressant therapy
- Uncontrolled, renal, vascular, neurologic or metabolic disease; hepatitis; cirrhosis; pulmonary disease; chronic renal failure; active cancer; or history of organ transplantation
- Reached menarche (in female patients)

6.2.1.3. Statistical Analysis Plan, Trial CP40563

The primary safety endpoint was incidence, severity, and timing of adverse events (AEs), serious adverse events (SAEs), vital sign measurements, and clinical laboratory test results. The secondary efficacy endpoints were time to alleviation of influenza signs and symptoms, duration of fever, duration of symptoms, time to return to normal health and activity, frequency of influenza-related complications and proportion of patients requiring antibiotics. The primary safety analysis was based on the safety population (defined as patients who received any portion of a single dose) where patients were analyzed according to the treatment they actually received. The study was not powered for a comparison between baloxavir marboxil and oseltamivir. All comparisons were descriptive.

The efficacy analysis was based on the intent-to-treat-infected (ITTI) population. The ITTI population included all patients who received any portion of a single dose and who had a laboratory confirmation of influenza infection (RT-PCR result) from any swab sample collected at baseline or during the study. Patients were grouped based on randomized treatment. The statistical analyses of efficacy endpoints conducted by the Applicant were descriptive including Kaplan-Meier plots. In addition, the statistics reviewer used the log rank, Wilcoxon, Peto and modified Peto tests to compare the time to alleviation of signs and symptoms of influenza in

baloxavir marboxil and oseltamivir treatment groups. Further, the statistics reviewer used the Hodges-Lehmann estimator to compare the median treatment group difference in time to alleviation of signs and symptoms of influenza and restricted mean survival times to compare the difference in corresponding means.

6.2.1.4. Results of Analyses, Trial CP40563

The mean and median ages of pediatric subjects in Trial CP40563 were 7 years old with ages ranging from 1 to 11 years old. Slightly more than half of the subjects (54%) in both treatment groups were female. All subjects in the baloxavir marboxil arm and 88% of oseltamivir subjects were from the United States, with remaining oseltamivir subjects coming from Eastern Europe. The majority of subjects (89%) were white, with the second most prevalent race comprised of black/African Americans (3% of baloxavir marboxil-treated subjects and 9% of oseltamivir-treated subjects), with an additional 4% of baloxavir marboxil belonging to other/multiple races and another 4% of baloxavir marboxil-treated subjects having an unknown racial status. The remaining baloxavir marboxil-treated subject was Asian. Slightly less than half (45%) of the subjects were Hispanic/Latino, and approximately half of the subjects (51%) received the influenza vaccine in the last 12 months.

Table 11. Baseline Demographic and Clinical Characteristics, Trial CP40563 (ITTI Population)

Characteristics	Baloxavir Marboxil 2 mg/kg or 40 mg N=80	Active Control (Oseltamivir) 30-75 mg N=43	Total N=123
Sex, n (%)			
Male	36 (46)	20 (46)	56 (46)
Female	44 (54)	23 (54)	67 (54)
Age, years			
Mean (SD)	6.7 (2.6)	6.7 (3.0)	6.7 (2.7)
Median (min, max)	7 (1, 11)	7 (1, 11)	7 (1,11)
Age groups (years), n (%)			
<5	20 (25)	10 (23)	30 (24)
5 to 12	60 (75)	33 (77)	93 (76)
Race, n (%)			
White	72 (89)	38 (88)	110 (89)
Asian	1 (1)	0	1 (1)
Black/African American	2 (3)	4 (9)	6 (5)
Other/Multiple	3 (4)	1 (2)	4 (3)
Unknown	2 (3)	0	2 (2)
Ethnicity, n (%)			
Hispanic	37 (46)	19 (44)	56 (45)
Non-Hispanic	43 (54)	24 (56)	67 (54)
Country of participation, n (%)			
United States	80 (100)	38 (88)	118 (96)
Other	0	5 (12)	5 (4)
Clinical characteristics, n (%)			
Received influenza vaccine (12 months)	41 (51)	22 (51)	63 (51)

Source: Statistics Reviewer's analysis
Abbreviations: ITTI, intent-to-treat-infected; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

The majority of pediatric subjects were influenza virus subtype A/H3 (66%) while approximately one-quarter of the subjects were influenza virus subtype A/H1N1 (24%). There were only a few

subjects (6%) who were influenza virus subtype B while 5% of baloxavir marboxil-treated subjects (and none of the oseltamivir-treated subjects) had unknown influenza virus subtypes.

Table 12. Influenza Virus Subtype at Baseline, Trial CP40563

Influenza Virus Subtype	Baloxavir N=75 n (%)	Oseltamivir N=40 n (%)	Total N=115 n (%)
A/H1N1	18 (24)	10 (25)	28 (24)
A/H3N2	47 (63)	28 (70)	75 (66)
B	5 (7)	2 (5)	7 (6)
H1N1 and B	1 (1)	0	1 (1)
Unknown	4 (5)	0	4 (3)

Source: Statistics Reviewer's analysis

Out of 199 subjects screened, 23 (12%) were screening failures. According to the Applicant, screening failures were mainly not randomized due to parent/caregiver/patient not willing/able to comply with study requirements.

Table 13. Patient Screening and Randomization, Trial CP40563

Disposition	No. Recorded
No. patients screened	199
No. patients not randomized	23
No. screening failures	23/199 (11.6%)
No. patients randomized	176

Source: Figure 2 of the Clinical Study Report

Patient disposition in Trial CP40563 is shown in Table 14. A total of 115 (98%) of the 117 subjects randomized to baloxavir marboxil and 58 (98%) of the 59 subjects randomized to oseltamivir received at least one dose of study treatment. Both safety and intent-to-treat (ITT) populations included all patients who received any portion of a single dose regardless of whether or not they had any follow-up visits. According to the Applicant, the ITTI population included all patients who received any portion of a single dose and who had a laboratory confirmation of influenza infection based on RT-PCR results from any swab sample collected at baseline or during the study. A total of 81 (69%) of the subjects randomized to baloxavir marboxil and 43 (73%) of the subjects randomized to oseltamivir were in the ITTI population.

The safety population had same number and percentage of subjects as the ITT population. Five (4%) subjects randomized to baloxavir marboxil and two (3%) subjects randomized to oseltamivir discontinued study drug and discontinued from the study. Discontinuation of the study drug was primarily due to adverse events in the baloxavir arm and withdrawal by the subject in both treatment arms. Discontinuation from the study was primarily due to withdrawal by the subject in both treatment arms. One subject who discontinued from the study due to "other reasons" was randomized in error.

Table 14. Patient Disposition, Trial CP40563

Disposition Category	Baloxavir Marboxil N=117 n (%)	Oseltamivir N=59 n (%)
Patients randomized	117 (100)	59 (100)
ITT population	115 (98)	58 (98)
ITTI population	81 (69)	43 (73)
Safety population	115 (98)	58 (98)
Discontinued study drug	5 (4)	2 (3)
Adverse event	2 (2)	0 (0)
Withdrawal by subject	2 (2)	2 (3)
Other	1 (1)	0 (0)
Discontinued study	5 (4)	2 (3)
Death	0 (0)	0 (0)
Lost to follow-up	0 (0)	0 (0)
Withdrawal by subject	3 (3)	2 (3)
Physician decision	1 (1)	0 (0)
Protocol deviation	0 (0)	0 (0)
Other[1]	1 (1)	0 (0)

Source: Tables 5, 6, and 7 of the Clinical Study Report
[1] Other reason was due to one patient being randomized in error
Abbreviation: ITT, intent-to-treat; ITTI, intent-to-treat-infected; N, number of subjects; n, number of subjects with at least one event

According to the Applicant, major protocol deviations were those that had an impact on patient safety, eligibility, study procedures, study assessments and data integrity and occurred in 21 (18%) of the subjects randomized to baloxavir marboxil and eight (14%) of the subjects randomized to oseltamivir. The Applicant stated that the majority of the major protocol deviations were due to incorrect study drug dosing and schedule or receiving prohibited medications mainly related to ibuprofen use for fever control. The Applicant stated that the second most common deviations were procedural; for example, two patients in the baloxavir marboxil group did not have blood tests for safety assessments during the study (at baseline or Day 6) due to failure of the team to obtain blood samples. Table 15 summarizes the major protocol deviations in Trial CP40563.

Table 15. Major Protocol Deviations, Trial CP40563 (Randomized Patients)

Protocol Deviation	Baloxavir Marboxil N=117 n (%)	Oseltamivir N=59 n (%)	Total N=176 n (%)
Total number of subjects with at least one major protocol deviation	21 (18)	8 (14)	29 (16)
Total number of subjects with at least one major protocol deviation involving medication	15 (13)	7 (12)	22 (13)
Total number of subjects with at least one major procedural protocol deviation	5 (4)	1 (2)	6 (3)

Source: Table 7 of the Clinical Study Report

As shown in Table 16, the median time to alleviation of influenza signs and symptoms was 138 hours in the baloxavir marboxil arm and 150 hours in the oseltamivir arm. However there was a large degree of overlap between the 95% confidence intervals (CIs) in the two treatment groups. The Hodges-Lehmann estimate of the median difference for the primary efficacy endpoint between the two treatment groups was 13 hours in favor of baloxavir marboxil, with

95% CI ranging from -18 hours in favor of oseltamivir to +44 hours in favor of baloxavir marboxil.

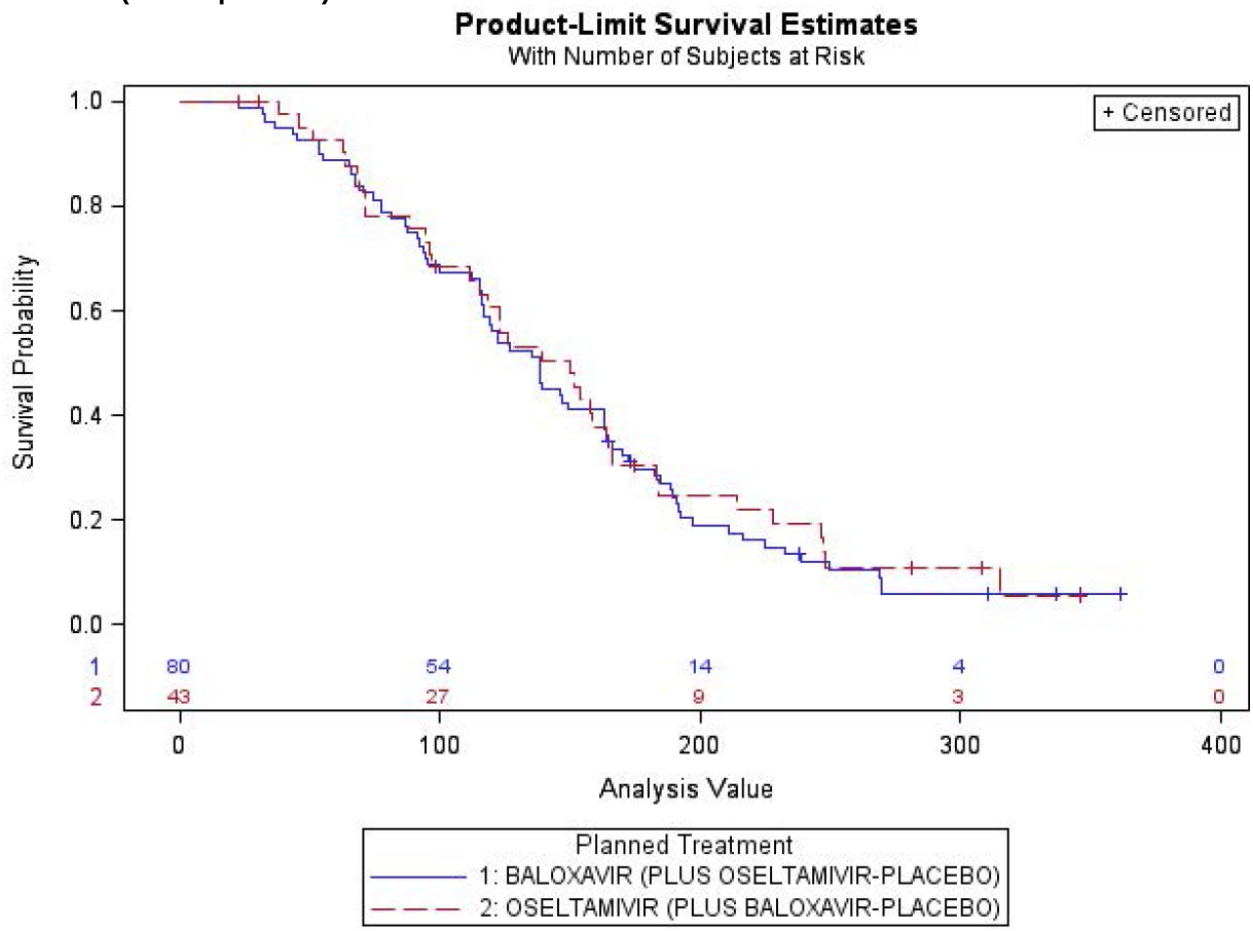
Table 16. Median Time to Alleviation of Influenza Signs and Symptoms, Trial CP40563 (ITTI Population)

Treatment Group	N	Median Hours (95% CI)
Baloxavir marboxil	80	138 (116, 163)
Oseltamivir	43	150 (112, 164)
Oseltamivir - Baloxavir		13[1] (-18, 44)

Source: Statistics Reviewer's analysis
[1] Hodges-Lehmann estimator and asymptotic 95% confidence interval
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected

As shown in Figure 1, baloxavir and oseltamivir treatment groups had similar time to alleviation of influenza signs and symptoms. There were no statistically significant differences between the two treatment groups using the unstratified log rank, Wilcoxon, Peto or modified Peto tests.

Figure 1. Kaplan-Meier Plot for the Time to Alleviation of Influenza Signs and Symptoms, Trial CP40563 (ITTI Population)



Source: Statistics Reviewer's analysis
Two-sided p-value for log-rank test =0.68, two-sided p-value for Wilcoxon, Peto and modified Peto =0.74
Abbreviations: ITTI, intent-to-treat-infected

6.2.2. Trial T0834 (Postexposure Prophylaxis of Influenza in Household Contacts)

6.2.2.1. Design, Trial T0834

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 with influenza-like symptoms were identified, and nasopharyngeal swabs were collected from these patients. The swabs were tested for influenza A or B using rapid influenza diagnostic tests. A nasopharyngeal swab was also collected from index patients and sent for virus typing and subtyping and for influenza viral titer. After influenza infection was confirmed in the index case, they were treated for influenza according to the local standard of care. Limited demographic information was collected for each index case: date of birth, sex, household size, smoking habits, influenza vaccination status within the previous 6 months, and time of influenza onset.

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. A single oral dose of study drug was administered at the study site on Day 1. In subjects 12 years of age and older, baloxavir marboxil was dosed as recommended for treatment of acute uncomplicated influenza in adults and adolescents ≥12 years of age. Subjects who weighed 40 kg to <80 kg received a single 40-mg dose, and subjects who weighed ≥80 kg received a single oral 80-mg dose of baloxavir marboxil. The baloxavir marboxil dose and formulation administered to subjects younger than 12 years of age are shown in Table 17.

Table 17. Dosage and Formulation of Baloxavir Marboxil in Subjects (Household Contacts) <12 Years of Age

Subject Weight	Baloxavir Marboxil Dose	Baloxavir Marboxil Formulation
<10 kg	1 mg/kg	2% granules
10-20 kg	10 mg	2% granules
20 to <40 kg	20 mg	Tablet
≥40 kg	40 mg	Tablet

Source: NDA 214410, CSR 1719T0834, Table 9-1, page 33

The doses used in subjects <12 years of age differ from those used in Trial CP40563 (b) (4) Trial T0834 was conducted in Japan, and baloxavir exposures are higher in Asians compared to non-Asians. Therefore, the Applicant used doses recommended in the Japanese product labeling for baloxavir marboxil (see Section 6.1).

Baloxavir marboxil was administered as a 20-mg tablet in subjects ≥12 years of age and as 2% granules in subjects <12 years weighing <20 kg of age; Shionogi and Company manufactured matching placebos for both the tablet and the granules.

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 (morning and evening) for the 10 days following study drug administration. Axillary temperature

was taken twice daily and entered into the electronic 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 electronic diary card. Reporting of influenza symptoms in subjects <12 years of age was limited to fever, cough and nasal discharge/nasal congestion.

6.2.2.2. Eligibility Criteria, Trial T0834

The trial had separate entry criteria for index patients and household contacts (study subjects); index patients had inclusion criteria only.

Index Patients

Inclusion Criteria

- Diagnosed with influenza by positive rapid influenza diagnostic test
- Onset of symptoms ≤48 hours, onset of symptoms defined as the time when temperature is first ≥37.5°C
- First member of their household with influenza virus infection in the 2018–19 influenza season
- Weight ≥10 kg at screening

Household Contacts (Study Subjects)

Inclusion Criteria

- Had lived with the index patient for ≥48 hours prior to providing informed consent
- Judged by investigator not to have influenza by clinical criteria:
  - Body temperature <37°C at screening
  - No influenza-like symptoms (cough, sore throat, headache, nasal discharge/congestion, feverishness or chills, muscle or joint pain, or fatigue)
- Women of child-bearing potential had to agree to use a highly effective method of contraception for 3 months after study drug administration

Exclusion Criteria

- Diagnosed with influenza during the 2018–19 influenza season
- Household member other than the index patient who was either diagnosed with influenza or strongly suspected to have had influenza during the 2018–19 influenza season
- Household member other than the index patient with influenza-like symptoms (body temperature >37.5°C, cough, sore throat, headache, nasal discharge/congestion, feverishness or chills, muscle or joint pain, or fatigue)
- Unable to live with the index patient from screening until Day 10
- Any underlying disease that required systemic or nasal treatment with antipyretics/analgesics, corticosteroids, or immunosuppressive agents

- Immunocompromise
- Receipt of an anti-influenza antiviral within the 30 days prior to screening
- Underlying disease with symptoms that met Grade 3 or higher Common Terminology Criteria for Adverse Events
- Pregnancy or lactation

Pediatric subjects of any age (including from birth) could be enrolled in this trial; however, no pediatric subjects <1 year of age were enrolled.

6.2.2.3. Statistical Analysis Plan, Trial T0834

The primary efficacy endpoint was the proportion of subjects who were infected with influenza virus (RT-PCR positive), and presented with fever and at least one respiratory symptom in the period from Day 1 to Day 10. Influenza-infected (RT-PCR positive) subjects with fever and at least one respiratory symptom were defined as subjects having a body temperature (axillary) of ≥37.5°C, having symptom of cough" and/or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe," assessed in the subject diary, and influenza virus positivity assessed by RT-PCR.

The modified intent-to-treat (mITT) population was the primary efficacy analysis population in this study. The mITT population included all randomized subjects who received the study drug and had postbaseline efficacy data available among household members of influenza-infected index patients. The mITT population was analyzed as randomized.

The per protocol set was used for supplementary analyses of the primary analysis of efficacy by the Applicant. The per protocol set included all subjects who were included in the mITT population and did not meet any of the following conditions:

- Subjects with any protocol inclusion or exclusion violations
- Subjects with study procedure violations

The safety analysis population included all randomized subjects who received at least one dose of the study drug. The subject who received the study drug without enrollment in the Interactive Web Response System was included in the safety analysis population. Subjects were analyzed according to the treatment that they actually received, rather than the treatment to which they were randomized, i.e., subjects who received baloxavir marboxil was included in the baloxavir marboxil group even if they were randomized to the placebo group.

All statistical tests were performed at a two-sided significance level of 0.05 unless stated otherwise.

The primary efficacy analysis used the relative risk (risk ratio) of the baloxavir marboxil group versus the placebo group, its 95% CI and p-value which were calculated using the modified Poisson regression approach (i.e., Poisson regression with sandwich estimator as a robust error variance) of a binary response (whether all of the following were confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment. The primary efficacy analysis was adjusted for the randomization strata (time from onset of influenza virus infection of index to informed consent of subject (<24 versus ≥24 hours), treatment given to index patient (baloxavir versus other), and age of subject (continuous). A p-

value was calculated for the null hypothesis that the true relative risk was one. The statistics reviewer adjusted for the correlation between contact cases within households (each household having one index patient) while the Applicant did not make this adjustment. The Applicant analyzed the contact cases as if they had multiple correlated observations. However there was only one observation per contact case so the Applicant's approach did not adjust for the correlation between multiple contact cases within a household.

Secondary efficacy analyses for the primary efficacy endpoint in the mITT population included the length of time from the study treatment to the first time point when fever, at least one respiratory symptom (cough and/or nasal discharge/nasal congestion) and influenza virus infection were all confirmed was plotted for each treatment group using the Kaplan-Meier method. Restricted mean survival time (RMST) up to Day 10 was estimated for each treatment group along with the difference between RMST in the two treatment groups. RMST is a measurement of the average survival from time 0 to a specified time point (e.g., 10 days) which is equivalent to the area under the Kaplan-Meier curve from the beginning of the study through that time point.

6.2.2.4. Results of Analyses, Trial T0834

Demographic characteristics for all household contact cases (subjects) are summarized by treatment group in the following table. The mean age in both treatment groups was 34 and ranged from age 1 to 87 years. Of the 749 subjects in Trial T0834, 71 (19%) in each treatment arm were <12 years of age; 303 subjects (81%) in the baloxavir marboxil arm and 304 (81%) in the placebo arm were ≥12 years of age. Unlike index patients where the majority were <10 years of age, only 14% of household contact cases were <10 years of age, while the majority of household contact cases were between 30 and 49 years of age and the proportion of contact cases who were 65 years of age and older was only 3%. Unlike index patients, over 75% of household contacts were females and a larger percentage (10%) were current smokers. Thirteen percent of household contacts were at high risk for influenza complications, while slightly more than 30% of the household contacts had received the influenza vaccine within the prior 6 months.

Table 18. Baseline Demographic and Clinical Characteristics of Subjects, Trial T0834 (mITT Population)

Characteristic	Baloxavir Marboxil N=374	Placebo N=375	Total N=749
Sex, n (%)			
Male	77 (21)	85 (23)	162 (22)
Female	297 (79)	290 (77)	587 (78)
Age, years			
Mean (SD)	33.5 (15.8)	33.6 (17.0)	33.5 (16.4)
Median (min, max)	37 (1, 87)	38 (1, 85)	38 (1, 87)
Age groups (years), n (%)			
<10	55 (15)	52 (14)	107 (14)
≥10 to <20	30 (8)	42 (11)	72 (10)
≥20 to <30	20 (5)	14 (4)	34 (5)
≥30 to <40	108 (29)	108 (29)	216 (29)
≥40 to <50	131 (35)	130 (35)	261 (35)
≥50 to <65	22 (6)	14 (4)	36 (5)
≥65	8 (2)	15 (4)	23 (3)

Characteristic	Baloxavir Marboxil N=374	Placebo N=375	Total N=749
Race, n (%)			
Asian	374 (100)	375 (100)	749 (100)
Ethnicity, n (%)			
Non-Hispanic	374 (100)	375 (100)	749 (100)
Country of participation, n (%)			
Japan	374 (100)	375 (100)	749 (100)
Clinical characteristics, n (%)			
Current smoker	38 (10)	37 (10)	75 (10)
High risk for influenza complications	46 (12)	52 (14)	98 (13)
Influenza vaccine in prior 6 months	131 (35)	124 (33)	255 (34)

Source: Statistics Reviewer's analysis
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

As shown in Table 19, there were 545 index patients in the PEP trial. The majority of households (72%) had only one household contact randomized, followed by households with two household contacts (20%), three household contacts (7%) and four or more household contacts (2%).

Table 19. Number of Randomized Household Contacts (Subjects) Enrolled for Each Index Patient, Trial T0834

Number of Household Contacts Randomized	Number of Index Patients With Randomized Study Subjects N=545 n (%)
1	393 (72)
2	108 (20)
3	36 (7)
≥4	8 (2)

Source: Clinical and Statistics Reviewer's analysis

As shown in the following table, the majority of household contacts were parents of the index patients (approximately 70%), while another 22 to 24% were siblings. Only 4% of household contacts were spouses of index patients and only 2% were children of index patients.

Table 20. Household Contact Relationship to Index Patient, Trial T0834

Relationship	Baloxavir Marboxil N=374 n (%)	Placebo N=375 n (%)
Parent	267 (71)	252 (67)
Sibling	83 (22)	89 (24)
Child	5 (1)	10 (3)
Spouse	13 (4)	14 (4)
Other	6 (2)	10 (3)

Source: Statistics Reviewer's analysis

As determined by RT-PCR, the majority of index patients were infected with A/H3N2 (49%) and A/H1N1 (47%) virus, while only 2% of the index patients had mixed influenza virus type/subtype infections, only 1% of the index patients were infected with type B virus (Table 21). One percent were RT-PCR-negative for influenza virus.

Table 21. Influenza Virus Subtype by RT-PCR in Index Patients at Baseline, Trial T0834

Influenza Virus Subtype	Number of Patients at Baseline N=545 n (%)
A/H1N1	255 (47)
A/H3N2	265 (49)
A/not determined	1 (<1)
B	5 (1)
Mixed infection	12 (2)
Influenza virus negative	7 (1)

Source: Statistics Reviewer's analysis
Abbreviations: RT-PCR, reverse transcription-polymerase chain reaction

As shown in Table 22, the percentage of household contacts with high risk factors for influenza complications at baseline appeared to be low and comparable in the two treatment arms. Subjects at most risk appeared to be children <5 years of age, followed by subjects with asthma and adults 65 years of age and older.

Table 22. Subjects With High Risk Conditions by Treatment Arm, Trial T0834

High Risk Condition	Baloxavir Marboxil N=374 n (%)	Placebo N=375 n (%)
Asthma	12 (3)	12 (3)
Endocrine disorder	5 (1)	5 (1)
Neurological or neurodevelopment disorder	1 (<1)	0
Age ≥65 years	8 (2)	15 (4)
Blood disorders	3 (1)	1 (<1)
Metabolic disorders	3 (1)	3 (1)
Children <5 years of age	14 (4)	20 (5)
Renal disorders	0	1 (<1)
Liver disorders	6 (2)	5 (1)

Source: Results from Table 14.1.6.1 of the Clinical Study Report

Patient Screening and Randomization

In their August 25, 2020 response to our query about missing information about the number of screened subjects for the PEP study, the Applicant noted that of 760 patients screened, 752 subjects were randomized (375 in the baloxavir marboxil group and 377 in the placebo group).[7] The number of screened subjects was not included in the CSR; this was 760 subjects, including nine who were rescreened. Table 23 shows patient screening and randomization for Trial T0834.

Table 23. Patient Screening and Randomization, Trial T0834

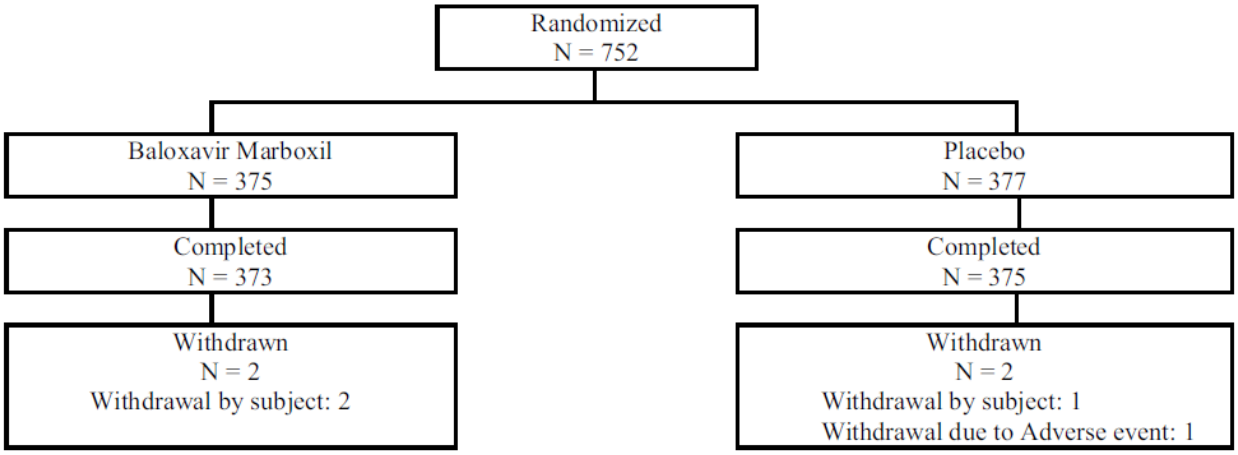
Disposition	No. Recorded
No. patients screened	760
No. patients rescreened	9
No. patients not randomized	8
No. screening failures[1]	8 (1.1%)
No. patients randomized	752

Source: Applicant's August 25, 2020 response to IR and Figure 10-1 of the Clinical Study Report
[1] No. patients screened-No. patients randomized

[7] See section 10.1 of the clinical study report (CSR)

As shown in Figure 2, 752 household contacts were randomized as subjects in addition to 545 index patients in 545 households. There were 375 subjects randomized to the baloxavir marboxil arm and 377 subjects randomized to the placebo arm. There were only two (0.5%) subjects in each treatment arm who withdrew from the study prior to completion with only one of these subjects withdrawing due to an adverse event.

Figure 2. Subject Disposition (All Randomized Subjects), Trial T0834



Source: Figure 10-1 of the Clinical Study Report

Patient disposition in Trial T0834 is shown in Table 24.

Table 24. Disposition of Subjects (Household Contacts), Trial T0834

Disposition Category	Baloxavir Marboxil N=375 n (%)	Placebo N=377 n (%)
Patients randomized	375 (100)	377 (100)
ITT/mITT population	374 (99.7)	375 (99.5)
Per protocol population	370 (98.7)	371 (98.4)
Safety population	374 (99.7)	375 (99.5)
Discontinued study drug	0	0
Adverse event	0	0
Lack of efficacy	0	0
Discontinued study	2 (0.5)	2 (0.5)
Death	0	0
Lost to follow-up	0	0
Withdrawal by subject	2 (0.5)	1 (0.3)
Physician decision	0	0
Protocol deviation	0	0
Adverse event	0	1 (0.3)

Source: Table 14.1.2, and Synopsis of the Clinical Study Report
Abbreviation: ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of subjects; n, number of subjects with at least one event

As shown in Table 25, for household contact subjects in households where index patients were RT-PCR positive for A/H1N1 there were 19% of the 180 placebo subjects who were RT-PCR positive for A/H1N1 by study Day 10 compared to only 6% of the 180 baloxavir marboxil subjects. For household contact subjects in households where index patients were RT-PCR positive for A/H3N2 there were 30% of the 183 placebo subjects who were RT-PCR-positive for A/H3N2 virus by Day 10 compared to only 11% of the 181 baloxavir marboxil subjects. None of the household contact subjects were RT-PCR positive for subtype B.

Table 25. Influenza Virus Subtype by RT-PCR, Trial T0834

	Household Contacts (Subjects)	
Influenza Virus Subtype	Baloxavir Marboxil n/N (%) by Day 10	Placebo n/N (%) by Day 10
A/H1N1	11/176 (6%)	34/180 (19%)
A/H3N2	20/181 (11%)	55/183 (30%)
B	0/2	0/3

Source: Statistics Reviewer's analysis
Abbreviations: RT-PCR, reverse transcription-polymerase chain reaction

The primary efficacy analysis comparing the percentage of household contact cases in the mITT population who were infected with influenza virus (RT-PCR-positive) with fever and at least one respiratory symptom from Day 1 to Day 10 showed that the number and percentage of subjects who met this definition (symptomatic, RT-PCR-positive influenza) was significantly lower for subjects in the baloxavir marboxil treatment group (1.9%) compared to subjects in the placebo arm (13.6%, p<0.0001). In addition to a highly significant p-value the relative risk of occurrence of the primary efficacy endpoint in baloxavir marboxil compared to placebo household contact subjects was only 0.14 with a 95% confidence interval ranging from 0.06 to 0.30. Similar results were obtained for the odds ratio and using the Mantel-Haenszel approach which does not adjust for the correlation of contact cases within the same household.

The results of the primary efficacy analysis are shown in Table 26.

Table 26. Primary Efficacy Analysis, Trial T0834

Treatment Group	Baloxavir Marboxil	Placebo
Number of subjects meeting the primary efficacy endpoint/ number of contact cases	7/374 (1.9%)	51/375 (13.6%)
Exact 95% CI	0.8, 3.8	10.3, 17.5
P-value placebo vs. baloxavir	<0.0001	

Source: Statistics Reviewer's analysis
P-Value obtained for primary GEE analysis using the modified Poisson regression approach with a log link for a binary response, adjusted for time from onset of influenza virus infection of index to informed consent of subject (<24 versus ≥24 hours), treatment given to index patient (baloxavir versus other), and age of subject (continuous)
Abbreviations: CI, confidence interval; GEE, generalized estimating equation

Unlike the statistics reviewer, the Applicant adjusted for household contact (subject) instead of index patient, where the Applicant's approach did not adjust for the correlation between contact cases within households in the analysis using generalized estimating equations (Applicant's relative risk =0.1378 instead of reviewer's 0.1359, Applicant's 95% CI =0.0633 to 0.2999 instead of reviewer's 95% CI =0.0617 to 0.2992). However, after rounding off the relative risk and 95% CI to two significant decimal places, the results obtained by the Applicant and the statistics reviewer were the same. They were also the same to two significant decimals when instead of using continuous age as a stratification variable, age group was dichotomized into <12 years old and subjects 12 years of age and older. Additional statistical analyses of the primary endpoint in this trial are shown in Table 27.

Table 27. Statistical Analyses of Primary Endpoint, Trial T0834

Measure of Association	Mantel-Haenszel	Generalized Estimating Equations
Odds ratio	0.11	0.12
95% CI	0.04, 0.29	0.05, 0.27
Relative risk	0.14	0.14
95% CI	0.05, 0.33	0.06, 0.30

Source: Statistics Reviewer's analysis
Relative risks obtained for primary GEE analysis using the modified Poisson regression approach with a log link for a binary response, adjusted for time from onset of influenza virus infection of index to informed consent of subject (<24 versus ≥24 hours), treatment given to index patient (baloxavir versus other), and age of subject (continuous).
Abbreviations: CI, confidence interval; GEE, generalized estimating equation

Subgroup Analysis of Subjects Age 12 and Older

As the vast majority of subjects were adults, the proportion of subjects ≥12 years of age who met the primary endpoint (PCR+ symptomatic influenza) was similar to the results for all subjects and significantly lower in those who received baloxavir (1%) compared to those who received placebo (13%, p<0.0001). Because baloxavir marboxil will not be approved in patients <12 years of age, these are the primary efficacy analysis results that are included in the label. See Section 16.2 for the subgroup analysis in subjects <12 years of age.

Table 28. Primary Efficacy Endpoint for Subjects Age 12 and Older, Trial T0834

Subjects ≥12 Years Old	Baloxavir Marboxil N=303	Placebo N=304
Subjects with RT-PCR-confirmed influenza, n (%)	4 (1)	40 (13)
95% CI	<1, 3	10, 17
P-value placebo vs. baloxavir	<0.0001	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; RT-PCR, reverse transcription-polymerase chain reaction

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Baloxavir Marboxil Dosing in Pediatric Patients 1 to <12 Years of Age for Treatment and Postexposure Prophylaxis of Influenza

Issue

(b) (4)

Despite significantly higher exposures in Asian versus non-Asian subjects 1 to <12 years of age, proposed labeling contains no dose adjustment based on race. In addition, inspections of analytical sites are typically conducted for studies such as CP40563 where PK data are pivotal for approval. However, an analytical site inspection was not feasible.

Background

Prior to this submission, baloxavir was approved for treatment of acute uncomplicated influenza for patients ≥12 years of age. Trial CP40563 enrolled pediatric subjects aged 1 to <12 years with

acute uncomplicated influenza and evaluated PK, safety and efficacy of baloxavir. The basis of approval for acute uncomplicated influenza in patients aged 1 to <12 years is extrapolation of efficacy from patients aged ≥12 years, i.e., demonstrating similarity of exposures in subjects 1 to <12 years of age versus ≥12 years of age. Additional information supporting approval are the efficacy results from Trial CP40563.

Analytical site inspections are conducted for studies such as CP40563 where PK data are pivotal to support approval. Due to the COVID-19 pandemic, OSIS could not perform an analytical inspection.[8]

Assessment

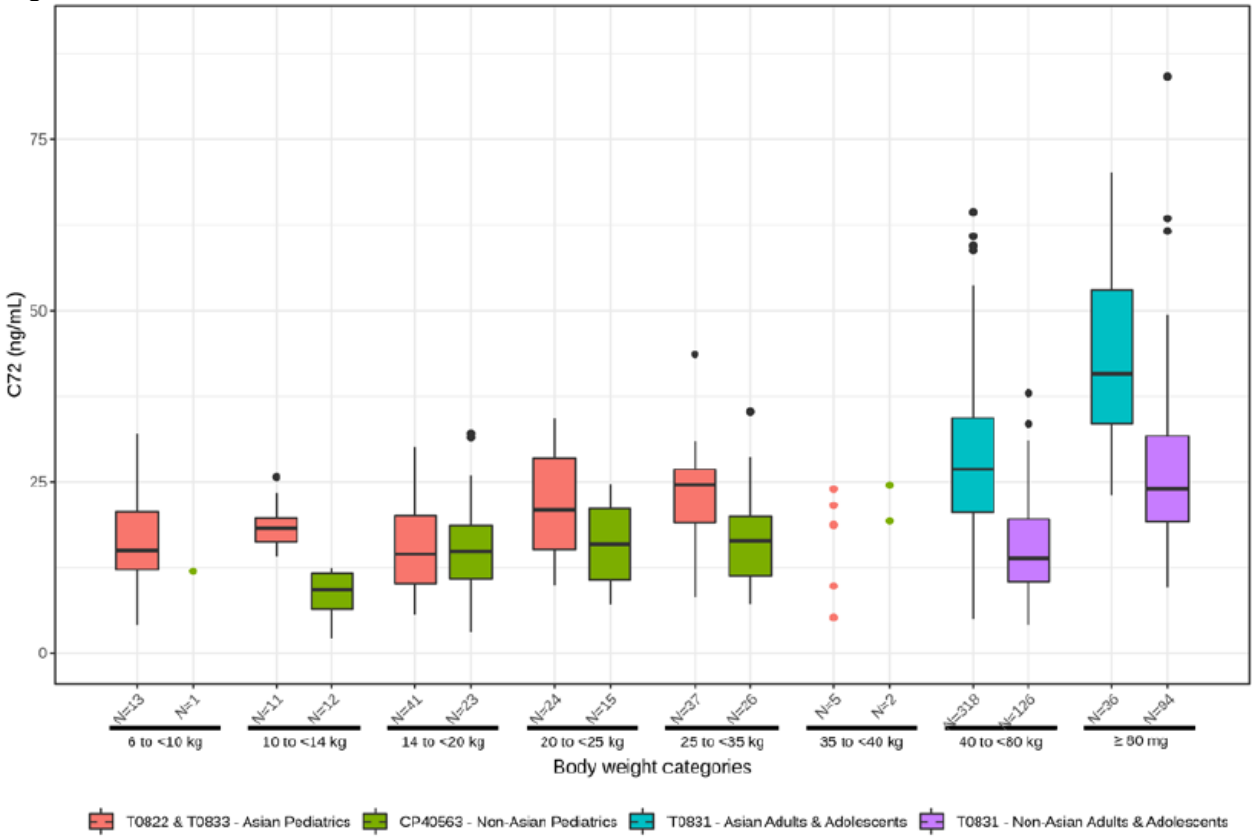
Trial CP40563 evaluated the PK and efficacy of baloxavir versus oseltamivir in otherwise healthy pediatric patients 1 to <12 years of age with influenza-like symptoms. The baloxavir arm enrolled 107 subjects. Mean (range) ages and weights of subjects enrolled in the baloxavir arm were 6.1 (1 to 11) years and 26 (7.6 to 64) kg. The study population in the baloxavir arm by race was 85% white, 5% black, 1% Asian, 1% American Indian or Alaska Native, and 10% multiple or unknown. The study population by ethnicity was 45% Hispanic and 55% non-Hispanic. Subjects in the baloxavir arm received either a single dose of 2 mg/kg if weight was <20 kg, or 40 mg if weight was ≥20 kg as granules for oral suspension. (b) (4) PK samples were collected through 216 hours postdose from a total of 107 patients, including 19 patients with intensive and 88 patients with sparse PK sampling.

Exposures generally overlapped between subjects in Trial CP40563 versus adults/adolescents. However, C_{72} values within the 10 to <14 kg weight group were 45% lower in Trial CP40563 versus adults/adolescents (Figure 3).[9] C_{72} values are of interest due to the observation of viral rebound observed at or after Day 3 postdose. As no association was identified between baloxavir exposure and development of resistance in Trial CP40563, C_{72} values in Trial CP40563 were acceptable. While overlapping exposures in Trial CP40563 versus adults/adolescents are supportive of proposed doses for the general population aged 1 to <12 years, baloxavir marboxil will not be approved in this age group due to the high incidence of baloxavir resistance-associated amino acid substitutions in comparison to that observed in adults and adolescents ≥12 years of age.

[8] See NDA 210854, OSIS memo dated April 6, 2020

[9] See Response to IR, NDA 214410, Supplement 018, p13-16

Figure 3. Observed Baloxavir C_{72} Values in Pediatrics vs. Adults/Adolescents



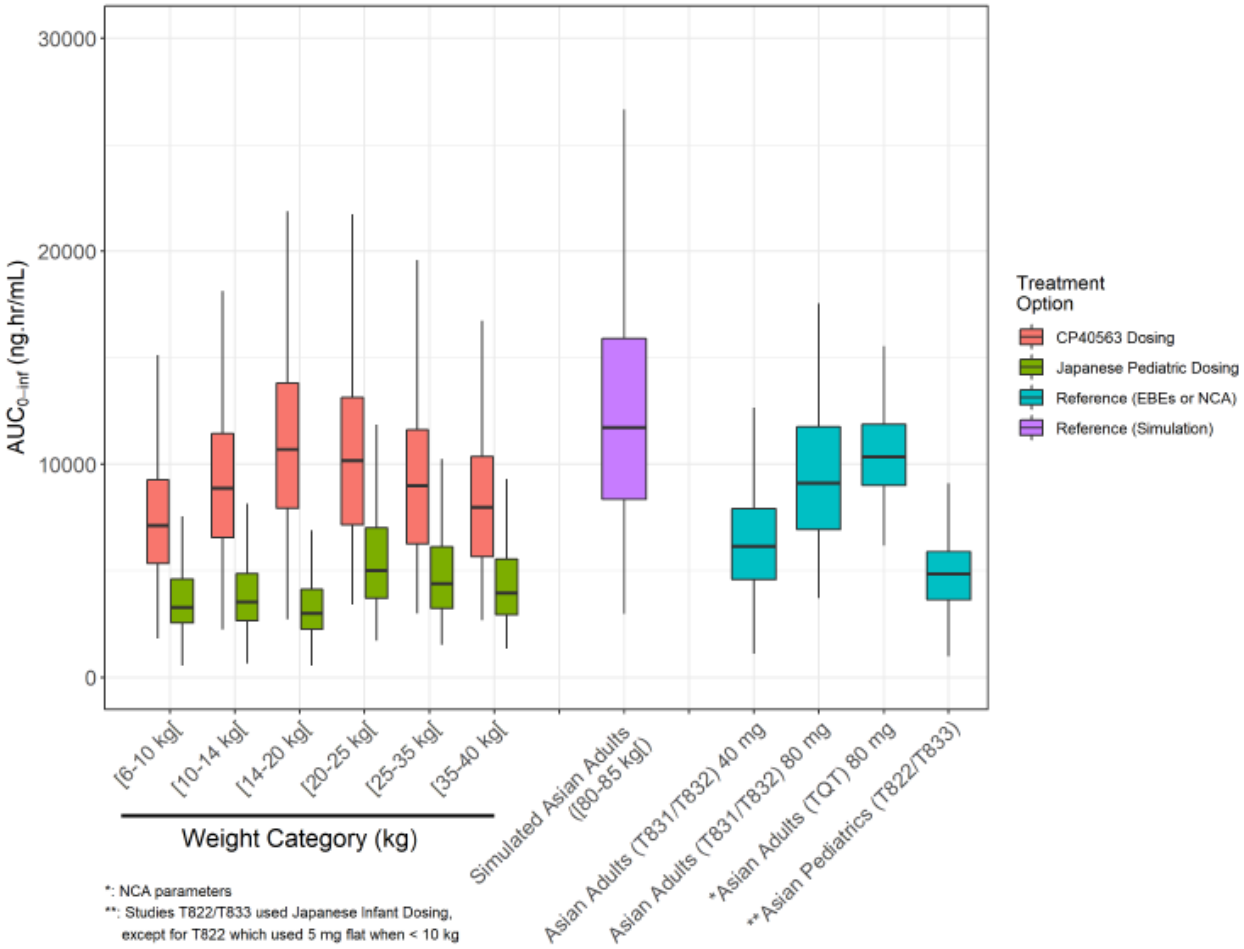
Source: Response to IR, NDA 214410 SN 0018, p16.
T0831: Approved adult/adolescent dosing was administered (T0831 CSR, NDA 214410 SN 0001, p10).
T0822 and T0833: Exposures in Asian subjects are not relevant, (b) (4)
Dosing in these studies was 0.5-1 mg/kg for those <40 kg and 40 mg for those ≥40 kg (b) (4) (b) (4)
Boxplot definitions: Median values are designated by the black lines in the center of the boxes. Boxes indicate the interquartile range (IQR, Q1–Q3). Whiskers extends from the hinge of the box to the smallest/highest value no further than 1.5*IQR from the hinge. For categories including less than 10 patients, a dot representation was used.
Abbreviations: C_{72}, concentration at 72 hours

(b) (4) However, as seen in Trial 1601T0831 (Trial T0831) in Figure 3, race (Asian versus non-Asian) significantly affects exposures. Pediatric Trials T0822 and T0833 enrolling Asian subjects administered 1 mg/kg to those weighing 5 to <10 kg; 10 mg to those 10 to <20 kg; 20 mg to those 20 to <40 kg; and 40 mg to those ≥40 kg. However, Asian subjects were included in the population PK model, which allowed for simulation of predicted exposures in Asian subjects 1 to <12 years receiving 2 mg/kg for patients <20 kg and 40 mg for patients ≥40 kg. Exposures in Asian subjects 1 to <12 years of age (b) (4) were expected to exceed exposures corresponding to approved dosing in adults/adolescents (most pronounced for AUC) (Figure 4). However, in an adult QT study, higher exposures were observed than exposures associated with approved adult dosing and the exposures in the QT study were considered safe.

Exposures in Asian subjects 1 to <12 years of age (b) (4) were expected to generally overlap with exposures in the QT study, with <15% of subjects exceeding exposures in the QT study (Figure 4). Overall, proposed dosing (b) (4)

(b) (4) regardless of race is acceptable. As influenza has no significant effect on the PK of baloxavir (see Section 6.1), acceptability of proposed dosing applies for both the treatment and PEP indications.

Figure 4. Predicted Baloxavir AUC Values in Asian Subjects 1 to <12 Years of Age Receiving (b) (4) (2 mg/kg for Patients <20 kg and 40 mg for Patients ≥40 kg) or Dosing Evaluated in Japanese Pediatric Studies Compared to Observed AUC Values in Asian Adults/Adolescents



Source: Response to IR, NDA 214410 SN 0023, p5. <15% of Asian pediatric subjects receiving CP40563 dosing expected to exceed exposures in the QT study (Response to IR, NDA 214410 SN 0023, p6).
Whisker boxplot definitions: Median values are designated by the black lines in the center of the boxes. Boxes indicate the interquartile range (IQR, Q1–Q3). Whiskers represent 1.5×IQR.
CP40563 dosing: 2 mg/kg for 5 to <20 kg and 40 mg for ≥20 kg
Japanese pediatric dosing: 1 mg/kg for 5 to <10 kg, 10 mg for 10 to <20 kg, 20 mg for 20 to <40 kg, and 40 mg for ≥40 kg
* PK data for the thorough QT Trial T0816 uses noncompartmental analysis parameters.
Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration time curve across the total time; EBE, empirical Bayes estimate; NCA, noncompartmental analysis; TQT, thorough QT

An analytical inspection could not be conducted for this application. Analytical inspections are typically done for submission such as these where PK data are pivotal. However, an inspection is not an absolute requirement for approval. In our review of the bioanalytical methods, we identified no deficiencies.

Besides demonstration of similar or higher exposures in subjects 1 to <12 years of age versus adults, additional information supporting approval were the efficacy results in Trial CP40563. The efficacy endpoint was time to alleviation of influenza signs and symptoms (TTAS) versus

the active control, oseltamivir. No difference in TTAS was observed; median (95% CI) TTAS was 138 (117, 163) in the baloxavir arm and 150 (115, 166) in the oseltamivir arm.[3]

Conclusion

Based primarily on demonstration of similar or higher exposures in subjects 1 to <12 years of age versus adults, proposed dosing (b) (4) regardless of race is acceptable. An analytical inspection was not conducted, and in our review of bioanalytical methods no deficiencies were identified. Additional data supporting approval for patients 1 to <12 years of age are the efficacy results in Trial CP40563. Note however, that baloxavir marboxil will not be approved in this age group due to the high incidence of baloxavir resistance-associated amino acid substitutions in comparison to that observed in adults and adolescents ≥12 years of age.

6.3.2. Design of Postexposure Prophylaxis Trial (T0834)

The single postexposure trial was not conducted under U.S. IND. The trial design was discussed in a face-to-face meeting between the Applicant and the Division of Antivirals (DAV) on September 20, 2018; however, the trial was to begin enrolling 1 month after the meeting, and changes could not be made to the design. At that meeting, the Applicant asked if a single trial could be used to support an indication for postexposure prophylaxis. In addition, the study design of Trial T0834 differed from that recommended in FDA guidance for industry, *Influenza: Developing Drugs for Treatment and/or Prophylaxis* for two important issues: treatment of index cases with influenza and studying households contacts instead of household units (April 2011). These two issues were discussed with the Applicant and were addressed in their Clinical Study Report. The three issues, use of a single trial to support the indication, treatment of index cases, and study of household contacts will be discussed separately in this Section.

6.3.2.1. Use of a Single Trial to Support the Indication of Postexposure Prophylaxis

Background

The Applicant submitted the study results for a single trial, T0834, to support the efficacy of postexposure prophylaxis in individuals following contact with an individual who has influenza. While regulations state that a new indication should be supported by two adequate and well-controlled trials, a single persuasive trial may be sufficient to support an indication. See FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). In the September 2018 meeting, the Applicant was informed that a single trial could support an indication for postexposure prophylaxis if the results of that trial were "robust."

Assessment

The primary efficacy endpoint for Trial T0834 was the proportion of subjects with fever and symptomatic influenza who were RT-PCR-positive for influenza in the period from Day 1 to Day 10. Seven subjects (2%) in the baloxavir marboxil arm compared to 51 subjects in the placebo arm (14%) met these criteria. Results of the primary efficacy analysis are shown in

Table 29. The primary efficacy analysis comparing baloxavir marboxil to placebo was highly statistically significant (p<0.0001). In addition to a highly significant p-value the relative risk for the primary efficacy endpoint for baloxavir-treated subjects compared to placebo-treated subjects was only 0.14 with a 95% confidence interval ranging from 0.06 to 0.30. See Section 6.2.2.4 for additional analyses involving odds ratios and relative risks.

These data were also analyzed in subjects 12 years of age and older and the findings remained statistically significant (see Section 6.2.2.4 for results of this analysis). Because baloxavir marboxil will not be approved in patients <12 years of age, the analyses for subjects age 12 years and older are the primary efficacy analysis results that will be included in the label.

Table 29. Primary Efficacy Analysis, Trial T0834

Treatment Group	Baloxavir Marboxil	Placebo
Number of subjects meeting the primary efficacy endpoint/ number of contact cases	7/374 (1.9%)	51/375 (13.6%)
Exact 95% CI	0.8, 3.8	10.3, 17.5
P-value placebo vs. baloxavir	<0.0001	

Source: Statistics Reviewer's analysis
P-value obtained for primary GEE analysis using the modified Poisson regression approach with a log link for a binary response, adjusted for time from onset of influenza virus infection of index to informed consent of subject (<24 versus ≥24 hours), treatment given to index patient (baloxavir versus other), and age of subject (continuous).
Abbreviation: CI, confidence interval; GEE, generalized estimating equation

Conclusion

The efficacy results for Trial T0834 were highly statistically significant, and therefore the results of this single study are supportive of the indication.

6.3.2.2. Treatment of Index Cases With Different Anti-Influenza Drugs

Background

Household contacts of index cases were enrolled in Trial T0834 and randomized to receive either baloxavir marboxil or placebo. The index cases were treated with an anti-influenza drug at the discretion of their physician. Household contacts were stratified by index case treatment with baloxavir versus treatment with a different anti-influenza drug. In the FDA guidance for industry, *Influenza: Developing Drugs for Treatment and/or Prophylaxis*, DAV recommends that all index cases receive the same care, i.e., either no index cases are treated with an active drug or all index cases or treated with the same drug (April 2011). Different drugs may affect viral shedding and possibly effect transmission, therefore, treatment of index cases with different antivirals may have affected the outcome.

Assessment

Subjects (household contacts) were stratified by whether their index case received baloxavir marboxil or another anti-influenza drug. The majority of index cases (53%) received baloxavir marboxil for treatment of influenza; 31% received oseltamivir, and a small percentage received laninamivir, zanamivir and peramivir. (Percentages were the same when the table had separate

columns for index cases in baloxavir and placebo arms for household contacts). Index patient treatment by anti-influenza drug is shown in Table 30.

Table 30. Index Patient Treatment for Influenza, Trial T0834

Influenza Treatment	Total[1] N=545 n (%)
Baloxavir marboxil	287 (53)
Oseltamivir	171 (31)
Laninamivir	51 (9)
Zanamivir	23 (4)
Peramivir	13 (2)

Source: Clinical and Statistics Reviewer's analysis
[1] Number of index patients with randomized household contacts

A subgroup analysis of the primary efficacy endpoint by index patient treatment for index patients treated with baloxavir marboxil and for those treated with other antivirals was conducted. Results are shown in Table 31.

Table 31. Proportion of Subjects Meeting Primary Efficacy Endpoint[1] by Index Case Treatment, Trial T0834

Treatment of Index Cases	Baloxavir Marboxil	Other Antiviral
Number of subjects	195	179
Number of household contacts meeting primary endpoint, n (%)	5 (3)	2 (1)

Source: Statistics Reviewer
[1] Primary endpoint – PCR positive for influenza, febrile and at least one respiratory symptom
Abbreviations: PCR, polymerase chain reaction

As shown in the previous table, the percentage of household contacts in the baloxavir marboxil treatment arm with symptomatic influenza in which the index case received baloxavir arm was 3% compared to 1% in household contacts in which the index cases were treated with other antivirals.

Conclusion

The numbers of household contacts (subjects) who met the primary endpoint were small in both arms, and it does not appear that index case treatment affected the outcome.

6.3.2.3. Use of Household Contacts Instead of Household Units

Background

DAV recommends that all members of an index patient's household, which is referred to as a household unit, be randomized to the same treatment arm, whether it is to the investigational drug arm or to placebo arm. In the other words, the entire household of a single index patient should be randomized and analyzed as a single household unit. The reason for this recommendation is twofold. First, different regimens raise concerns about drug sharing and second, intrahousehold correlation. In Trial T0834, individual household contacts were enrolled as individual subjects and randomized to baloxavir marboxil or placebo. Therefore, different family members within a household (individual subjects), were randomized separately and may have received different study treatments (baloxavir marboxil or placebo).

Assessment

Household contacts (subjects) in Trial T0834 were randomized to receive baloxavir marboxil or placebo. Baloxavir marboxil or placebo was administered as a single dose at the study site; therefore, drug sharing was not an issue. The statistical reviewer's primary efficacy analysis used generalized estimating equations (GEE) to account for the correlation of contact cases within households with the same index patient. Results from this analysis were very similar to the Applicant's GEE approach that adjusted for contact cases instead of index patients, probably because there was no correlation issue for the majority of households which had only one contact case per household. Table 29 compares the percentage of contact cases with fever and symptomatic influenza who were PCR-positive for influenza in the two treatment groups. See Section 6.2.2.4 for additional analyses involving odds ratios and relative risks.

These data were also analyzed in subjects age 12 and older and the findings remained statistically significant (see Section 6.2.2.4 for results of this analysis). Because baloxavir marboxil will not be approved in patients <12 years of age, these are the primary efficacy analysis results that are included in the label (Table 29).

Conclusion

DAV prefers use of a household unit in prophylaxis trials instead of use of individual household contacts as subjects because of the risks of drug sharing and intrahousehold correlation. Because study drug was administered as a single dose, drug sharing was not an issue in this trial. As shown in the preceding table, analysis of the primary endpoint accounting for correlation of contact cases within households did not reveal intrahousehold correlation. Therefore, use of household contacts instead of household as a unit did not appear to affect the trial results.

6.3.2.4. Overall Conclusions

Trial T0834 was not conducted under a U.S. IND and DAV initially had concerns that results from a single trial may not support the efficacy of postexposure prophylaxis and also had several concerns regarding the trial design. The efficacy results of Trial T0834 were statistically robust and are sufficient to support the indication for use of baloxavir marboxil in PEP. Against the advice of DAV, the trial allowed treatment of the index patients with any anti-influenza drug. However, a subgroup analysis of the primary endpoint revealed that different anti-influenza treatment of index cases did not affect the efficacy results. Finally, individual household contacts of the index cases were enrolled as subjects instead of enrolling the entire household units as the study unit for randomization, treatment, and analysis. Because baloxavir marboxil and placebo were administered as a single dose and because the use of household contacts as the study unit did not have an impact on the intrahousehold correlation analysis, the efficacy conclusions were not affected. In conclusion, the single study for PEP showed statistically robust efficacy that was not impacted by the use of different anti-influenza treatments for index cases or from the use of household contacts as subjects. However, baloxavir marboxil will not be approved for postexposure prophylaxis in pediatric patients <12 years of age due to high frequencies of treatment-emergent baloxavir resistance observed in this age group.

6.3.3. Insufficient Information to Evaluate PEP Efficacy Against for Influenza Type B Virus Infection

Background

Type B viruses are generally 5-10 fold less susceptible to baloxavir in cell culture, and antiviral activity has been observed to be reduced in type B virus infections compared to type A virus infections in adult/adolescent studies based on virus shedding (see clinical virology reviews)[1,2] and published analyses (Ince et al. 2020). In addition, type B viruses have typically circulated at lower frequencies than type A viruses in recent years, and thus the number of type B virus infections may often be too low to adequately evaluate efficacy in this subset.

Assessment

In the PEP trial (Trial T0834), overall, there were 720 subjects housed with index patients infected with type A virus, whereas there were only five subjects housed with index patients infected with type B virus (Table 32). There was a statistically significant impact of baloxavir marboxil prophylaxis on infection events in subjects overall and across combined influenza A virus subtypes (A/H1N1 and A/H3N2); however, there was inadequate representation of influenza type B virus infections in index patients in this study to evaluate the impact of prophylaxis on prevention of type B virus infections (Table 32).

Table 32. Primary Efficacy Analysis in PEP Trial by Influenza Virus Subtype

Parameter	Baloxavir Marboxil	Placebo
Subjects associated with A/H1N1or A/H3N2-infected index patients, n	357	363
Symptomatic infections in A/H1N1-associated subjects, n (%)	7 (1)	51 (14)
95% CIs	1, 4	11, 18
P-value placebo vs. baloxavir	<0.001	
Subjects associated with A/H3N2-infected index patients, n	181	183
Symptomatic infections in A/H3N2-associated subjects, n (%)	5 (3)	32 (17)
95% CIs	1, 6	12, 24
P-value placebo vs. baloxavir	0.001	
Subjects associated with type B–infected index patients, n	2	3
Symptomatic infections in type B–associated subjects, n (%)	0	0
95% CIs	0%, 84%	0%, 71%
P-value placebo vs. baloxavir	—	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; PEP, postexposure prophylaxis

While the number of type B virus infections have typically been lower (comprising approximately 5% to 43% of infections) than type A infections across six baloxavir marboxil treatment trials evaluated to date, in a pivotal trial in otherwise healthy subjects at high risk for influenza complications, in which type B virus comprised 43% of infections, the impact of baloxavir marboxil treatment on the primary endpoint (time to improvement of symptoms) was statistically significant compared to placebo in the type B virus subset.[2] In addition, in pediatric trials, there was no statistically significant difference between time to alleviation of symptoms between type A and type B virus subsets, although the numbers were small (see Section 19.1.5).

Conclusion

PEP treatment with baloxavir marboxil provided statistically significant protection from clinical influenza overall, including for influenza virus type A subtypes; however, there were too few type B infections (likely due to the low prevalence of type B virus in the community), to adequately assess the impact of PEP in this subset. Given the lack of data, a Limitations of Use statement was considered that would have indicated that PEP has not been adequately evaluated against type B virus infection; however, the review team concluded that the efficacy against type B virus infection demonstrated in the therapeutic setting, in at least one adequately powered trial, could be extrapolated to PEP, and that the PK parameters associated with clinical efficacy against type B virus in the treatment setting would also apply to the PEP setting. Therefore, the review team decided that the PEP indication should reflect the therapeutic indication in making no explicit reference to influenza virus type in labeling.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The prior approval for baloxavir marboxil (NDA 210854) included a comprehensive nonclinical package. Xofluza has adequate clinical trial experience for PEP indication and in patients taking baloxavir marboxil tablets and 2% granules. The current product labeling adequately reflects the current knowledge concerning potential safety risks identified in nonclinical studies.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Baloxavir inhibits influenza virus PA protein endonuclease resulting in inhibition of viral RNA synthesis. No other FDA-approved antiviral drug shares this mechanism of action for the treatment of influenza. The structure of baloxavir marboxil and its metabolite, baloxavir, were analyzed by reviewers from the Division of Applied Regulatory Science, and the structures were not similar to any chemical structure in their database with a clear link to anaphylaxis or hypersensitivity. In addition, there was no similarity to structures that bind to a non-IgE receptor in mast cells. Thus, there are no drug class specific risk factors.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

The safety update report (SUR) was submitted on May 19, 2020. The Clinical Study Reports described in this review were complete; therefore, no additional clinical information was described in the SUR. The SUR described postmarketing reports submitted to the Roche global safety database. Baloxavir marboxil is marketed in Japan, United States, Australia, Canada, Switzerland, Thailand, and Singapore. Since Xofluza product launch in March 2018 until safety database closure on February 22, 2020, the Applicant estimates that more than (b) (4) patients

have received baloxavir marboxil. The SUR was reviewed to provide updates to section 6.2, Postmarketing Experience, and section 10, Overdose, of the baloxavir marboxil package insert.

Review of Overdoses in Safety Update Report

Since baloxavir marboxil was first marketed, there have been a total of 99 postmarketing adverse event reports of baloxavir marboxil overdose. Of AE reports that included patient age, 45 were reported in children or in patients younger than 12 years of age. Of the 99 reports of overdose, 14 patients had symptoms associated with overdose that were reported as additional adverse events. Postmarketing adverse events of symptomatic overdoses are shown in Table 33.

Table 33. Postmarketing Reports of Baloxavir Marboxil Overdoses That Were Symptomatic

Demographics	Country	Weight	Dose Received	Recommended Dose	AE
49-yo F	Japan	Missing	80 mg qd x 2	Single 80-mg dose	Acute pancreatitis
50-yo M	Japan	Missing	20 mg qd x 4	Single 40-mg dose	Hypersensitivity reaction
88-yo F	Japan	Missing	40 mg qd x2	Single 40-mg dose	↓O2 saturation, admitted and diagnosed with bile duct cancer
42-yo M	U.S.	74 kg	80 mg	Single 40-mg dose	↑ BP
? Age F	Japan	65 kg	80 mg	Single 40-mg dose	Queasy
72-yo F	U.S.	108 lb	80 mg	Single 40-mg dose	Out of breath
14-yo F	U.S.	126 lb	80 mg	Single 40-mg dose	Allergic reaction
16-yo F	U.S.	135 lb	80 mg	Single 40-mg dose	Dizzy, feels like concussion, ↓ short term memory
7-yo F	Japan	25.4 kg	40 mg	20 mg	Pollakiuria
10-yo	Japan	30 kg	40 mg	20 mg	Light headed
11-yo F	Japan	Missing	40 mg	20 mg	Diarrhea
10-yo	Japan	Missing	“adult dose”	Missing	Vomiting
5-yo F	Japan	18.5 kg	20 mg	10 mg	Erythema multiforme
9-yo	Japan	27 kg	40 mg	20 mg	Malaise and vomiting

Source: NDA 214410, SN 017, Safety Update Report, section 9.2 and Appendix 2b
Abbreviations: AE, adverse event; BP, blood pressure; F, female; M, male; O2, oxygen; qd, once a day; yo, year-old;

As shown in Table 33, six symptomatic overdoses were reported in adults, two in adolescents, and six in children. Three of the overdoses in adults were in patients who took baloxavir marboxil daily instead of as a single dose, and three were patients received a single 80-mg dose instead of a single 40-mg dose. Both adolescents also received a single 80-mg dose instead of a single 40-mg dose. Pediatric patients were all from Japan, and all received double the amount that they should have received.

There were two AEs of an allergic reaction (allergic reaction and hypersensitivity reaction) and two of vomiting. However, because of the variety of symptoms reported and organ systems involved, no consistent clinical picture was associated with baloxavir marboxil overdose, and section 10, Overdose, of the package insert, was not updated at this time.

Update of Section 6.2, Postmarketing Experience, of the Package Insert

According to FDA guidance for industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, decisions regarding inclusion of postmarketing adverse event reports in the package insert should be based on: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. The

rationale for revisions of section 6.2, Postmarketing Experience, are addressed individually (January 2006). (b) (4) At this time, inclusion of specific postmarketing adverse events in the package insert remains under discussion with the Applicant.

Lip Edema/Swelling

There were 16 reports of lip edema/swelling in the Roche global safety database since the baloxavir marboxil product launch. After review of these reports, 11 adverse event reports were consistent with an allergic reaction to baloxavir marboxil. In these 11 postmarketing reports, eight patients also had other symptoms of allergic reactions, such as urticaria, facial or eyelid swelling, and difficulty breathing. Three patients had no other allergic symptoms but lip swelling occurred within 12 hours of receiving baloxavir marboxil; two of these patients had history of allergic reactions and the third was treated with diphenhydramine. Because of the clear association of lip edema or swelling with baloxavir marboxil, lip edema or swelling should be included in the description of other allergic reactions (swelling of the face, eyelids, or tongue) for completeness.

Abdominal Pain

The most commonly reported adverse events in clinical trials of otherwise healthy adults and adolescents with influenza are gastrointestinal (diarrhea in 3% of subjects and vomiting in (b) (4)% of subjects; see Table 3 of the Xofluza package insert) (Genentech 2018). Gastrointestinal adverse events are also commonly reported postmarketing. Vomiting, bloody diarrhea, melena, and colitis are included in the Postmarketing Experience section of the baloxavir marboxil label. The Applicant provided all postmarketing reports of abdominal pain (N=128) since the time baloxavir marboxil was first marketed. A total of 63 of these reports were considered by this reviewer as possibly related to baloxavir marboxil. Sixty-two of the 63 reports included age: 16 occurred in pediatric patients, 15 in adolescents, and 31 in adults. The majority of AE reports (N=55) were from Japan. Of the 63 reports, 48 patients also reported additional symptoms; in 39 of the 48 patients, the symptoms were gastrointestinal and in 32 the additional symptom was diarrhea. We have recommended including abdominal pain in the postmarketing experience section of the package insert because of the frequency of reports.

Hepatobiliary: Jaundice and Abnormal Liver Function Tests

In nonclinical repeat dose oral toxicity studies in rats, liver effects were observed at the high baloxavir marboxil dose. In nonclinical repeat dose oral toxicity studies in monkeys, increases in liver enzymes were observed after baloxavir marboxil doses of 20 mg/kg/day or higher. Because of these findings, liver enzymes were monitored in Phases 1 and 2 trials of baloxavir marboxil. Increases in hepatic enzymes were reported in multiple human trials, but increases were Grade 1 or mild. For example, 6 of 910 otherwise healthy subjects (0.7%) in the trials enrolling otherwise healthy adult and adolescent subjects with acute uncomplicated influenza had an increase in

alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times but ≤5 times the upper limit of normal.

Because of the preclinical findings, postmarketing adverse event reports of patients with increased liver function tests (LFTs) were reviewed for the time period from February 27, 2015, until database lock on February 22, 2020. In this time period there were seven adverse event reports of jaundice and 58 adverse event reports of increased LFTs. Baloxavir marboxil causation could be ruled out in three adverse events of jaundice due to concomitant conditions (bile duct cancer, Grave's disease, and hemolytic anemia), and one case had too little information for assessment of causation. The remaining three postmarketing AE reports of jaundice that could be associated with baloxavir marboxil are described briefly below.

- A 27-year-old Japanese female with a history of atopic dermatitis and unspecified gastrointestinal disorder was diagnosed with influenza and treated with baloxavir 40 mg on (b) (6) She complained of feeling queasy and having abdominal pain and a decreased appetite 1 week later. On (b) (6) she was noted to be jaundiced and was diagnosed with acute hepatitis (ALT of 1,181 IU/L and total bilirubin of 9.18 mg/dL). Tests for hepatitis B and C were negative. Her bilirubin and increased LFTs decreased gradually and had resolved by (b) (6). The physician considered the adverse event temporally related to baloxavir marboxil but could not rule out a relationship to herbal medications that the patient also received.
- A 77-year-old Japanese female was diagnosed with influenza A and received baloxavir marboxil on (b) (6) She complained of hematuria later the same day. The patients had laboratory tests the next day and had an ALT of 231 IU/L, a total bilirubin of 6.9 mg/dL, and 3+ blood in the urine. Her bilirubin and LFTs gradually decreased over the next 2 months. No cause for the jaundice was identified.
- An 88-year-old Japanese female, who was a patient in a rehabilitation facility, was diagnosed with influenza and treated with baloxavir marboxil on (b) (6) The rehabilitation staff noted that the patient appeared jaundiced on (b) (6) She was transferred to the hospital where her total bilirubin was 1.69 mg/dL. The hospital physician refused to provide additional information; however, the jaundice was reported to have resolved.

There have been 58 postmarketing adverse events of increased LFTs. Of these, only eight either included enough information to assess causation or were not related to another condition, such as rhabdomyolysis. Two of the eight patients with increased LFTs also had jaundice and are discussed previously. Six patients had increased LFTs discovered when laboratory tests were obtained to analyze another condition such as syncope, weakness and decreased appetite, or altered consciousness with arthralgia and diarrhea. In subjects with available information, the increased LFTs were mild and resolved in approximately 2 weeks.

Although there were few cases of jaundice reported, we recommend inclusion of jaundice in the Postmarketing Experience section of the baloxavir marboxil label because of the seriousness of the adverse event. Increased LFTs were observed in a small percentage of clinical subjects. Because increased LFTs were an incidental finding in postmarketing adverse event reports, the actual number of patients with increased LFTs is likely to be higher than appreciated and increased LFTs are likely to be observed in clinical practice. In addition, hepatotoxicity was observed in preclinical studies of baloxavir marboxil. Therefore, we recommend inclusion of abnormal liver enzymes in the Postmarketing Experience section of the label.

Interstitial Lung Disease or Pneumonitis

As part of the SUR, the Applicant was asked to summarize hypersensitivity reactions and related adverse events. The Applicant searched their global safety database using the Medical Dictionary for Regulatory Activities (MedDRA) hypersensitivity standard MedDRA query. This standard MedDRA query included adverse events, which were categorized as hypersensitivity, anaphylaxis, angioedema, urticaria, and serious cutaneous AEs. The Applicant identified four serious adverse event reports that did not fit into any of the hypersensitivity subcategories; three of these were due to interstitial lung disease or pneumonitis:

- Interstitial lung disease: An 85-year-old Japanese male with concurrent mycobacterial infections and diabetes, who was receiving multiple other medications developed symptoms of interstitial lung disease on the same day as he received baloxavir marboxil.
- Interstitial lung disease: A 70-year-old Japanese female developed cough, pyrexia, and worsening respiratory status 2 days after receiving baloxavir marboxil. She improved on steroids.
- Pneumonitis: A 53-year-old female experienced malaise, dyspnea, and 80% oxygen saturation 2 days after receiving baloxavir marboxil and was diagnosed with pneumonitis.

After this information was submitted, DAV requested that the Applicant search their global safety database for all adverse events of interstitial lung disease or pneumonitis. Seven additional adverse event reports for drug-induced or drug-related interstitial lung disease that were considered by the reporter as possibly related to baloxavir marboxil were identified. The adverse events occurred in subjects from 55 to 81 years of age who were on multiple medications; therefore, it was difficult to definitively ascertain the etiology for any of the cases. However, because health care providers considered these cases possibly related to baloxavir and because of the seriousness of these adverse events, we recommend including interstitial lung disease and pneumonitis in the package insert.

Hemorrhage-Related Adverse Events

In the SUR, the Applicant stated that a signal for hemorrhage had arisen but had been refuted. A table of hemorrhage-related AEs was requested; and is included as Table 34. The table includes 219 adverse hemorrhage-related events.

Table 34. Hemorrhage-Related Adverse Events

System Organ Class Preferred Term	No. Patients With at Least One AE	No. of Serious AEs	No. of Nonserious AEs	Total No. of AEs
Total	206	78	141	219
Blood/lymphatic system				
Coagulopathy	1	1	0	1
Disseminated intravascular coagulation	6	6	0	6
Hemorrhagic diathesis	1	1	0	1
Immune thrombocytopenic purpura	1	1	0	1
Nervous system				
Cerebral hemorrhage	1	1	0	1
Subarachnoid hemorrhage	1	1	0	1
Thalamus hemorrhage	1	1	0	1

System Organ Class Preferred Term	No. Patients With at Least One AE	No. of Serious AEs	No. of Nonserious AEs	Total No. of AEs
Eye				
Conjunctival hemorrhage	1	0	1	1
Eye hemorrhage	1	1	0	1
Vascular				
Hematoma	1	0	1	1
Hemorrhage	6	3	3	6
Internal hemorrhage	3	3	0	3
Respiratory, thoracic, and mediastinal				
Epistaxis	59	1	58	59
Hemoptysis	4	1	3	4
Pulmonary alveolar hemorrhage	1	1	0	1
Gastrointestinal				
Diarrhea hemorrhagic	1	1	0	1
Enterocolitis hemorrhagic	2	2	0	2
GI hemorrhage	2	2	0	2
Hematemesis	2	2	0	2
Hematochezia	32	7	25	32
Melena	20	20	0	20
Mouth hemorrhage	1	1	0	1
Small intestine hemorrhage	1	1	0	1
Upper GI hemorrhage	1	1	0	1
Skin and subcutaneous tissue				
Subcutaneous hemorrhage	1	0	1	1
Purpura	1	0	1	1
Musculoskeletal and connective tissue				
Hematoma muscle	1	1	0	1
Muscle hemorrhage	2	2	0	2
Renal and urinary				
Cystitis hemorrhage	3	3	0	3
Hematuria	23	1	22	23
Renal hemorrhage	1	1	0	1
Reproductive and breast				
Genital hemorrhage	1	0	1	1
Hematospermia	1	0	1	1
Menorrhagia	2	0	2	2
Metrorrhagia	16	1	15	16
Postmenopausal hemorrhage	1	1	0	1
Uterine hemorrhage	1	1	0	1
Vaginal hemorrhage	1	0	1	1
Investigations				
Activated PTT prolonged	1	1	0	1
Blood urine present	1	0	1	1
Increased international normalized ratio	11	6	5	11
PT prolonged	1	1	0	1

Source: NDA 214410, SN032 Response to Clinical IR, Table 6, pages 29-31
Abbreviations: AE, adverse event; GI, gastrointestinal; PTT, partial thromboplastin time; PT, prothrombin time

The most commonly reported adverse events were epistaxis (N=59), hematochezia (N=32), hematuria (N=23), and melena (N=20). A total of 78 reports were serious, and there were seven fatal cases. Five fatal AEs were disseminated intravascular coagulation in subjects with sepsis, severe pneumonia, and multi-organ failure. Two fatal AEs were “hemorrhage” and included one patient who had experienced a thalamic hemorrhage 2 weeks before receiving baloxavir

marboxil and the AE report for the second patient contained insufficient information for assessment.

The majority of reports were from Japan (N=218). In reports with gender provided, 113 were female and 70 male. In analysis of reports with age provided, 37 AEs were reported in children <12 years of age, 15 reports in adolescents ≥12 years and <18 years of age, 88 reports in adults ≥18 years of age to <65 years of age, and 54 in patients ≥65 years of age. On analysis of data on time to onset, 114 (52%) occurred within 6 days of receiving baloxavir marboxil.

(b) (4), (b) (5)

The Postmarketing Experience section of the U.S. prescribing information for baloxavir marboxil currently includes bloody diarrhea, melena, and colitis and does not included any other hemorrhage-related AEs.

(b) (4)

They argued that hemorrhage-related adverse events were not observed in preclinical or clinical trials and that there is no known mechanism for baloxavir marboxil to cause hemorrhage. The Applicant cited articles from the medical literature that associated hemorrhage with influenza. The Applicant queried the PharMetrics Plus database, which includes approximately 105 million U.S. medical and pharmacy claims. The number of bleeding AEs were 1.18 per 100 patients (95% CI of 1.16, 1.2) who received antivirals and 1.67 (95% CI of 1.65, 1.7) for patients who did not receive antivirals. The Applicant noted that the number of bleeding AEs were higher in patients who were not treated, confirming that influenza itself is associated with bleeding adverse events. Finally, the Applicant addressed the postmarketing reports and observed the following issues:

- Melena: Because none of the cases identified the source of bleeding by endoscopy, the cause of bleeding/melena is unclear. In addition, many of the GI hemorrhage cases occurred in patients with diarrhea, so GI bleeding may have been related to diarrhea or to influenza infection.
- Epistaxis: Epistaxis may have been related to sample collection for influenza diagnosis. The Applicant also notes that epistaxis is common, particularly in children and that epistaxis may also be associated with rhinitis and sinusitis, which are commonly observed in patients with influenza.
- Hematuria: The Applicant cites an article by Tsuneharu and Masahiro in which hematuria was discovered in 2.8% to 16% of patients during health screenings.
- Increased prothrombin time: In both reports of increased PT, the patients were also receiving warfarin and the condition that necessitated warfarin, as well as other important information, were lacking in the AE reports.

DAV reviewed the Council for International Organizations of Medical Sciences reports for the following hemorrhage-related adverse event reports: hematochezia, hematuria, epistaxis, and

increased PT. There were 41 postmarketing adverse event reports of hematochezia that were associated temporally with receipt of baloxavir marboxil and could not be explained by other causes. Of these, 17 (41%) were associated with diarrhea. Five reports of hematochezia were associated with colitis. Because of the seriousness of hematochezia, we recommended that this adverse event be added to the Postmarketing Experience section of the package insert.

There were 30 AE reports of hematuria that were possibly related to baloxavir marboxil use. Gross hematuria was typically reported within 3 days of receipt of baloxavir marboxil and was not associated with frequency or pain or with underlying renal disease. Most of the cases of hematuria were reported in adults (89% of reports with age provided). In the 26 cases with gender provided, 10 patients (38%) were male, and 16 were female (62%). Because hematuria could indicate a serious condition, we recommend that it be included in the package insert.

There have been 96 postmarketing adverse event reports of epistaxis to the Roche global safety database; all of the reports are temporally related to use of baloxavir marboxil and have no other etiology described in the report. The majority of AEs were reported in patients <18 years of age (50 or 60% of AE reports that included the patient age). Multiple AE reports were associated with other bleeding disorders such as melena, bloody sputum, metrorrhagia, and hematuria. Because of the increased frequency of the AE reports, we recommended that epistaxis be added to the Postmarketing Experience section of the package insert.

There was a single report of increased PT submitted. Increased PT occurred in a patient with multiple confounding illnesses and thus will not be included in the baloxavir marboxil label.

7.4. FDA Approach to the Safety Review

Approach to Assessment of Clinical Trial Data

Data from two Phase 2 trials (Trials CP40563 and T0834) and two single-arm, open-label trials conducted in Japan, were analyzed individually to support safety for baloxavir marboxil in the treatment of acute, uncomplicated influenza in pediatric patients from 1 to <12 years of age and for influenza postexposure prophylaxis in patients 1 year of age and older. The safety review was analyzed by trial for pediatric patients. Resistance data from a third open-label trial conducted in Japan (Trial T0835) were submitted; except for summary data on baloxavir resistance, the remainder of the safety data from this trial were not submitted.

The results of this trial are not described in this section of the review (see Section 7.7.2 for a discussion of Trial T0835). Safety results for pediatric patients in Trials CP40563 and T0834 were not pooled because different doses were used in different trials and because of the different pharmacokinetics in Asian and non-Asian subjects. In addition, safety data were not pooled because subjects in the pediatric trials (Trial CP40563 and two Japanese pediatric trials) had symptomatic influenza infection, while the pediatric subjects in Trial T0834 were healthy and received treatment to prevent influenza. Also, treatment-emergent AEs (TEAEs) were protocol-defined as any AE occurring from the time of first study treatment dose until Study Day 29 in Trial CP40563, but in Trial T0834, they were defined as any AE occurring until Study Day 15.

Adequacy of Applicant's Clinical Safety Assessments

Clinical safety assessments in Trial CP40563 included evaluations of AEs, vital sign measurements, and laboratory tests; assessments in Trial T0834 included evaluations of AEs and laboratory test assessments. In Trial CP40563, subjects were seen at the study site on Days 1, 2, 4, 6, 10 and 29; study visits in Trial T0834 were on Days 1, 5, 11, and 15. Follow-up visits were also scheduled for subjects who discontinued treatment prematurely due to AEs. No major data quality or integrity issues were identified that would preclude performing a safety review for these NDAs. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in Trials CP40563 and T0834, as well of two Japanese pediatric trials, were reviewed and found to be acceptable.

Adverse events in Trials CP40563 and T0834 were graded using Common Terminology Criteria for Adverse Events.

7.5. Adequacy of Clinical Safety Database

Overall, the safety database of subjects who received baloxavir marboxil in Trials CP40563 and T0834, and the supportive Japanese trials, including 302 adults and adolescents, and 327 subjects 1 to <12 years of age is adequate to assess the safety of baloxavir marboxil for the proposed indication of postexposure prophylaxis and for treatment of pediatric patients with acute, uncomplicated influenza. In all trials of baloxavir marboxil, baloxavir marboxil was administered at the study site on Day 1. Treatment was observed. Because treatment of baloxavir marboxil is as a single dose, all subjects received the entire course of baloxavir marboxil.

Duration of study drug exposure in safety population in Trial CP40563 is shown in Table 35. Baloxavir marboxil was administered as a single observed dose, and 100% of the subjects in the safety population received the entire dose of baloxavir. The active control in Trial CP40563, oseltamivir, was administered twice-daily for 5 days. All 58 subjects in the oseltamivir arm received at least one dose of study drug; the mean duration of oseltamivir treatment was 5.3 days.

Table 35. Duration of Exposure, Safety Population, Trial CP40563

Parameter	Baloxavir Marboxil N=115	Oseltamivir N=58
Duration of treatment (units)	1 day	5 days
Mean (SD)	1 (0)	5.3 (0.7)
Median (min, max)	1 (1, 1)	5.0 (1, 6)
Patients treated, by duration, n (%)		
Any duration (at least 1 dosage)	115 (100)	58 (100)

Source: NDA 214410, CSR CP40563, Table 10, page 56
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

As shown in Table 36, 117 subjects were randomized to baloxavir and the safety population included 115 subjects. Two subjects were not treated with study drug and were excluded from the safety population. An additional five subjects discontinued the study prematurely including two subjects who discontinued due to adverse events, two with withdrawn consent, and one due to physician decision. One subject randomized to the oseltamivir arm was not included in the safety population, because the subject did not receive study drug. One additional subject

discontinued the study prematurely because of withdrawn consent. Overall, the number of subjects who discontinued the study was small, which suggests that the trial was well conducted with subjects followed closely.

Table 36. Patient Disposition, Trial CP40563

Disposition Outcome	Baloxavir Marboxil N=115 n (%)	Oseltamivir N=58 n (%)
Patients randomized	117	59
ITT/mITT population	115	58
Safety population	115	58
Discontinued study drug[1]	2 (1.7)	0
Adverse event	2 (1.7)	0
Discontinued study[1]	3 (0.2)	1 (1.7)
Withdrawal by subject	2 (1.7)	1 (1.7)
Physician decision	1 (0.9)	0

Source: adds.xpt; Software: R
[1] Subjects included are those in the safety population.
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group

Duration of exposure is not shown for Trial T0834, because single dose baloxavir marboxil and placebo were administered by study personnel as a single dose at the study site.

As shown in Table 37, one randomized subject in the baloxavir marboxil arm and one in the placebo arm were excluded from the safety population, because the subjects did not receive the study drug. In addition, one subject was excluded from the placebo arm because of good clinical practice noncompliance.

Table 37. Patient Disposition, Trial T0834

Disposition Outcome	Baloxavir Marboxil N=375 n (%)	Placebo N=377 n (%)
Patients randomized	375	377
ITT/mITT population	374	375
Per-protocol population	370	371
Safety population	374	377
Discontinued study	1 (0.2)	2 (0.5)
Did not receive study drug	1 (1.4)	1
GCP noncompliance	0	1

Source: NDA 214410, CSR T0834, Table 11-1, page 62 and Table 12-1, page 88.
Abbreviations: GCP, good clinical practice; ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The safety evaluation for baloxavir marboxil was adequate. The demonstrated safety profile of baloxavir marboxil both for the treatment of acute, uncomplicated influenza in pediatric patients from 1 to <12 years of age and the postexposure prophylaxis of influenza in patients 1 year of age and older is acceptable at the proposed doses. Baloxavir marboxil arms had similar or less frequent overall treatment-emergent AEs compared to placebo and to active comparators.

Serious adverse events were reported rarely, and there were no trends or clustering of serious AEs identified in the individual trials.

Treatment-emergent adverse drug reactions (e.g., those that were considered by the investigator to be drug related) were reported in three subjects (3%) who received baloxavir marboxil in Trial CP40563, and in seven subjects (2%) who received baloxavir marboxil in Trial T0834. Because of the small number of adverse reactions, the safety analysis focuses on treatment-emergent adverse events. The most common treatment-emergent adverse events in Trial CP40563 were vomiting and diarrhea; the most common TEAEs in Trial T0834 were nasopharyngitis and headache. The majority of adverse events were mild in severity.

The overall safety assessment is based on data summarized in the following subsections.

7.6.1. Safety Findings and Concerns, Trial CP40563

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Trial CP40563

In Trial CP40563, reports of treatment-emergent adverse events were reported at a similar rate in the baloxavir marboxil (46%) and oseltamivir arm (53%) 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 SAEs or deaths in either treatment arm.

Table 38. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Days 1 to 29, Trial CP40563

Event Category[1]	Baloxavir Marboxil N=115 n (%)	Oseltamivir N=58 n (%)	Risk Difference (95% CI)
Any TEAE	53 (46.1)	31 (53.4)	-7.4 (-23.1, 8.4)
Grades 3-4[2]	1 (0.9)	2 (3.4)	-2.6 (-7.6, 2.4)
SAE	0	0	0.0 (0.0, 0.0)
AE leading to discontinuation of study drug	2 (1.7)	0	1.7 (-0.7, 4.1)

Source: adae.xpt; Software: Python
[1] Includes treatment-emergent TEAE defined as those AEs with observed or imputed onset date on or after the start date of trial treatment.
[2] Grading scale: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
Abbreviations: AE, adverse event; CI, confidence interval; SAE, serious adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event;

7.6.1.2. Deaths, Trial CP40563

There were no deaths in Trial CP40563.

7.6.1.3. Serious Adverse Events, Trial CP40563

There were no serious adverse events in Trial CP40563.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial CP40563

Two subjects in the baloxavir marboxil arm discontinued Trial CP40563 prematurely due to adverse events. One subject was a 7-year-old white female who developed a rash on Day 3; the

rash was mild, did not require treatment, and resolved within 24 hours. The second subject discontinued the trial prematurely because of an adverse event reported as “overdose” of the oseltamivir placebo; however no adverse event associated with the “overdose” was reported. There were no premature discontinuations due to adverse events in the oseltamivir arm.

7.6.1.5. Treatment-Emergent Adverse Events, Trial CP40563

Treatment-emergent adverse events that were reported in at least 2% of patients in the baloxavir marboxil arm are shown in Table 39. The percentage of subjects with a TEAE was slightly higher in the oseltamivir arm (53.9%) compared to the baloxavir marboxil arm (46.1%). The most commonly reported TEAE in both arms was vomiting, which was reported more frequently in subjects who received oseltamivir (15.5%) than in subjects who received baloxavir marboxil (6.1%). The only TEAE reported in a higher percentage of subjects who received baloxavir marboxil than subjects who received oseltamivir, with a difference >2%, was diarrhea, which was reported in six (5.2%) of subjects who received baloxavir marboxil and one (1.7%) of subject who received oseltamivir.

Of note, there were five TEAEs of medication errors and three of accidental overdose in the baloxavir marboxil arm. The five medication errors were related to dosing mistakes at a single site, which dosed subjects with 2 mL (4 mg) of baloxavir marboxil instead of 2 mg/kg. Three subjects in the baloxavir marboxil arm had accidental overdoses of the oseltamivir placebo but not of baloxavir marboxil.

Table 39. Treatment-Emergent Adverse Events[1] Occurring in ≥2% of Subjects in Baloxavir Marboxil Arm, Phase 3 Safety Population, Trial CP40563

Adverse Event[1,2]	Baloxavir Marboxil N=115 n (%)	Oseltamivir N=58 n (%)	Risk Difference[3] (95% CI)
Any TEAE	53 (46.1)	31 (53.4)	-7.4 (-23.1, 8.4)
Diarrhea	6 (5.2)	1 (1.7)	3.5 (-1.8, 8.8)
Rhinorrhea	4 (3.5)	1 (1.7)	1.8 (-3.0, 6.5)
Rash	2 (1.7)	0	1.7 (-0.7, 4.1)
Nausea	2 (1.7)	0	1.7 (-0.7, 4.1)
Rhinitis allergic	2 (1.7)	0	1.7 (-0.7, 4.1)
Medication error	5 (4.3)	2 (3.4)	0.9 (-5.1, 6.9)
Upper respiratory tract infection	5 (4.3)	2 (3.4)	0.9 (-5.1, 6.9)
Bronchitis	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Cough	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Accidental overdose	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Abdominal pain	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Pharyngitis streptococcal	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Headache	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Otitis media	3 (2.6)	4 (6.9)	-4.3 (-11.4, 2.9)
Vomiting	7 (6.1)	9 (15.5)	-9.4 (-19.7, 0.9)

Source: adae.xpt; Software: Python
[1] TEAEs defined as those AEs with observed or imputed onset date on or after the start date of trial treatment.
[2] Coded as MedDRA preferred terms
[3] Risk differences are comparisons of the total BXM group with the OST group.
Abbreviations: AE, adverse event; BXM, baloxavir marboxil; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; OST, oseltamivir; TEAE, treatment-emergent adverse event

The majority of TEAEs in Table 39 were mild in intensity. There was one Grade 3 TEAE, abdominal pain, in a subject in the baloxavir marboxil arm. There were two Grade 3 TEAEs of vitamin D deficiency in the oseltamivir arm. There were no Grade 4 TEAEs.

Four treatment-related adverse events occurred in patients in the baloxavir marboxil arm: flushing, morbilliform rash, rash, and accidental overdose of oseltamivir placebo. Flushing and morbilliform rash occurred in the same subject. Both the flushing and morbilliform rash began on Day 2, were treated with diphenhydramine, and resolved by Day 9. The subject with a rash was a 7-year-old white female who developed a Grade 2 rash on Day 3 (48 hours after receiving baloxavir marboxil). The rash resolved the next day. The subject was withdrawn from the study. There were six treatment-related AEs in five subjects in the oseltamivir arm: vomiting (two patients, three AEs), diarrhea, soft feces, and sleep terror.

7.6.1.6. Laboratory Findings, Trial CP40563

Safety laboratory tests were obtained on Days 1 and 6. There were no laboratory abnormalities reported as adverse events. There was one Grade 3 or Grade 4 laboratory value in the trial, which was hyperkalemia in a subject in the baloxavir marboxil arm.

7.6.2. Supportive Pediatric Safety Data From Other Studies

The safety results for two open-label, uncontrolled trials (T0822 and T0833) in pediatric subjects were submitted to support the safety of baloxavir marboxil in pediatric patients. Both trials were conducted in Japan and were not conducted under U.S. IND. Both trials were conducted in pediatric subjects <12 years of age with acute, uncomplicated influenza; subjects were limited to pediatric patients weighing <20 kg in Trial T0833. Safety monitoring was identical in both trials with adverse events followed for 21 days after receipt of baloxavir marboxil. Lower baloxavir marboxil doses were used in the two Japanese trials than in Trial CP40563; however, baloxavir marboxil exposures are higher in Asians compared to non-Asians. Please see Section 6.3.1 for a discussion of the pharmacokinetics of baloxavir marboxil in pediatric patients.

In Trial T0822, 107 pediatric subjects with influenza received a single oral dose of baloxavir marboxil. The tablet formulation of baloxavir marboxil was used, and baloxavir marboxil was dosed by subject weight with consideration given to tablet size as shown in Table 40.

Table 40. Baloxavir Marboxil Dosing in Pediatric Subjects in Trial T0822

Subject Weight	Baloxavir Marboxil Dose	Baloxavir Marboxil Tablet
5 to <10 kg	5 mg	One-half 10-mg tablet
10 to <20 kg	10 mg	One 10-mg tablet
20 to <40 kg	20 mg	One 20-mg tablet
≥40 kg	40 mg	Two 20-mg tablets

Source: NDA 214410, CSR T0822, Table 5-1, page 29.

The mean age of subjects in T0822 was 7.3 years (ranging from 1 to 11 years of age). Forty-eight percent of subjects were female, and 52% were male. All subjects were Asian.

There were no serious adverse events, no deaths, and no premature study discontinuations due to adverse events. TEAEs were reported in 37 subjects (34.6%). There were no Grade 3 or Grade 4 TEAEs reported. TEAEs observed in >2% of subjects were vomiting in eight subjects (7.5%),

diarrhea in three subjects (2.8%), and pharyngitis in three subjects (2.8%). Adverse events that were judged by the investigator as drug-related were diarrhea in two subjects and soft feces in one subject. One subject reported urticaria on Day 1, but this was judged by the investigator to be unrelated to baloxavir marboxil.

Trial T0833 enrolled subjects who were <12 years of age and who weighed <20 kg. Baloxavir marboxil was administered as granules, which were poured directly in the mouth, i.e., the granules were not reconstituted with water. Baloxavir marboxil was administered by weight. Subjects who weighed <10 kg received a single 1-mg/kg dose and subjects who weighed ≥10 kg to <20 kg received a single 10-mg dose.

A total of 33 subjects were enrolled in Trial T0833. The mean age was 2.4 years; 67% of subjects were female, and 100% were Asian.

There were no serious adverse events, no deaths, and no premature study discontinuations due to adverse events. TEAEs were reported in 18 subjects (54.5%). There were no Grade 3 or Grade 4 TEAEs reported. TEAEs observed in more than one subject were vomiting in six subjects (18.2%) and in two subjects (6.1%) each: nasopharyngitis, upper respiratory tract infection, and otitis media. One drug-related AE, thrombocytosis on Day 12, was reported.

The TEAEs observed in Trials T0822 and T0833 were similar to those observed in Trial CP40563 in pediatric subjects 1 to <12 years of age with acute uncomplicated influenza. Vomiting was the most commonly observed TEAE in Trial CP40563 and in both supportive Trials T0822 and T0833. Diarrhea was reported in ≥2% of pediatric subjects in both Trials CP40563 and T0822. In addition, there were no serious adverse events in Trial CP40563 or in Trials T0822 or T0833 and there were no Grade 3 or Grade 4 TEAEs reported in Trials T0822 or T0833, confirming that the majority of TEAEs observed with baloxavir marboxil are mild in intensity.

7.6.3. Safety Findings and Concerns, Trial T0834

7.6.3.1. Overall Adverse Event Summary, Trial T0834

As shown in Table 41, in Trial T0834, the percentage of subjects with any treatment-emergent AE was similar in both the baloxavir marboxil arm and the placebo arm in the pediatric subgroup, as well as in adults and adolescents. There were no AEs leading to premature study discontinuation in either arm. There was one SAE in the placebo arm (atypical psychosis); there were no serious adverse events in the baloxavir marboxil arm.

Table 41. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Days 1 to 15, Trial T0834

	1 to <12 Years of Age		≥12 Years of Age	
Event Category[1]	Baloxavir Marboxil N=72 n (%)	Placebo N=71 n (%)	Baloxavir Marboxil N=302 n (%)	Placebo N=304 n (%)
Any TEAE	18 (25.0)	18 (25.4)	65 (21.5)	60 (19.7)
Grades 3-4[2]	0	0	0	1 (0.3)
SAE	0	0	0	1 (0.3)
AE leading to discontinuation of study drug	0	0	0	0

Source: adae.xpt; Software: Python
[1] Includes treatment-emergent AE defined as AEs reported after the dose of randomized study drug.
[2] Grading scale: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.3.2. Deaths, Trial T0834

There were no deaths in Trial T0834.

7.6.3.3. Serious Adverse Events, Trial T0834

There were no serious adverse events in the baloxavir marboxil arm.

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial T0834

There was one premature discontinuation due to an adverse event; a subject in the placebo arm discontinued the trial because of atypical psychosis.

7.6.3.5. Treatment-Emergent Adverse Events, Trial T0834

The percentage of subjects with a TEAE was similar in the baloxavir marboxil arm (22.2%) and the placebo arm (20.5%). The only adverse events reported in at least 2% of subjects in the baloxavir marboxil arm were nasopharyngitis (6.4%) and headache (2.1%). As shown in Table 42, these AEs occurred at a similar frequency in baloxavir marboxil and placebo.

Table 42. Treatment-Emergent Adverse Events[1] Occurring in ≥2% of Subjects who Received Baloxavir Marboxil in the Phase 3 Safety Population, Trial T0834

	Baloxavir Marboxil N=374	Placebo N=375
Preferred Term[2]	n (%)	n (%)
Nasopharyngitis	24 (6.4)	25 (6.7)
Headache	8 (2.1)	6 (1.6)

Source: NDA 214410, CSR 17190834, Table 12-5, pages 91-12.
[1] Treatment-emergent adverse event defined as AEs reported after the dose of randomized study drug. Terms included are those that occurred in at least six subjects in the baloxavir marboxil arm
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event

All of the TEAEs in the baloxavir marboxil arm were mild in intensity. There were no Grade 3 or Grade 4 AEs in the baloxavir marboxil arm.

The percentage of drug-related TEAEs was low in both treatment arms: 1% in the baloxavir marboxil arm and 0.2% in the placebo arm. There were four drug-related TEAEs in the baloxavir marboxil arm (nausea in two patients and one subject each with diarrhea and rash). There was one drug-related TEAE, diarrhea, in the placebo arm.

TEAEs were examined by age to compare adverse events in pediatric subjects from >1 year of age to <12 years of age to adverse events in adults and adolescents (≥12 years of age). The percentage of subjects in the baloxavir marboxil arm with TEAEs was similar in pediatric subjects (25.0%) and in adults and adolescents (21.5%). The most commonly reported TEAE in both age groups was nasopharyngitis, which was reported in 8.3% of pediatric subjects and in 6.0% of adult and adolescent subjects. TEAEs reported in at least two subjects in the baloxavir marboxil arm for either the pediatric age group or in the adult/adolescent age group are shown in Table 43.

Table 43. Treatment-Emergent Adverse Events Reported in ≥2 Pediatric Subjects or ≥2 Adult/Adolescent Subjects, Phase 3 Safety Population, Trial T0834

	≥1 Year to <12 Years of Age		≥12 Years of Age	
Adverse Event[1,2]	Baloxavir Marboxil N=72 n (%)	Placebo N=71 n (%)	Baloxavir Marboxil N=302 n (%)	Placebo N=304 n (%)
Any TEAE	18 (25.0)	18 (25.4)	65 (21.5)	60 (19.7)
Nasopharyngitis	6 (8.3)	6 (8.5)	18 (6.0)	19 (6.2)
Pyrexia	2 (2.8)	0	0	1 (0.3)
Bronchitis	1 (1.4)	0	2 (0.7)	0
Headache	2 (2.8)	0	6 (2.0)	6 (2.0)
Cough	2 (2.8)	0	1 (0.3)	0
Diarrhea	0	0	2 (0.7)	1 (0.3)
Gastroenteritis	0	0	2 (0.7)	1 (0.3)
Dizziness	0	0	2 (0.7)	0
Pharyngitis	0	0	4 (1.3)	1 (0.3)
Nausea	0	0	3 (1.0)	1 (0.3)

Source: adae.xpt; Software: Python
[1] Treatment-emergent adverse event defined as AEs reported after the dose of randomized study drug. Terms included are those that occurred in at least two subject.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

Because of the different patient populations enrolled, the types of TEAEs in subjects who received baloxavir marboxil in Trial T0834 differed from those seen in influenza treatment trials of baloxavir marboxil. In Trial T0834, which enrolled subjects who did not have influenza, nasopharyngitis and headache were reported in ≥2% of subjects; while in trials of subjects with acute, uncomplicated influenza, TEAEs reported in ≥2% of subjects were diarrhea (3%), bronchitis (3%), nausea (2%), and sinusitis (2%) (Genentech 2018).

Because the pediatric population in Trial T0834 did not have influenza and the pediatric subjects in Trial CP40563 did have influenza, the safety results from Trials CP40563 and T0834 cannot be pooled. While vomiting and diarrhea were reported more frequently in Trial CP40563, the most common TEAEs in pediatric subjects in Trial T0834 were respiratory AEs, headache, and pyrexia.

7.6.3.6. Laboratory Findings, 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 aggravated in severity from baseline. The decision of whether to classify a laboratory abnormality as an AE was the responsibility of the investigator or subinvestigator. Laboratory abnormalities classified as TEAEs are shown in Table 44. The percentage of pediatric subjects (>1 year to <12 years of age) was similar in the baloxavir marboxil and placebo arm; however, laboratory TEAEs were reported more often in adults and adolescents (≥12 years of age) in the baloxavir marboxil arm (5%) compared to the placebo arm (2.6%). Laboratory TEAEs were more commonly reported in adults and adolescents than in pediatric subjects; the reason for this is unclear.

Laboratory TEAEs that were reported in more than one subject in the baloxavir marboxil arm were increased ALT and urine with blood, protein or glucose. All laboratory TEAEs were mild in intensity. Increased ALT was reported in four baloxavir marboxil subjects and one placebo subject. Hepatoxicity was observed in preclinical studies of rats and monkeys, and Grade 1 increases in ALT have been reported in Phase 1 trials of baloxavir marboxil. Blood in the urine was reported in six subjects in the baloxavir marboxil arm compared to one in the placebo arm. Protein in the urine and glucose in the urine were reported in two subjects in the baloxavir marboxil arm each; neither were reported in the placebo arm. The reason for abnormalities in the urine is unclear. See the discussion of hematuria in Section 7.3 (SUR).

Table 44. Laboratory Adverse Events, Safety Population, Trial T0834

	>1 Year to <12 Years of Age		≥12 Years of Age	
Adverse Event[1,2]	Baloxavir Marboxil N=72 n (%)	Placebo N=71 n (%)	Baloxavir Marboxil N=302 n (%)	Placebo N=304 n (%)
Laboratory-related AE	2 (2.8)	2 (2.8)	15 (5.0)	8 (2.6)
Alanine aminotransferase increased	1 (1.4)	0	3 (1.0)	1 (0.3)
Neutrophil count decreased	1 (1.4)	0	0	0
Blood urine present	1 (1.4)	0	5 (1.7)	1 (0.3)
Protein urine present	1 (1.4)	0	1 (0.3)	0
Blood uric acid increased	0	1 (1.4)	1 (0.3)	0
Hepatic function abnormal	0	1 (1.4)	1 (0.3)	0
Platelet count increased	0	1 (1.4)	0	0
Glucose urine present	0	0	2 (0.7)	2 (0.7)
Aspartate aminotransferase increased	0	0	1 (0.3)	1 (0.3)
Gamma-glutamyl transferase increased	0	0	1 (0.3)	0
Hyperuricemia	0	0	1 (0.3)	0
Protein total decreased	0	0	1 (0.3)	0
C-reactive protein increased	0	0	0	2 (0.7)
Glucose tolerance impaired	0	0	0	1 (0.3)
Granulocytopenia	0	0	0	1 (0.3)
Neutrophil count increased	0	0	0	1 (0.3)
Renal glycosuria	0	0	0	1 (0.3)
White blood cell count increased	0	0	0	1 (0.3)

Source: adae.xpt; Software: Python
[1] Treatment-emergent adverse event defined as AEs reported after the dose of randomized study drug. Terms included are those that occurred in at least one subject.
[2] Coded as MedDRA preferred terms
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Trial T0834 was not conducted under U.S. IND and only hepatic enzymes tests values were evaluated by toxicity grading. ALT and AST were graded as ≤3X upper limit of normal (ULN), >3 to ≤5 X ULN, or >5 to ≤20 X ULN. One subject in the baloxavir marboxil arm and three in the placebo arm had an ALT value >3 to ≤5X ULN; all other values were ≤3 X ULN. Total bilirubin was graded as ≤1.5 X ULN or >1.5 to ≤3 X ULN; all results were ≤1.5 X ULN.

Other laboratory values were reported as either high or low. When the laboratory results were evaluated to identify laboratory abnormalities that were reported in ≥2% of subjects who received baloxavir marboxil and were observed in more subjects in the baloxavir marboxil arm than in the placebo arm with a difference of at least 2%, only two abnormalities were identified: high eosinophil counts (12.6% in the baloxavir marboxil arm compared to 10.4% in the placebo arm) and low hemoglobin levels (9.1% in the baloxavir marboxil arm compared to 6.4% in the placebo arm). There was more than a 2% different between the two treatment arms for both laboratory tests, but the difference was less than 3% for both. Such a small difference is unlikely to have had a clinical impact. In addition, neither of these laboratory abnormalities (eosinophilia or anemia) were classified as an adverse event, which could indicate that the investigators did not consider the abnormalities as clinically significant.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Potential Transmission of Baloxavir Resistance in PEP Trial

Background

Treatment-emergent resistance to baloxavir has been observed in approximately 3% to 11% of subjects in adult/adolescent treatment trials (See Clinical Virology Reviews)[1,2] and in approximately 22% to 26% of subjects in pediatric treatment trials (Table 47). Treatment-emergent resistance to baloxavir is associated with prolonged viral RNA shedding, relative to placebo (see Original NDA and Supplement 1 Clinical Virology Reviews,)[1,2] which raises the risk of transmission of virus with reduced susceptibility to household contacts. Baloxavir resistance was observed in 15 of 31 baloxavir marboxil prophylaxis failures (influenza viral RNA positive postbaseline) evaluated and some of these events may represent cases of transmitted resistance.

Assessment

The Applicant carried out PA gene sequencing for all RT-PCR-positive subjects and baseline samples from index patients with at least one household contact (subject) who was RT-PCR-positive at baseline or postbaseline. Analyses of the sequence data and subject circumstances were preformed to identify:

- Resistance-associated substitutions (RAS) and their frequency in index patients and subjects
- Cases of transmitted RAS variants as indicated by the presence of:
  - RAS variants in index patients prior to exposure to baloxavir marboxil

  - RAS variants in subjects at baseline (prior to exposure to baloxavir marboxil) in the baloxavir marboxil arm
  - RAS variants in subjects in the placebo arm prior to baloxavir marboxil rescue therapy, overall and after exposure to index cases who had received baloxavir marboxil
- Cases of potentially transmitted resistance as indicated by subjects in the baloxavir marboxil arm with RAS variants who were exposed to index cases who had received baloxavir marboxil.

Resistance-Associated Substitution Identification and Frequency

Postbaseline PA sequencing was obtained for 31 (12 A/H1N1 and 19 A/H3N2) subjects in the baloxavir marboxil arm and 95 (36 A/H1N1 and 59 A/H3N2) subjects in the placebo arm. Sequencing was considered successful for the purpose of establishing frequencies of resistance if it captured codons for PA amino acid positions 23 and 38; however, all sequencing data were included in initial analyses to identify substitutions potentially associated with prophylaxis failure (Table 91). In the baloxavir marboxil arm, RAS variants (E23K or I38M/T) were identified postbaseline in 48% (15 of 31) of subjects evaluated overall and in 100% (7 of 7) of subjects meeting the primary endpoint.

In the placebo arm, RAS were identified postbaseline in 2% (2 of 95) of subjects, both of whom met the primary endpoint (Table 45). Among subjects who were viral RNA-positive postbaseline and evaluated for resistance, the presence of a resistant variant at the first time point sequenced (13/31 in the baloxavir arm and 0/95 in the placebo arm) was highly correlated with baloxavir marboxil prophylaxis (Table 45; P<0.0001, Fisher's exact test).

In the baloxavir marboxil prophylaxis arm, the median age of subjects with a RAS variant was 37 years (n=15), compared to 32 years (n=24) for subjects infected with wild-type virus and 37 years (n=374) for all subjects in the baloxavir marboxil arm. The median age of index patients who were treated with baloxavir marboxil and associated with subjects infected with a RAS variant in the baloxavir marboxil arm was 7 years (n=9), compared to 8 years (n=9) for index patients treated with baloxavir marboxil and associated with subjects infected with wild-type virus and 9 years (n=169) for all index patients treated with baloxavir and associated with a subject in the baloxavir marboxil arm. The frequencies of resistant variants among subjects evaluated for resistance postbaseline in the baloxavir marboxil arm in the <12-year-old and ≥12-year-old subsets were 36% (5/14) and 59% (10/17), respectively.

Emergent RAS were defined as RAS variants arising in subjects who had wild type virus at the first time point sequenced and who were evaluated for resistance at additional time points after baloxavir marboxil prophylaxis (n=15 in the baloxavir marboxil treatment arm) or after baloxavir marboxil rescue therapy (n=4 in the placebo arm). Emergent RAS were identified in two (including in one subject who met the primary endpoint) of 15 (13%) longitudinally evaluated subjects prophylaxed with baloxavir marboxil and in two (both subjects met the primary endpoint) of four (50%) longitudinally evaluated subjects receiving baloxavir rescue therapy in the placebo arm (Table 45).

Table 45. PA Gene Sequence Analysis: RAS Associated With Treatment Arms and Events in Trial T0834

	Baloxavir Marboxil					Placebo				
Event Category	Subjects Evaluated for RAS at Baseline	Subject Evaluated for RAS Postbaseline	Total RAS	RAS at First Postbaseline Time Point (n per Substitution)	Emergent RAS (n per Substitution)[5]	Subjects Evaluated for RAS at Baseline	Subjects Evaluated for RAS Postbaseline	Total RAS	RAS at First Time Point Sequenced (n Substitutions)	Emergent RAS (n per Substitution)[7]
Subjects	15	31	15	13[3]	2	24	95	2	0	2
RT-PCR-positive at baseline[1]	15	10	4	2 (2 I38T)[4]	2 (1 I38T; 1 E23K)[6]	24	25	0	0	0
RT-PCR-positive postbaseline only[2]		21	11	11 (6 I38T; 1 I38M; 4 E23K)	0		70	2	0	2 (I38T)
Primary endpoint met	1	7	7	6 (3 I38T; 1 I38M; 2 E23K)	1 (I38T)	11	50	2	0	2 (I38T)

Source: FDA Virology analysis
RAS: Resistance-associated substitution(s) in virus.
[1] Two and zero subjects type/subtype mismatch index in BXM and PBO, respectively.
[2] Four and seven subjects type/subtype mismatch index in BXM and PBO, respectively.
[3] One of 13 subjects was subtype-mismatched with index patient.
[4] Subjects (b) (6) were positive at Day 1 but first sequenced on Days 5 and 6, respectively.
[5] Fifteen subjects with wild-type virus at the first time point sequenced were evaluated longitudinally after baloxavir marboxil prophylaxis was initiated.
[6] First seq at Day 1; RAS identified on Day 8 (I38T) and Day 11 (E23K).
[7] Four subjects with wild-type virus at the first time point sequenced were evaluated longitudinally after baloxavir marboxil rescue therapy was initiated.
Abbreviations: BXM, baloxavir marboxil; PA, polymerase acidic; PBO, placebo; RAS, resistance-associated substitution; RT-PCR, reverse transcription-polymerase chain reaction

Transmitted Resistance: Evaluation of Pre-Baloxavir Marboxil Exposure Sequences in Subjects and Index Patients

RAS variants detected in index patients or subjects prior to baloxavir exposure would represent transmission of resistant virus from community. No resistant variants were detected in 127 (52 A/H1N1 virus-infected and 75 A/H3N2 virus-infected) index patients evaluated for substitutions at PA amino acid positions E23 or I38 at baseline prior to initiation of antiviral therapy (longitudinal sequencing was not carried out on index patients to identify resistant variants that may have emerged in those treated with baloxavir marboxil). Among the 15 subjects in the baloxavir marboxil arm who were evaluated for resistance prior to prophylaxis, none were identified who had resistant virus. Of the 100 subjects in the placebo arm evaluated at baseline and/or post baseline, 47 of whom were evaluated after their associated index patient initiated baloxavir therapy, none harbored baloxavir-resistant virus prior to baloxavir marboxil rescue therapy. Together these results indicate a lack of detection of baloxavir resistance in index patients or subjects in the absence of exposure to baloxavir, including in the 47 subjects in the placebo arm who were evaluated after exposure to index patients who had received baloxavir marboxil.

Potential Transmitted Resistance

While there were no cases of verifiable transmission of resistance among subjects evaluated prior to exposure to baloxavir marboxil, some subjects with resistant virus may represent potential cases of transmitted resistance. In these cases, resistant virus was only identified after baloxavir marboxil treatment, and the emergence of resistance in the index patient was not detected at baseline or evaluated postbaseline. Based only on the treatment of the index patient and the presence of RAS variants at the first sequencing time point in the only infected subject or multiple infected subjects in a household, there were five subjects who represent cases of potential transmitted resistance that could not be circumstantially ruled out (Table 46, subjects with potential transmitted resistance in bold).

Transmission of resistance was not considered likely in households where more than one subject was infected and only one subject had a resistant virus (index cases PFF511, PRM503, and PSC509), the resistant virus in the subject did not match the subtype in the index patient (index case PNB506), or for subjects who were associated with index patients who did not receive baloxavir marboxil (index cases PQE504, PRB501, PRB517, PTA507, PHC504, and PLA502) (Table 46).

However, in an analysis of the frequency of baloxavir RAS variants observed at the first sequencing time point in subjects based on the antiviral treatment of index patients, there was a trend toward an increased incidence of baloxavir RAS in subjects exposed to baloxavir marboxil–treated index patients (8/60, 13.3%) versus neuraminidase-treated index patients (4/67, 5.9%), although the difference was not statistically significant (P=0.2254, Fisher’s exact test).

Table 46. Resistance by Household in Trial T0834

Index ID	Index Age	Index Treatment	Subject	Subject Arm	Subject Age	Day RT-PCR Positive[1]	Day First Sequenced	Day of RAS Detection	RAS	Day of Baloxavir Rescue Therapy in Subject	Subject Virus Subtype
PEB502	11	Baloxavir	(b) (6)	**Baloxavir**	**43**	**4**	**11**	**11**	**E23K**		**A/H1N1**
PFF506	10	Baloxavir		**Baloxavir**	**44**	**11**	**11**	**11**	**I38M**		**A/H3N2**
PFK502	81	Baloxavir		**Baloxavir**	**77**	**7**	**7**	**7**	**I38T**		**A/H3N2**
PJA508	3	Baloxavir		**Baloxavir**	**4**	**1**	**5**	**5**	**I38T**		**A/H3N2**
				Placebo	38	3	3	5	I38T	3	A/H3N2
				Placebo	6	3	3	5	I38T	3	A/H3N2
				Placebo	38	9	9	WT	WT		A/H3N2
PNA508	2	Baloxavir		**Baloxavir**	**51**	**7**	**7**	**7**	**E23K**	**-**	**A/H1N1**
				Baloxavir	27	Negative	Negative	Negative	Negative		Negative
PFF511	5	Baloxavir		Baloxavir	3	1	1	11	E23K		A/H3N2
				Placebo	41	Negative	Negative	Negative	Negative		Negative
				Placebo	7	4	4	WT	WT		A/H3N2
PNB506	7	Baloxavir		*Baloxavir*	*10*	*7*	*7*	*7*	*E23K*		*A/H1N1*
				Baloxavir	36	Negative	Negative	Negative	Negative		Negative
PRM503	7	Baloxavir		Baloxavir	9	4	4	4	I38T		A/H3N2
				Placebo	36	3	3	WT	WT		A/H3N2
PSC509	7	Baloxavir		Baloxavir	37	14	14	14	I38T		A/H3N2
				Placebo	6	2	2	WT	WT		A/H3N2
PQE504	5	Zanamivir		Baloxavir	36	7	7	7	I38T		A/H3N2
PRB501	4	Oseltamivir		Baloxavir	44	8	8	8	E23K		A/H1N1
				Placebo	9	Negative	Negative	Negative	Negative		Negative
PRB517	5	Oseltamivir		Baloxavir	8	12	12	12	I38T		A/H1N1
PTA507	4	Oseltamivir		Baloxavir	36	1	1	8	I38T		A/H3N2
				Placebo	2	1	1	WT	WT		A/H3N2
PHC504	9	Zanamivir		Baloxavir	51	1	6	6	I38T		A/H1N1
PLA502	8	Peramivir		Baloxavir	41	9	9	9	I38T		A/H1N1
				Baloxavir	50	Negative	Negative	Negative	Negative		Negative
				Placebo	10	Negative	Negative	Negative	Negative		Negative

Source: FDA Virology analysis
Bold: Cases of potential transmitted resistance
Day 1 is baseline
[1] Subjects RT-PCR positive at Day 1 determined by baseline STYPPCR. For subjects negative at baseline, the relative Day of RT-PCR results positive postbaseline is indicated (Derived from PCRPDY from ADQS0).
[2] (Italicized) Subject virus subtype (A/H1N1) did not match the index patient subtype (A/H3N2).
[3] RT-PCR positive, fever (≥37.5ºC) and at least one respiratory symptom (primary endpoint).
Abbreviations: RAS, resistance-associated substitution; RT-PCR, reverse transcription-polymerase chain reaction; WT, wildtype

Conclusion

Data are needed from additional studies to adequately assess the risk of transmission of treatment-emergent resistance. In Trial T0834, detection of virus with reduced susceptibility to baloxavir was not detected at baseline (preprophylaxis or prerescue therapy) in any subject associated with an index patient treated with baloxavir marboxil or overall. There were five cases of potential transmission of resistance represented by subjects who were household contacts of an index patient who had been treated with baloxavir marboxil, who had resistant virus at the first time point sequenced, and with circumstances making transmission of resistant virus more likely, as described above; however, selection of resistant virus in these subjects, rather than transmission of resistant virus from the index patient, cannot be ruled out. The Applicant is evaluating the transmission of baloxavir-resistant virus in a trial designed to provide a more definitive assessment of the risk of transmission.

While transmission of resistant virus could not be confirmed in this trial, the frequency of resistance observed in clinical and virologic prophylaxis failures should be reported in labeling to communicate the risk of resistance in the PEP setting.

Recommend labeling edits: Report the frequency of resistance in PEP studies based on the number evaluated for resistance after Xofluza prophylaxis, (b) (4) The frequency of resistance among household contacts who were RT-PCR positive after receiving baloxavir marboxil and evaluated for resistance better communicates the risk of resistance among patients who become infected in this setting.

7.7.2. Increased Frequency of Baloxavir Resistance in Pediatric Patients Compared to Adults and Adolescents

Background

Higher frequencies of treatment-emergent resistance to influenza virus antivirals are often observed in pediatric subjects, including for NAIs (Hoffmann La-Roche 2019). As noted in Section 7.7.1, treatment-emergent resistance to baloxavir has been observed in approximately 3% to 11% of subjects in adult/adolescent treatment trials (See Clinical Virology Reviews),[1,2] whereas in pediatric trials, treatment-emergent resistance to baloxavir has been observed in approximately 22% to 26% of subjects in Trials CP40563, T0822, and T0833 (Table 47). Summary data from a recently completed, single-arm pediatric trial carried out in Japan (T0835; data received September 23, 2020), indicated an overall frequency of treatment-emergent resistance to baloxavir of 43.6% (Table 52). The increased frequency of resistance may lead to prolonged shedding, or to prolonged illness, and may potentiate the transmission of baloxavir-resistant virus.

Assessment

Treatment-emergent resistance in Trials CP40563, T0822, and T0833 was evaluated for all subjects with paired baselined and postbaseline sequencing data to identify known and potentially new baloxavir RAS. Trial CP40563 is described in Section 6.2, and Trials T0822 and T0833 are described in Section 3.2. Trial T0822 was a single-arm, open-label PK and efficacy

study carried out in Japan in 108 otherwise healthy patients 6 months to ≤12 years of age with weight-based dosing of baloxavir marboxil tablets (5 to <10 kg, 5 mg; 10 to <20 kg, 10 mg; 20 to <40 kg, 20 mg; ≥40 kg, 40 mg). Trial T0833 was a single-arm open-label PK and efficacy study carried out in Japan in 33 otherwise healthy subjects <12 years of age and <20 kg dosed by weight with 2% granules of baloxavir marboxil (<10 kg, 1 mg/kg; 10 to <20 kg, 10 mg).

Substitutions meeting the criteria of conferring reduced susceptibility in cell culture were considered RAS in this analyses (Table 47, bold/underlined); all substitutions designated as RAS in pediatric studies and included in subsequent analyses were identified in previous studies and analyses (Ince et al. 2020).[1,2] Potential RAS were those that were either associated with virus rebound or were identified as treatment-emergent in more than one subject across baloxavir clinical trials reviewed to date and that have yet to be evaluated for their impact on susceptibility in cell culture (Table 47, bold); a subset of these substitutions were recommended for further evaluation of their impact on susceptibility in cell culture.[10]

Overall, the frequency range of treatment-emergent RAS in pediatric trials was 22.4 to 25.6%, whereas frequencies in adult and adolescent trials have ranged from approximately 3% to 11%. The highest frequency of treatment-emergent RAS were observed in A/H3N2 virus, while no RAS were observed in type B viruses in pediatric trials (Table 47), consistent with previous observations in adult/adolescent studies in which the highest frequencies of RAS were observed in A/H3N2 virus and very few RAS were observed in type B virus.[1,2]

Of note, no substitutions previously associated with reduced susceptibility to oseltamivir were detected as treatment-emergent in any of the 36 subjects treated with oseltamivir who were evaluated. The lack of treatment-emergent resistance observed in the oseltamivir arm is in contrast to what has been observed in other pediatric studies (Hoffmann La-Roche 2019); however, oseltamivir resistance has more often occurred in A/H1N1 virus, which was represented by only 8 of the 36 subjects evaluated for oselstamivir resistance in Trial CP40563 (Table 47).

[10] See PMR 1

Table 47. Treatment-Emergent Substitutions Identified in Pediatric Studies

Study	Treatment	Gene	Type/Subtype	Subjects With Paired Baseline and Postbaseline Sequencing	Any TE Variant	TE RAS	% of Subjects With RAS	TE Substitutions (n, if multiple)[2]
CP40563	Baloxavir	PA	All	58	20	13	22.40%	
			A/H1N1	12	5	2	16.70%	I38S/T, K328E[3], T363I[4], P653T
			A/H3N2[1]	44	15	11	25%	E23K(1), I38M(1)/T(9), E80K, T208I, E399K, I690V[4]
			B	2	0	0	0%	
		PB1	All	5	0	0	0%	
			A/H1N1	2	0	0	0%	
			A/H3N2	3	0	0	0%	
			B	0	0	0	0%	
		PB2	All	5	0	0	0%	
			A/H1N1	2	0	0	0%	
			A/H3N2	3	0	0	0%	
			B	0	0	0	0%	
	Oseltamivir	NA	All	36	4	0	0%	
			A/H1N1	8	0	0	0%	
			A/H3N2	26	4	0	0%	I28T, T242I, H264Y, S416G
			B	2	0	0	0%	
		PA	All	33	1	0	0%	
			A/H1N1	5	1	0	0%	F611L
			A/H3N2	26	0	0	0%	
			B	2	0	0	0%	

Study	Treatment	Gene	Type/Subtype	Subjects With Paired Baseline and Postbaseline Sequencing	Any TE Variant	TE RAS	% of Subjects With RAS	TE Substitutions (n, if multiple)[2]
T0822[5]	Baloxavir	PA	All	78	23	20	25.6%	
			A/H1N1	2	0	0	0%	
			A/H3N2	70	23	20	28.6%	**A37T(1)**, **I38M(3)/T(15)**, S60P, T162A, **E199G(1)**, N412D, V517A, S526F, E623K
			B	8	0	0	0%	
		PB1	All	25	2	0	0%	
			H1N1	2	0	0	0%	
			H3N2	20	2	0	0%	I205M, G250E, M290T
			B	3	0	0	0%	
		PB2	All	25	5	0	0%	
			H1N1	2	0	0	0%	
			H3N2	20	5	0	0%	G60D, V105M, E171K, K197R, R353K, I385V
			B	3	0	0	0%	
T0833	Baloxavir	PA	All	26	11	6	23.1%	
			A/H1N1	6	5	2	33.3%	**E23K/G/R(1)**, **I38T(1)**, Y24H, V122A, R356K, G/W406W
			A/H3N2	9	4	4	44.4%	I38M(2)/T(2), I201T
			B	11	2	0	0%	N354K, L578I, E680K
		PB1	All	15	1	0	0%	
			A/H1N1	1	0	0	0%	
			A/H3N2	4	0	0	0%	
			B	10	1	0	0%	**A/T34T[4, 6]**
		PB2	All	15	0	0	0%	
			A/H1N1	1	0	0	0%	
			A/H3N2	4	0	0	0%	
			B	10	0	0	0%	

Source: FDA Virology analysis
[1] Only 43 subjects had paired baseline. Subject CP40563 (b) (6) had no BL sequencing but was included because of an I38T substitution identified in postbaseline sequencing was assumed to be treatment-emergent for this analysis.
[2] RASs are bold and underlined. RASs in bold have not been evaluated for their impact on baloxavir suscept bility in cell culture and were treatment-emergent in more than one subject (b) (6) (within type/subtype) in an analysis of sequence data from all baloxavir marboxil trials submitted to the FDA to date (T0821, T0822, T0831, T0832, T0833, T0834, and CP40563) or were associated with rebound (A34T, T363I, I690V).
[3] Identified in more than one subject.
[4] Associated with virus rebound (any rise in virus titer).
[5] In Trial T0822, two subjects with coinfections (A/H1N1+A/H3N2 and A/H3N2+B) were successfully evaluated for both viruses.
[6] Phenotyping in a reverse genetics system was attempted but no virus was recovered.
Abbreviations: NA, not applicable; PA, polymerase acidic; RAS, resistance-associated substitution; TE, treatment-emergent

Frequency of Treatment-Emergent Resistance by Age and Weight

Treatment-emergent RAS frequency in pooled data from pediatric Trials T0822, T0833, and CP40563 was evaluated based on age and weight. Treatment-emergent RAS were observed most frequently in subjects weighing between 10 and <20 kg (33.9% overall; and up to 50% among A/H3N2-infected subjects), and least frequently in subject weighing <10 kg (16.7% overall) (Table 48). The frequency among pediatric subjects weighing ≥20 kg or ≥40 kg was approximately 19%. Among cumulative age groups, the frequency of treatment-emergent RAS was highest in subjects <5 years of age (36.5% overall, and up to 58.6% among A/H3N2-infected subjects) (Table 48). Importantly, while the lowest frequency was observed in subjects ≥8 years of age (16.4% overall), the downward trend does not continue with increased age, as frequencies rise in subject ≥10 years of age (24.1%) (Table 48). These data do not reveal a clear age or weight-based cut-off for reduced frequency of treatment-emergent RAS.

Table 48. Frequency of Baloxavir Marboxil Treatment-Emergent RAS in Pediatric Trials by Age and Weight Bands: Pooled Analysis of Trials T0822, T0833, and CP40563

	All			A/H1N1[1]			A/H3N2[1]			B[1]		
Parameter	Evaluated (n)	RAS (n)	% RAS	Evaluated (n)	RAS (n)	% RAS	Evaluated (n)	RAS (n)	% RAS	Evaluated (n)	RAS (n)	% RAS
Weight categories												
<10 kg	12	2	16.7	2	1	50	4	1	25	6	0	0
10 to <20 kg	56	19	33.9	9	1	11.1	36	18	50	9	0	0
≥20 kg	95	18	18.9	8	2	25	80	16	20	5	0	0
≥40 kg	16	3	18.8	1	0	0	15	3	20	0	0	NA
Age categories												
<5 years	52	19	36.5	10	2	20	29	17	58.6	12	0	0
≥5 years	111	20	18	9	2	22.2	91	18	19.8	8	0	0
<6 years	67	21	31.3	11	2	18.2	39	19	48.7	15	0	0
≥6 years	96	18	18.8	8	2	25	81	16	19.8	5	0	0
<7 years	78	22	28.2	13	2	15.4	48	20	41.7	15	0	0
≥7 years	85	17	20	6	2	33.3	72	15	20.8	5	0	0
<8 years	102	29	28.4	16	3	18.8	66	26	39.4	18	0	0
≥8 years	61	10	16.4	3	1	33.3	54	9	16.7	2	0	0
<9 years	115	30	26.1	16	3	18.8	77	27	35.1	19	0	0
≥9 years	48	9	18.8	3	1	33.3	43	8	18.6	1	0	0
<10 years	134	32	23.9	17	3	17.6	94	29	30.9	20	0	0
≥10 years	29	7	24.1	2	1	50	26	6	23.1	0	0	NA
<11 years	151	36	23.8	18	4	22.2	109	32	29.4	20	0	0
≥11 years	12	3	25	1	0	0	11	3	27.3	0	0	NA

Source: FDA Virology analysis
[1] Mixed infections excluded
Abbreviations: RAS, resistance-associated substitution

Association of RAS With Selected Baseline Parameters

The baseline characteristics of vaccination status, hemagglutination inhibition (HI) titer, baseline virus titer, and age were evaluated for their association with treatment-emergent resistance (Table 49). Vaccination status, HI titer, weight, and age were selected for this analysis as they are associated with variation in pre-existing immunity, which may constrain virus replication after initial infection and influence the frequency at which treatment-emergent resistant variants are selected.

In addition, baseline virus titer may correlate with the effective viral population size upon which baloxavir selection initially acts, and thereby could influence the frequency of selection of resistant virus. In this analysis, lower HI titer (median 20 versus 40 HI ratio), younger age (median 5 versus 7 years of age), and lower weight (which covaries with age) were statistically significantly associated with treatment-emergent RAS (Table 49).

Table 49. Association of Treatment-Emergent RAS With Baseline Characteristics in Type A Virus Infections

Baseline Characteristic (ITTI, Type A Infections)	All		CP40563		T0822		T0833	
	TE RAS	No TE RAS	TE RAS	No TE RAS	TE RAS	No TE RAS	TE RAS	No TE RAS
Vaccination within 6 months								
% Vaccinated (n)	41% (39)	26% (100)	54% (13)	26% (42)	40% (20)	22% (49)	17% (6)	44% (9)
P-value TE vs. No TE RAS (Fisher's exact)	0.1011		0.092		0.1514		0.5804	
Baseline HI antibody titer to subtype (dilution ratio)								
N	26	57			20	48	6	9
Median	20	40			20	40	10	10
95% CI lower limit	10	20	No data		10	40	10	10
95% CI upper limit	40	40			40	80	160	20
P-value TE vs. No TE RAS (Mann-Whitney)	0.0188				0.0148		0.8022	
Baseline virus titer (log_{10} $TCID_{50}$/mL)								
N	39	101	13	43	20	49	6	9
Median	5.7	5.25	5	4.75	5.7	6.2	6.35	7
95% CI lower limit	4.75	4.75	4.5	4	4.7	5	5.5	4.7
95% CI upper limit	6	5.7	6	5.25	6.5	6.8	7.5	7.5
P-value TE vs. No TE RAS (Mann-Whitney)	0.5353		0.2774		0.4355		0.8881	
Weight (kg)								
N	39	101	13	43	20	49	6	9
Median	18.9	25	22.7	26	20.05	25	13	11.8
95% CI lower limit	15.5	22.3	15.8	20.5	15.5	23.7	7.9	8.4
95% CI upper limit	23.3	26.7	31.5	29.99	26.6	28.3	16.3	18.5
P-value TE vs. No TE RAS (Mann-Whitney)	0.004		0.3385		0.0051		0.9828	

Baseline Characteristic (ITTI, Type A Infections)	All		CP40563		T0822		T0833	
	TE RAS	No TE RAS	TE RAS	No TE RAS	TE RAS	No TE RAS	TE RAS	No TE RAS
Age (years)								
N	39	101	13	43	20	49	6	9
Median	5	7	7	7	6	9	2.5	1
95% CI lower limit	3	7	3	5	3	7	0	0
95% CI upper limit	7	8	9	8	9	9	4	5
P-value TE vs. No TE RAS (Mann-Whitney)	0.011		0.5861		0.0121		0.9808	

Source: FDA Virology analysis
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution; TE, treatment-emergent; ITTI, intent-to-treat-infected

The association of increased frequency of treatment-emergent resistance with lower baseline HI titer and younger age is consistent with the analysis of frequency by age and weight bands and previous reports that have evaluated these associations in pediatric subjects (Hirotsu et al. 2020) and with the hypothesis that fewer immunological constraints on virus replication may allow selection of resistant virus. Counterintuitively, there was no clear association with vaccination within 6 months. Likewise baseline virus titer was not clearly associated with the frequency of treatment-emergent resistance. As additional data are accumulated, the reasons for these associations, or lack there-of, may be better elucidated.

Impact on Baloxavir Treatment-Emergent RAS on Selected Outcomes

In a combined analysis of subjects infected with type A virus and evaluated for treatment-emergent resistance, treatment-emergent RAS were statistically significantly associated with increased time to sustained virus negativity (Table 50), consistent with a statistically significant association with increased rates of virus rebound (Table 51). Treatment-emergent RAS were also associated with a trend toward increases in time to alleviation of symptoms (Table 50).

Table 50. Association of Treatment-Emergent RAS With TTSVN and TTAS in Type A Virus Infections in Pediatric Studies

	ALL		CP40563		T0822		T0833	
Endpoint	**TE RAS**	**No TE RAS**	**TE RAS**	**No TE RAS**	**TE RAS**	**No TE RAS**	**TE RAS**	**No TE RAS**
TTSVN[1]								
N	39	100	13	42	20	49	6	9
Median (hours)	192	24	168	24	180	24	228	192
95% CI lower limit	144	24	72	24	144	24	24	24
95% CI upper limit	216	48	216	24	264	48	264	216
P-value TE vs. No TE RAS	<0.0001		<0.0001		<0.0001		0.2344	
TTAS[2]								
N	38	100	13	42	19	49	6	9
Median (hours)	100.3	74.86	126.9	116.3	69.62	42.78	193.7	38.92
95% CI lower limit	69.62	53.7	91	87.6	38.23	28.57	25	21.67
95% CI upper limit	144.4	94.7	216.5	163.2	116.9	68.4	272.8	154.3
P-value TE vs. No TE RAS	0.0997		0.4743		0.1372		0.0663	

Source: FDA Virology analysis
[1] TTSVN was defined by the last time point after which no positive time point was reported. For subjects who did not achieve negativity and who were not assessed at Day 11 or later, TTSVN was imputed as 264 hours (Day 12). Analyses includes all subjects who were evaluated for treatment-emergent resistance. All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA)
[2] TTAS is a composite of similar endpoints from each study; there were minor differences in the definition of time to alleviation of symptoms or illness between studies. Analyses includes all subjects who were evaluated for treatment-emergent resistance, including those who did not achieve alleviation within the defined observation period; the reported time to event value was used for each subject. All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution; TE, treatment emergent; TTAS, time to alleviation of symptoms; TTSVN; time to sustained virus negativity

Table 51. Association of Treatment-Emergent RAS With Virus Rebound in Pediatric Studies in Type A Virus Infections

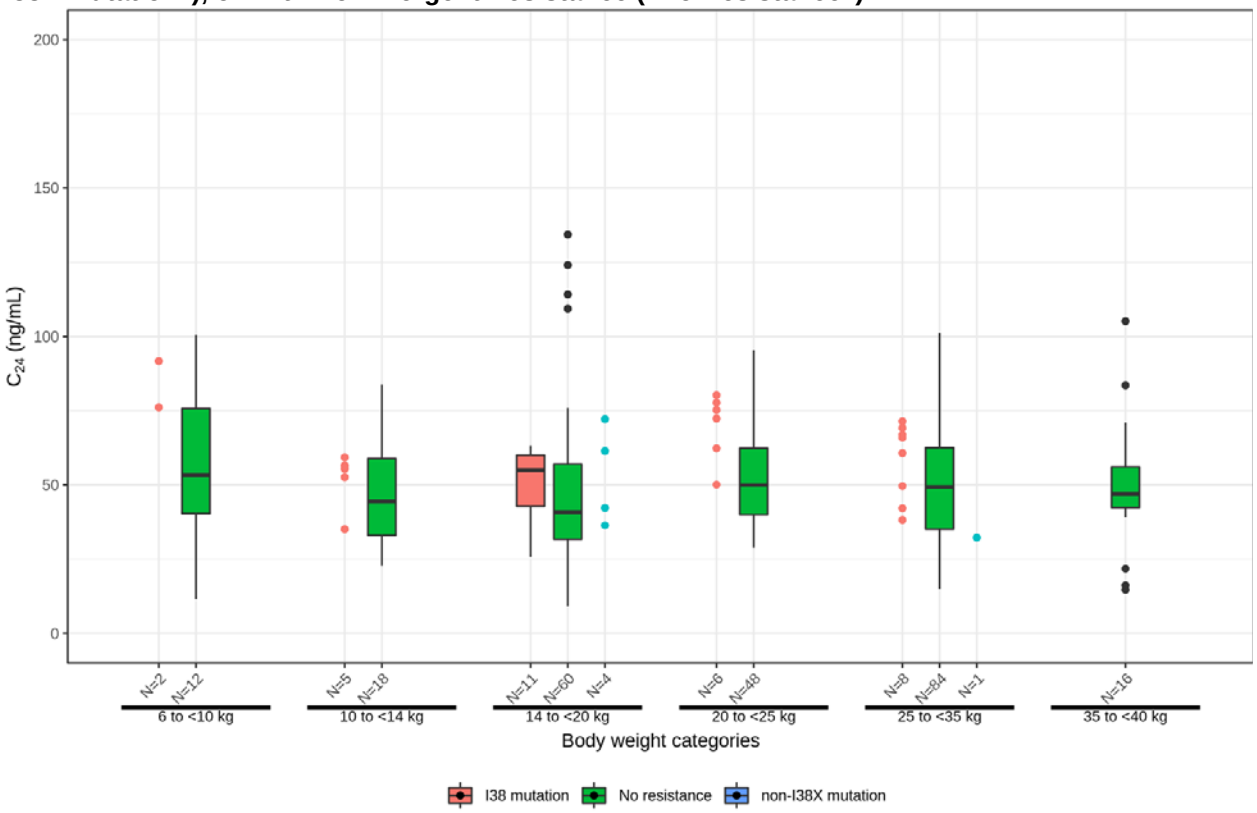
	% of Subjects in Each Resistance Category With Virus Rebound[1] (n/N)			
Resistance Category	**All**	**CP40563**	**T0822**	**T0833**
TE RAS	79% (31/39)	77% (10/13)	80% (16/20)	83% (5/6)
No TE RAS	21% (21/101)	21% (9/43)	14% (7/49)	56% (5/9)
P-value[2]	<0.0001	0.0004	<0.0001	0.5804

Source: FDA Virology analysis
[1] Rebound was defined as any rise in virus titer relative to the previous time point
[2] Fisher's exact test
Abbreviations: RAS, resistance-associated substitution; TE, treatment-emergent

Association of Resistance With Pharmacological Parameters

FDA virology analysis of pooled data from pediatric treatment trials (T0822, T0833, and CP40563) indicate that there is no statistically significant association of serum baloxavir concentrations at 24 or 72 hours post administration with treatment-emergent RAS. Median C_{24} values were 61.05 ng/mL (n=34; 95% CI, 52.6-67.6 ng/mL) versus 55.5 ng/mL (n=83; 95% CI, 49.4-64.4 ng/mL) for subjects with and without RAS, respectively, and the median C_{72} values were 17.24 ng/mL (n=13; 95% CI, 15.15-28.55 ng/mL) versus 16.53 ng/mL (n=39; 95% CI, 12.87-19.97 ng/mL). C_{24} and C_{72} values in subjects with treatment-emergent RAS were numerically higher compared to those without treatment-emergent RAS, although the difference was not statistically significant. These results are consistent with the findings reported by the Applicant, who compared the distributions of C_{24} and C_{72} values in subjects with and without RAS across weight bands in pooled data from both PEP and pediatric treatment trials and found no clear association between these parameters and treatment-emergent resistance (Figure 5 and Figure 6).

Figure 5. Baloxavir C_{24} Values in Subjects With I38X RAS ("I38X Mutation"), Non-I38X RAS ("Non-I38X Mutation"), or With No Emergent Resistance ("No Resistance")[1]

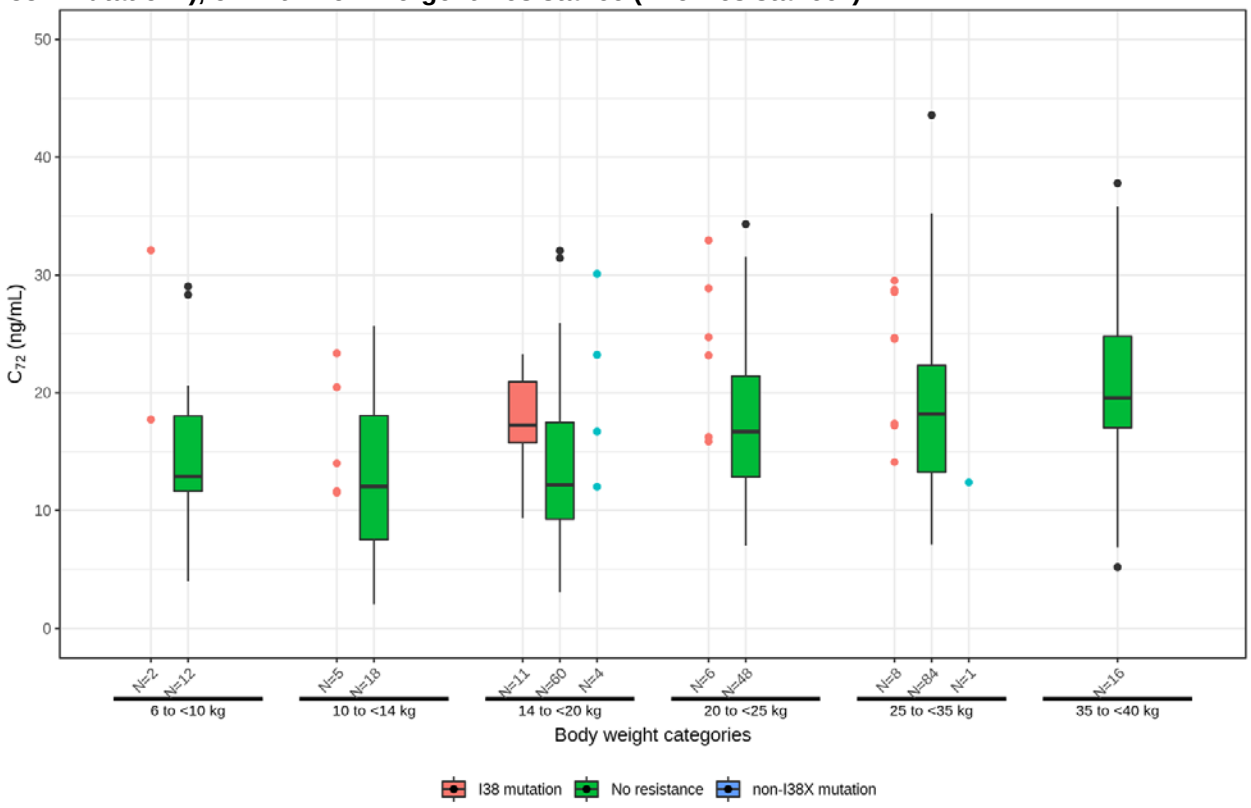


Source: Applicant analysis

[1] Data are pooled from Trials CP40563, T0822, T0833, and T0834 and stratified by the indicated body weight bands

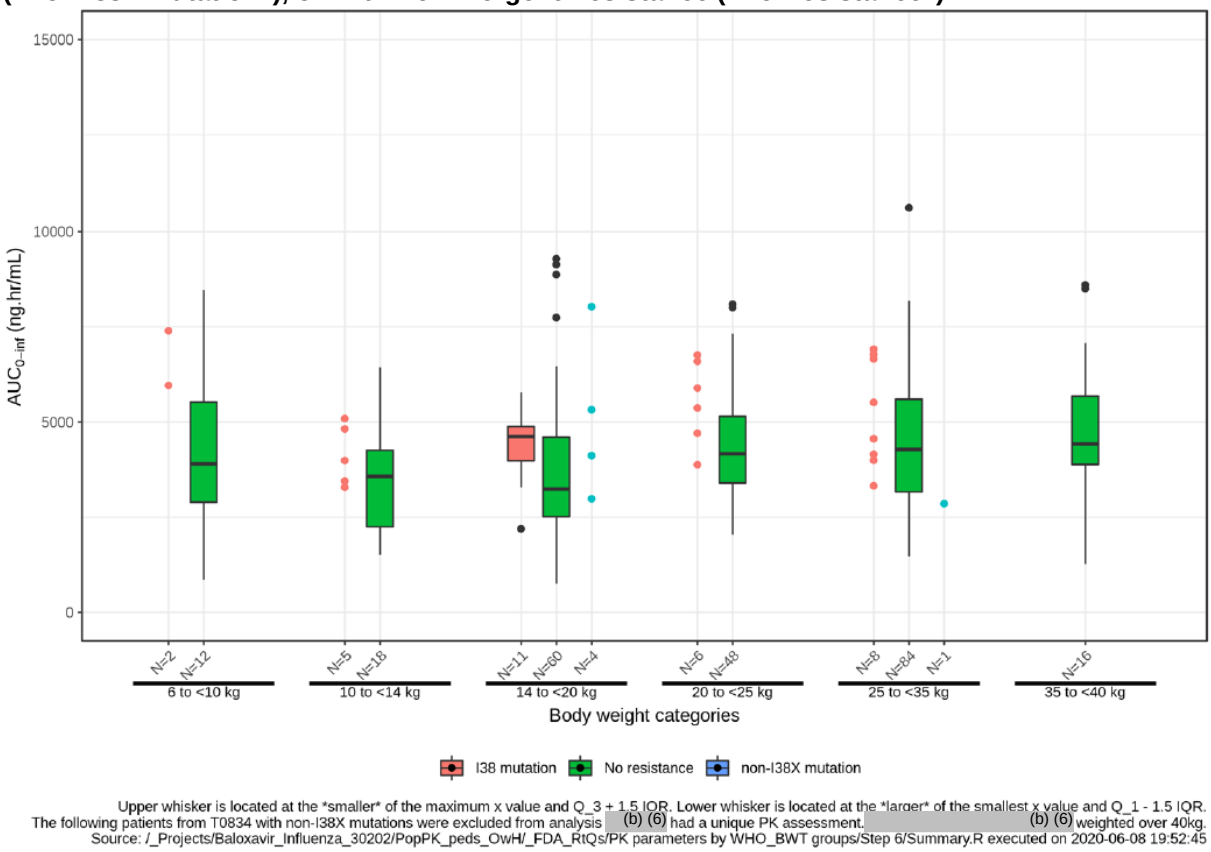
Abbreviations: C_{24}, concentration at 24 hours; RAS, resistance-associated substitution

Figure 6. Baloxavir C_{72} Values in Subjects With I38X RAS ("I38X Mutation"), Non-I38X RAS ("Non-I38X Mutation"), or With No Emergent Resistance ("No Resistance")[1]



Source: Applicant analysis
[1] Data are pooled from Trials CP40563, T0822, T0833, and T0834 and stratified by the indicated body weight bands
Abbreviations: C_{72}, concentration at 72 hours; RAS, resistance-associated substitution

Figure 7. Baloxavir $AUC_{0\text{-}inf}$ Values in Subjects With I38X RAS ("I38X Mutation"), Non-I38X RAS ("Non-I38X Mutation"), or With No Emergent Resistance ("No Resistance")[1]



Source: Applicant analysis
[1] Data are pooled from Trials CP40563, T0822, T0833, and T0834 and stratified by the indicated body weight bands
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve over the total time; RAS, resistance-associated substitution

Additional Supportive Data From Pediatric Trials of Baloxavir Marboxil

Preliminary, top-line results from a recently completed pediatric study of baloxavir marboxil carried out in Japan in otherwise healthy pediatric subjects weighing <20 kg (Trial T0835) and submitted by the Applicant provided additional information regarding the frequency and impact of treatment-emergent resistance in pediatric subjects. In this trial, subjects diagnosed with influenza virus were dosed according to weight, with subjects weighing <10 kg and ≥3 months of age dosed with 2 mg/kg, and subjects weighing 10 to <20 kg dosed with 20 mg/kg of baloxavir marboxil. Of the 43 subjects in the ITTI population, 39 were evaluated for baloxavir resistance by PA sequencing of baseline and postbaseline samples to identify RAS at positions E23 or I38.

Overall, 43.6% (17/39) of subjects had treatment-emergent RAS, including 2/9 (22.2%) and 15/20 (75%) of subjects infected with A/H1N1 and A/H3N2 virus, respectively (Table 52). None of the 10 (0%) subjects with type B virus infections had treatment-emergent RAS detected. Similar frequencies of treatment-emergent resistance were detected in the 10 to <20 kg weight group (43.8% [14/32]; receiving 20 mg baloxavir marboxil) and <10 kg weight group (42.9% [3/7]; receiving 2 mg/kg), indicating that the increased dose per kg did not impact the frequency of treatment-emergent resistance in this study.

Table 52. Frequency of Treatment-Emergent RAS (E23 or I38 Substitutions) by Weight/Dose Band in ITTI Subjects With Paired Baseline and Postbaseline PA Sequence Data in Trial T0835

Body Weight	Overall Frequency of RAS	Virus Type/Subtype A/H1N1pdm	Virus Type/Subtype A/H3	Virus Type B
Overall	43.6% (17/39)	22.2% (2/9)	75.0% (15/20)	0.0% (0/10)
≥10 to <20 kg [20 mg BXM]	43.8% (14/32)	25.0% (2/8)	85.7% (12/14)	0.0% (0/10)
<10 kg [2 mg/kg BXM]	42.9% (3/7)	0.0% (0/1)	50.0% (3/6)	---

Source: Applicant analysis
Abbreviations: BXM, baloxavir marboxil; ITTI, intent-to-treat-infected; RAS, resistance-associated substitution; PA, polymerase acidic

As observed in the pediatric treatment trials submitted to support the pediatric supplemental NDA, median time to alleviation of illness was prolonged in subjects with treatment-emergent RAS compared to those without (40.0 hours versus 30.6 hours, respectively) (Table 53) and the median time to cessation of viral shedding was prolonged in subjects with treatment-emergent RAS compared to those without (216 hours versus 156 hours, respectively) (Table 54).

Table 53. Analysis of Time to Alleviation of Illness by RAS Status in ITTI Subjects With Paired Baseline and Postbaseline PA Sequence Data in Trial T0835

Summary Statistics	Subjects With Treatment-Emergent RAS	Subjects Without Treatment-Emergent RAS
n	17	22
Median (hours)	40.0	30.6
95% CI (hours)	19.9, 92.6	23.8, 74.1

Source: Applicant analysis
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected; RAS, resistance-associated substitution; PA, polymerase acidic

Table 54. Analysis of Time to Sustained Cessation of Influenza Virus Shedding by RAS Status in ITTI Subjects With Paired Baseline and Postbaseline PA Sequence Data in Trial T0835

Summary Statistics	Patients With Treatment-Emergent RAS	Patients Without Treatment-Emergent RAS
n	17	22
Median (hours)	216.0	156.0
95% CI (hours)	168.0, 288.0	24.0, 192.0

Source: Applicant analysis
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected; RAS, resistance-associated substitution; PA, polymerase acidic

Overall, these data consistently demonstrate a substantially higher frequency of treatment-emergent resistance in pediatric patients that can reduce the impact of treatment on the duration of illness and result in prolonged virus shedding; however, the frequencies of treatment-emergent RAS observed in Trial T0835 are from a relatively small number of subjects and there was no comparator arm.

Conclusion

Based on the analysis of data submitted to the NDA, the frequency of treatment-emergent resistance in pediatric trials was approximately 2- to 15-fold higher (including top-line results from Trial T0835) than what has been observed in adult/adolescent trials, and treatment-emergent resistance was associated with prolonged shedding and a consistent trend toward prolonged time to alleviation of illness in each pediatric trial. In placebo-controlled adult/adolescent trials, treatment-emergent resistance has resulted in virus rebound and prolonged median time to sustained virus negativity compared to placebo and prolonged median

time to alleviation of illness, although not in comparison to placebo. Treatment-emergent resistance in type B virus infections has remained rare, possibly due in part to the reduced activity of baloxavir against type B virus. Among type A virus infections, A/H3N2 infections have exhibited the highest frequency of treatment-emergent resistance in both pediatric and adult/adolescent studies (approximately 1.5- to 2-fold higher than A/H1N1 infections).

Risk of Transmission of Baloxavir-Resistant Virus

The increased frequency of treatment-emergent resistance to baloxavir in the pediatric population and the association of treatment-emergent baloxavir resistance with virus rebound and prolonged shedding increases the potential risk of transmission of baloxavir-resistant virus from pediatric patients. While, transmission of resistant virus was not definitively demonstrated among the 46 households evaluated in which the index patient received baloxavir marboxil treatment in the postexposure prophylaxis trial, there were at least five cases of potentially transmitted resistance that could not be ruled out (see Section 7.7.1). When antiviral resistant influenza virus is not widely circulating, the most likely source for resistant virus in household and community outbreaks has been from antiviral selection in a treated individual (Saito et al. 2002; Schilling et al. 2004).

Prior to baloxavir marboxil approval in Japan and the United States, baloxavir RAS were extremely rare among viruses sampled in surveillance studies (Gubareva et al. 2019; Takashita et al. 2019b). Since approval, cases of apparent or suspected transmission of baloxavir-resistant influenza viruses have been documented in published studies (Takashita et al. 2019a; Takashita et al. 2019c; Imai et al. 2020), and additional cases continue to be reported in ongoing surveillance (NIID 2020); however, baloxavir-resistant virus prevalence remains low and is only sporadically detected, indicating it is not yet widely circulating or rising in frequency (CDC 2020; NIID 2020). I38 substitutions have been shown to have variable impacts on replication capacity of influenza virus in cell culture studies (Omoto et al. 2018; Chesnokov et al. 2020; Imai et al. 2020), while recently collected I38 variants have demonstrated comparable transmissibility to wild type virus in ferrets (Imai et al. 2020).

Frequency and Impact of Treatment-Emergent Resistance for Other Currently Approved Influenza Antivirals

As with baloxavir, treatment-emergent resistance to oseltamivir occurs at higher frequency in children. In an analysis of the Influenza Resistance Information Study (IRIS), treatment-emergent resistance was evaluated using allele-specific RT-PCR targeting known oseltamivir resistance-associated mutations (IRIS) (NIH 2009; Roosenhoff et al. 2020). Lina et al. found that 11.8% of patients 1 to 5 years of age and 1.4% of patients >5 years of age in IRIS who were infected with influenza A virus and treated within 48 hours of symptoms onset had postbaseline resistance detected which was associated with longer duration of viral RNA shedding (10.9 versus 8.1 days for patients with and without treatment-emergent resistance to oseltamivir) (Lina et al. 2018). No oseltamivir resistance was observed in the approximately 330 type B virus-infected subjects in this study (Roosenhoff et al. 2020). Among type A virus, frequency of oseltamivir resistance among the 1622 subjects evaluated postbaseline was 1.9% and 5.8% in A/H1N1 and A/H3N2 virus infections, respectively. In type A subtype and age subsets, the highest frequencies of postbaseline oseltamivir resistance observed within age group bands were 36.4% (4/11) in subjects <1 year of age and 15% (31/206) in subjects up to 5 years of age

infected with A/H1N1 virus. Overall, frequencies of postbaseline oseltamivir resistance were 8.5% (42/493) for subjects ≤5 years of age and 1.6% (7/438) for subjects 6 to 12 years of age (NIH 2009).

In an analysis of the percentage of subjects with symptoms resolution on Day 6 in the IRIS study, including all influenza virus-infected, oseltamivir-treated subjects for whom there were data (n=1730), there was a trend toward a lower percentage of resolution in subjects with resistance (55.9%, n=59) compared to those without resistance (61.4%, n=1671), although this difference was not statistically significant (P=0.4464; Cochran-Mantel-Haenszel) (NIH 2009). Among subjects treated within 48 hour of symptoms onset, there was no difference observed in time to improvement of symptoms between subjects with (4 days [n =47]) and without (5 days [n =1115]) postbaseline oseltamivir resistance (Lina et al. 2018).

In other, smaller studies, treatment-emergent resistance to oseltamivir has been observed to range up to 27% in pediatric subjects, although with variable impacts on duration of virus shedding, and no consistent impact on clinical outcome (Kiso et al. 2004; Stephenson et al. 2009).

Treatment-emergent resistance in pediatric patients to currently approved NAIs other than oseltamivir has remained less frequent. In the pediatric trials evaluating peramivir, treatment-emergent resistance was observed in approximately 3 to 8% of subjects.[11] Zanamivir is indicated for patients 7 years of age and older and treatment-emergent resistance in the pediatric population has been identified rarely (Yates et al. 2013). It should be noted that in some studies of treatment-emergent resistance to NAIs, relatively insensitive phenotypic-based assays were used, or virus isolates were amplified in cell culture prior to analyses. These approaches may obscure resistant viral variants from detection, particularly because NAI-resistant variants often emerge as a mixture with wild type virus.

Prior to the increase in widespread, circulating adamantane resistance beginning around 2003 (Bright et al. 2005), treatment-emergent resistance to amantadine and rimantadine was consistently observed at high frequency in pediatric patients. Reported frequencies of postbaseline adamantane resistance for type A virus (adamantanes are not active against type B virus) have ranged from 28% (31/111) (Saito et al. 2003) to 45% (10/22) in pediatric subjects, and was observed in untreated individuals in some cases (Hall et al. 1987). Prior to the widespread circulation of adamantane-resistant influenza A virus, it was recognized in the clinical experience that there was a relatively low barrier to resistance to adamantanes, that resistance emerged frequently during treatment, and that resistant viruses were relatively fit and were transmitted to community contacts (Saito et al. 2003).

Treatment-emergent resistance to baloxavir has been consistently above 19% in pediatric studies, and up to 44% in the most recent pediatric study submitted, and is associated with a substantial increase in the duration of virus shedding as well as prolonged the duration of illness (Table 50) (Hirotsu et al. 2020; Ince et al. 2020; Ison et al. 2020; Sato et al. 2020; Uehara et al. 2020). Given the relatively elevated frequency of treatment-emergent baloxavir resistance in pediatric subjects, and the associated prolonged virus shedding, there may be an increased risk to caregivers and household and community contacts, including those at high risk influenza

[11] See original NDA 206426 and Supplement 004

complications, of contracting virus with reduced susceptibility to baloxavir, which may limit their treatment options.

Based on the totality of data regarding baloxavir resistance in pediatric patients, the review team concluded that baloxavir marboxil will not be approved at this time in pediatric patients 1 to <12 years of age for treatment or PEP, because there is an unknown but potentially elevated risk of transmission of baloxavir-resistant virus from pediatric patients to close contacts and to community members. The effectiveness of baloxavir marboxil treatment on patients who are initially infected with a baloxavir-resistant virus is currently unknown; however, widespread baloxavir resistance could have major public health implications if the loss of baloxavir marboxil as an effective treatment option coincides with widespread resistance to one or more NAIs in the future. Additional data are needed to evaluate and potentially mitigate the risks associated with baloxavir resistance in the pediatric population, including an understanding of the risk of transmission of resistant virus to household contacts and the potential for alternative treatment strategies to reduce treatment-emergent resistance to baloxavir.

Strategies to Limit Risk Associated With Treatment-Emergent Resistance in Pediatric Patients

The lack of a clear association of treatment-emergent resistance with serum C_{24} and C_{72} values indicates that increased baloxavir doses or repeat baloxavir dosing may not reduce the incidence of treatment-emergent resistance. Low serum hemagglutination inhibition titer and younger age were associated with treatment-emergent resistance, consistent with lower levels of pre-existing immunity observed in young children, which may allow for selection of resistant virus. Given the potential for treatment-emergent resistance to affect the clinical response to treatment, as well as the increased potential for transmission of resistance from pediatric patients, studies should be considered to evaluate measures to mitigate treatment-emergent resistance in the pediatric population. With the development of baloxavir marboxil, evaluations of combination antiviral therapy for influenza may be an option and should be considered for the pediatric population, which both exhibit higher frequencies of treatment-emergent resistance and are more often the source of infection in households (Table 47, Table 90, (Lau et al. 2012)). The potential benefits include both the preservation of multiple classes of influenza drugs and improved clinical efficacy.

Additional measures were considered to address the high frequency of treatment-emergent resistance in pediatric subjects and potential associated risks. Additional language was considered for inclusion in labeling that would highlight the increased frequency of treatment-emergent resistance in pediatric subjects and associated prolongation of virus shedding that could increase the potential for transmission of resistant virus to household or community contacts.

The review team also concluded that labeling should include a statement highlighting the elevated frequency of treatment-emergent resistance in pediatric subjects, consistent with labeling for other influenza virus antivirals (Hoffmann La-Roche 2019).

In addition, a postmarketing requirement (PMR) will be issued to the Applicant to evaluate the impact of the following substitutions identified in pediatric studies on the susceptibility of virus to baloxavir in cell culture: PA substitutions R269I, V330I, K328E and T363I in A/H1N1 virus and I554V in A/H3N2 virus. These substitutions were identified as treatment-emergent in more than one subject (K328E) or were associated with virus rebound (T363I) or were associated with

baseline EC_{50} values ≥3-fold the median normalized EC_{50} value within virus subtypes (R269I, V330I, and I554V).

Additional Data Needed to Address the Risk Posed by Treatment-Emergent Resistance

Due to the high frequency of treatment-emergent baloxavir resistance observed in pediatric subjects <12 years of age in the clinical trials submitted with these applications, the review team concluded that because of the risk of widespread transmission of baloxavir resistance, particularly from prolonged viral shedding in this age group, it would not be prudent to approve baloxavir marboxil for use in treatment or postexposure prophylaxis in pediatric patients 12 years of age and younger at this time.

Additional data that may be helpful in addressing this risk include data from a currently ongoing trial in which the Applicant is evaluating the transmission of baloxavir-resistant virus from infected subjects treated with baloxavir marboxil, including pediatric subjects, to untreated household contacts. These data may help to establish the risk of transmission of resistant virus that emerges during treatment; however, it is not clear at this time that the transmission study will adequately model the risk of transmitted baloxavir resistance, particularly from pediatric subjects, in the population. In addition, there is an ongoing Pediatric Research Equity Act (PREA) PMR study of baloxavir marboxil treatment in pediatric patients from birth to <1 year of age which may shed additional light on the development of baloxavir resistance in the youngest pediatric patients. (b) (4)

7.7.3. Potential for Medication Errors With Baloxavir Marboxil Granule Formulation in Pediatric Patients 1 to <12 Years of Age

Background

A new formulation of baloxavir marboxil, granules for oral suspension, 2 mg/mL or for enteral use, was developed by the Applicant for use in pediatric patients and in other patients who are unable to swallow a pill. Baloxavir marboxil oral suspension will be supplied to pharmacies as dry granules in a bottle. Prior to dispensing to a patient or parent/caregiver, 20 mL of water will be added to the bottle by a pharmacist or other healthcare provider. Each bottle contains 40 mg of baloxavir per 20 mL of volume and the final concentration will be 2 mg/mL. Patients ≥12 years of age will receive a weight-based dose of 40 mg, or one bottle of granules for oral suspension, 2 mg/mL for patients weighing (b) (4) kg to <80 kg and 80 mg, or two bottles, for patients weighing ≥80 kg. (b) (4) Recommended dosage of the suspension is included in Table 2 of section 2.2, Recommended Dosage, of the proposed package insert (Genentech 2018). (b) (4)

Assessment

If a dosing error occurs and a patient is underdosed, baloxavir marboxil may not be effective. However, in the Phase 2, dose-finding trial of baloxavir marboxil in adults, efficacy was observed at all doses studied (single oral doses of 10 mg, 20 mg and 40 mg).[12] The Applicant chose to use the highest dose in Phase 3 partly because safety findings were not dose-related and to help prevent the development of amino acid substitutions conferring antiviral resistance. However, in Phase 3, resistance did not correlate with trough concentration. While it is possible that underdosing may result in decreased efficacy, there are no data from clinical trials to clearly define this risk.

Safety and pharmacokinetic data were reviewed to determine safety at the highest exposures of baloxavir marboxil in clinical trials and to predict what exposures may be observed in pediatric patients who receive overdoses of baloxavir marboxil. The highest dose of baloxavir marboxil that has been studied in clinical trials is a single 80-mg dose in the thorough QT (TQT) trial, which was submitted with the original NDA. This study was conducted in 63 Japanese subjects, who received a single 40-mg dose of baloxavir marboxil, a single 80-mg dose of baloxavir marboxil, or moxifloxacin. The pharmacokinetics of baloxavir marboxil differ in Asian and non-Asian patients; baloxavir exposure is approximately 35% lower in non-Asians as compared to Asians (Genentech 2018). Therefore, the exposures in Asian subjects in the TQT study were substantially higher than what would be observed in non-Asians who received a single 80-mg dose. In this study, no adverse events were reported in subjects in the baloxavir marboxil 40-mg

[12] See Clinical Review of NDA 210854

arm, two subjects (3%) reported AEs in the baloxavir marboxil 80-mg arm, and two subjects (3%) reported AEs in the placebo arm. The two AEs in the baloxavir marboxil 80-mg arm were moderate headache and mild nasopharyngitis.

Baloxavir exposures in non-Asian and Asian pediatric subjects are compared to baloxavir exposures in Asian adult subjects who received a single 80-mg dose in the TQT study in the following table.

Table 56. Median Baloxavir Exposure in Pediatric Subjects (Weighing 10 to 14 kg) and Asian Adults (TQT Study)

Parameter	40-mg Dose (Non-Asian Pediatrics)[1]	20-mg Dose (Non-Asian Pediatrics)[2]	20-mg Dose (Asian Pediatrics)[3]	80-mg Dose Asian Adults (TQT Study)[3]
$AUC_{0\text{-}inf}$ (ng*h/mL)	6928	2695	8887	10350
C_{max} (ng/mL)	164	87.4	163	298

[1] NDA 214410, response to FDA Labeling Comments submitted July 16, 2020, Table 1
[2] NDA 214410, response to FDA Information Request submitted May 21, 2020, Table 4
[3] NDA 214410, response to FDA Information Request submitted June 9, 2020, Table 3
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve over the total time; C_{max}, maximum plasma concentration; TQT, thorough QT

Baloxavir exposure increases in a dose proportional manner in adults. Assuming the same in pediatrics, doubling the dose (in error), for example by administering the entire 40-mg baloxavir granules to a 10-kg infant, may result in exposures in Asian pediatric subjects that exceed those observed in adults in the TQT study. Therefore, medication errors that result in double the prescribed dose or more will result in exposures for which there are no safety data.

The Applicant provided all Council for International Organizations of Medical Sciences reports of overdose since baloxavir marboxil was first marketed. Overall, there have been 99 postmarketing adverse events of overdose to the Roche global safety database. The most commonly reported overdoses were adults who received a single 80-mg dose instead of a single 40-mg dose. The overdoses in pediatric subjects generally occurred when patients received the dose intended for the next highest weight band, e.g., when a patient weighing10 to 20 kg received the dose recommended for pediatric patients weighing 20 to 30 kg (based on approved baloxavir dosing in Japan). Of the 99 reports of overdoses, 13 reports had adverse events associated with the overdose. The types of AEs associated with overdose varied; the System Organ Class (SOC) with the most AEs reported was the gastrointestinal SOC. Five gastrointestinal AEs were reported but the type varied: nausea, vomiting, diarrhea and acute pancreatitis. No specific AE or cluster of AEs was observed with postmarketing adverse events of overdose.

Conclusion

(b) (4)

This could result in underdoses or in overdoses in pediatric patients. If a patient is underdosed, there may be a risk of decreased baloxavir marboxil efficacy. If overdoses occur, it is possible that baloxavir exposures in patients who receive an overdose will be higher than those observed in any clinical trials of baloxavir. Although there are no safety data available for these exposures, the safety data from the highest exposures are reassuring with few AEs and no severe or serious AEs

reported. In addition, no clear pattern of AEs has been observed in postmarketing reports of overdose.

DAV will be issuing a complete response letter for pediatric patients <12 years of age. (b) (4) The Applicant had planned to provide educational materials to pharmacists, pediatricians, and consumers as a mitigation strategy for limiting dosing errors. These would have included visual aids, dosing cards, information sheets, e-mails describing dosage, print journal ads, and speaker programs. Reviewers from the Division of Medication Error Prevention and Analysis agreed that the mitigation strategies proposed by the Applicant, (b) (4) in the package insert would be reasonable for reducing overdose and underdose errors. CDER will encourage use of these mitigation strategies for any future labeling for pediatric patients.

8. Therapeutic Individualization

8.1. Intrinsic Factors

In Trial CP40563, the impact of race (Asian versus non-Asian) was found to significantly impact the PK of baloxavir for pediatric subjects 1 to <12 years of age. However, no dose adjustment is required based on race (see Section 6.3.1).

8.2. Drug Interactions

No new drug interaction information was submitted.

8.3. Plans for Pediatric Drug Development

At the time of the original Xofluza approval in October 2018, PREA PMRs for treatment of acute, uncomplicated influenza were issued for patients birth to <12 months of age (PMR 3503-1) and for patients 12 months to <12 years of age (PMR 3503-2). Because NDA 210854/S-05 for treatment of acute uncomplicated influenza will not be approved in patients 1 to <12 years of ages, PMR 3503-2 will again be deferred, while PMR 3503-1 remains deferred, as noted below. However, because NDA 210854/S-04 will be approved for postexposure prophylaxis only in adults and adolescents (12 years of age and older), new PREA PMRs will be issued for postexposure prophylaxis in patients from birth to <12 months of age (PMR 3961-1) and in patients 12 months to <12 years of age (PMR 3961-2). The Applicant has agreed to these PREA PMRs. In addition, in order to further characterize emergence of baloxavir resistance in pediatric patients, a separate PMR (b) (4) was also agreed upon by the Applicant to submit the complete Clinical Study Report and datasets for Trial T0835, a non-IND study which evaluated safety, pharmacokinetics, and effectiveness of baloxavir marboxil in Japanese pediatric patients <12 years of age and <20 kg in weight.

The Applicant is currently conducting an open-label, single-arm trial (CP40559) of baloxavir marboxil for the treatment of acute, uncomplicated influenza in pediatric subjects from birth to ≤1 year of age. (b) (4)

The Applicant also plans to submit pharmacokinetic data to support the extrapolation of efficacy from adults and adolescents who have acute, uncomplicated influenza and who are at high risk of high-risk pediatric patients. These data will be submitted to support extension of the indication for the treatment of acute, uncomplicated influenza to pediatric patients.

Finally, the Applicant is conducting a trial of baloxavir marboxil to prevent transmission of influenza from treated subjects to untreated contacts without influenza. This trial will enroll pediatric patients as untreated contacts but not as subjects. This is the first transmission trial of an anti-influenza drug conducted under FDA IND. This trial includes pediatric subjects ≥5 years of age. After review of the trial results, the need for additional pediatric data will be discussed internally and with the Applicant.

The totality of data regarding pediatric use of baloxavir marboxil, including the risk of transmission of resistance-associated amino acid substitutions, will be reviewed. In addition, DAV may request additional studies to address the increased frequency of treatment-emergent RAS in pediatric patients if needed in the future.

8.4. Pregnancy and Lactation

Assessment of fertility and early embryonic development was conducted in rats. There were no effects on female or male fertility parameters observed up to the highest dose tested.

Baloxavir and its related metabolites was detected in milk from lactating Sprague Dawley rats. Maximum milk concentration of baloxavir was reached 2 hours post dosing and maximum plasma concentration was reach 1-hour post dosing. After 24 hours, baloxavir was undetectable in plasma and milk.[1]

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 214410 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama on August 18, 2020. As such, OPQ recommends approval of this NDA from a quality perspective.

Baloxavir marboxil, granules for oral suspension, 40 mg/20 mL (2 mg/mL), consists of white to light yellow granules for oral suspension. Each bottle contains 40 mg (nominal) of baloxavir marboxil and is supplied in an amber glass bottle with a child-resistant screw cap. The granules must be constituted with 20 mL of water to yield a 2 mg/mL oral suspension. Based on the chemical stability and microbiological evaluation of the in-use stability studies, adequate support was provided for the post-constitution hold time of 10 hours at 20–25°C after the product is prepared with drinking water or sterile water.

The Biopharmaceutics assessment evaluated the data supporting the proposed dissolution method, dissolution acceptance criterion and need for bridging between the drug product used in Phase 1 clinical studies (2% w/w granules (20 mg/g) packaged inside a sachet (administered

directly to the mouth of the subject with a glass (200 mL) of water)) and the to-be-marketed formulation (2 g of granules containing 40 mg of baloxavir marboxil (20 mg/g) inside a bottle to be constituted with 20 mL water to make it an oral suspension before administration). The bridging between tablets, granules, and granules for suspension, is supported by the data and information and is found to be adequate.

For additional details, refer to the OPQ Integrated Quality Review.

9.1. Device or Combination Product Considerations

Not applicable to this application.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Human Subjects Protection

The Applicant states the clinical trials were conducted in accordance with the principles of the "Declaration of Helsinki" and with International Conference on Harmonisation good clinical practice requirements. The studies were reviewed and approved by the appropriate Ethics Committees and Institutional Review Boards. Trial T0834 was conducted according to FDA requirements, under investigational new drug application regulations (IND 126653).

Clinical Site Inspections

Inspection sites were chosen from the two pivotal trials, Trials CP40563 and T0834. Four sites were selected, two U.S. sites from Trial CP40563 and two Japanese sites from Trial T0834. These sites were chosen based on enrollment, efficacy outcome, number of adverse events, and previous inspection history. After travel was restricted due to the global COVID-19 pandemic, in-person inspection of the Japanese sites was no longer possible. Reviewers from Office of Scientific Investigations (OSI) requested pertinent documents from the Japanese sites in order to conduct a remote inspection.

On inspection of the four study sites, no deficiencies were noted at three of the sites. At the other site, OSI inspectors observed that one adverse event had not been reported. That adverse event, a kidney infection, would not have affected conclusions regarding safety. OSI reviewers determined that the studies were conducted adequately, and that the data from these sites were acceptable in support of the applications.

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators* (February 2013)(see Section 23), and by 21 CFR 54.4. All of the investigators in Trials CP40563 and T0834 responded to the request for information about financial disclosures. None of the 316

investigators for Trial CP40563 or 107 investigators for Trial T0834 are employed by the Applicant. No investigators have financial interests or arrangements with the Applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoints were predefined in the protocols and not vulnerable to investigator bias. In addition, both trials were randomized, controlled, and double-blind, which would minimize the potential for investigator bias to play a role. Finally, <1% of investigators had financial interests or arrangements with the Applicant, and these investigators with financial interests enrolled <1.5% of the subjects.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

No Advisory Committee meeting was held for these applications.

III. Appendices

12. Summary of Regulatory History

On April 24, 2018, Genentech (the Applicant) submitted an new drug application (NDA) for review. On October 24, 2018, Xofluza (baloxavir marboxil), 20-mg, 40-mg tablet was approved for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

Genentech requested a pre-NDA meeting on July 24, 2019, to discuss the results of the Phase 3 miniSTONE 2 trial (CP40563) and the Phase 3 BLOCKSTONE study (1719T0834/XV41428), as well as the content and format for the planned original NDA (new formulation) and the Pediatric and postexposure prophylaxis (PEP) supplemental NDA (sNDA). On July 29, 2020, the U.S. Food and Drug Administration (FDA) granted the meeting scheduled for October 10, 2020. In advanced of the meeting, the FDA provided preliminary comments on October 3, 2020. On October 8, 2020, Genentech cancelled the scheduled meeting because the preliminary comments were sufficient.

On January 23, 2020, Genentech submitted an original NDA 214410 to provide a new Xofluza formulation (baloxavir marboxil granules for oral suspension) for use in pediatrics as part of the accompanying efficacy supplements (S-04, 05) submission to fulfill PREA PMRs 3503-2, 3503-3, and postmarketing commitments (PMCs) 3503-8, 9 (bioequivalence study for oral granules) under NDA 210854. The Xofluza for oral suspension is available in a 2 mg/mL strength after constitution in sterile water or drinking water. Genentech has provided the following data for the following applications for review:

Table 57. Summary of Regulatory History

Application Number	Application Information
NDA 214410	To add a new dosage formulation [granules for oral suspension (2 mg/mL)
NDA 210854/ S-04	To add a new indication for postexposure prophylaxis of influenza in patients 1 year of age and older, and respond to PMC 3503-8 with the following study: Study 1719T0834 entitled "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Efficacy of a Single Dose of Baloxavir Marboxil in the Prevention of Influenza Virus Infection"
NDA 210854/ S-05	To expand the patient population for the treatment of acute uncomplicated influenza in otherwise healthy patients 1 year of age and older who have been symptomatic for no more than 48 hours, and respond to PREA PMR 3503-2, 3, and PMC 3503-9 with the following studies: Trial CP40563 entitled "A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study To Assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients 1 to <12 Years of Age With Influenza-Like Symptom" (PMR-2) Study 1705T0833 entitled "An Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of S-033188 2% Granules After Administration of a Single Dose to Otherwise Healthy Pediatric Patients With Influenza" (PMR-3) Trial 1703T0831G entitled "A Phase 1 Study to Evaluate the Bioequivalence of S-033188 20-mg Tablet and S-033188 Granules 2%" (PMC-9)

Source: NDA 214410; NDA 210854/S-04;NDA 210854/S-05 submissions
Abbreviations: PREA, Pediatric Research Equity Act; PMC, postmarketing commitment; PMR, postmarketing requirement

All efficacy and safety data are contained in the original NDA 214410. The two efficacy supplements under NDA 210854 will cross-referenced NDA 214410. NDA 214410 and sNDAs 210854/S-04, 05 will be reviewed together.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Baloxavir marboxil is an influenza virus polymerase acidic (PA) endonuclease inhibitor. The proposed indication for Baloxavir marboxil is for use as a tablet or 2% granules formulation for the treatment of acute uncomplicated influenza in otherwise healthy patients 1 year of age and older and in patients 12 years of age and older who are at high risk of developing influenza-related complications, who have been symptomatic for no more than 48 hours. The second proposed indication with these applications is postexposure prophylaxis of influenza in patients 1 year of age and older following contact with an individual who has influenza.

The prior approval of baloxavir marboxil (NDA 210854) included a comprehensive nonclinical package. Baloxavir marboxil has adequate clinical experience in adolescents and adults.

Recommendation: The nonclinical package supports approval of Xofluza.

13.2. Individual Reviews of Studies Submitted to the NDA

There were no additional studies submitted to the NDA. Toxicology studies in juvenile animals to support approval were submitted with the original NDA for Xofluza (NDA 210854).

14. Clinical Pharmacology: Additional Information and Assessment

14.1. Bioequivalence Study

Trial 1703T081G (Trial T081G) is a single-center, randomized, two-sequence, two-period crossover, open-label Phase 1 study to evaluate the bioequivalence of S-033188 (baloxavir marboxil) 20-mg tablet and S-033188 (baloxavir) granules 2%.

A total of 28 subjects were administered a single oral dose of one S-033188 20-mg tablet (reference) or 1 g of S-033188 granules 2% (test) in the fasted state in Periods 1 and 2. Washout period was 28 days.

S-033188 granules 2% were administered directly into the mouth followed by water. This mode of administration differs slightly than that used in Trial CP40563 where S-033188 granules 2% were constituted with water first to form an oral suspension and administered with an oral dispenser. The biopharmaceutics group concluded that the difference in mode of administration was not expected to affect absorption.

The 90% confidence intervals (CIs) of the Geometric Least Squares Mean ratios for C_{max} and AUC were contained within the bioequivalence criteria range (0.80 to 1.25) after single doses of one S-033188 20-mg tablet and 1 g of S-033188 granules 2% (Table 58). These results indicate that 1 g of S-033188 granules 2% is bioequivalent to one S-033188 20-mg tablet.

Table 58. Results of Statistical Analysis for Pharmacokinetic Parameters of S-033447 Between One S-033188 20-mg Tablet and 1 g of S-033188 Granules 2%

Plasma S-033447			
Parameter	Geometric Least Squares Mean[a]		Geometric Least Squares Mean Ratio[a] (90% CI: lower, upper)
	One 20-mg tablet N = 27	1 g of granules 2% N = 27	1 g of granules 2% / one 20-mg tablet
C_{max} (ng/mL)	42.0	38.4	0.9135 (0.8302 - 1.0052)
$AUC_{0\text{-last}}$ (ng·hr/mL)	2948	2853	0.9679 (0.9057 - 1.0344)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	3038	2941	0.9682 (0.9065 - 1.0342)
$t_{1/2,z}$ (hr)	101	100	0.9910 (0.9671 - 1.0155)
MRT (hr)	124	126	1.0163 (0.9988 - 1.0341)

Source: CSR. P. 48
[a] The analysis was based on the linear mixed effects model: ln (Parameter) = Treatment + Group + Period + Subject + Random error, where treatment, group, and period were fixed effects, and subject was random effect. Results were exponentiated to present geometric least squares mean and ratio.
Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration time curve over the total time; $AUC_{0\text{-last}}$, area under the concentration time curve from 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; MRT, mean residence time; $t_{1/2,z}$, terminal half-life

Analytical and clinical site inspections were not conducted by OSIS because both sites are located in a country (Japan) where official travel is discouraged by U.S. State Department due to the Covid-19 pandemic. Refer to Dr. James J. Lumalcuri's memorandum on March 30, 2020, for details.

14.2. Pharmacometrics Review

14.2.1. Population PK Analysis

14.2.1.1. Review Summary

The Applicant's population pharmacokinetic (PK) analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the population PK model is adequate in characterizing the PK profile of baloxavir marboxil in pediatrics (1 to <12 years of age). The interindividual variability for apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) are modest. Shrinkages were modest for CL/F, Vc/F, intercompartmental clearance (Q/F) and apparent peripheral volume of distribution (Vp/F), large for absorption rate constant (K_a) and substantial for T_{LAG}. The estimated PK parameters, such as CL/F and Vc/F appear reasonable. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 59.

Table 59. Specific Comments on Applicant's Final Population PK Model

Utility of Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Body weight and race significantly influenced the apparent clearance (CL/F, Q/F) and volume (Vc/F, Vp/F) parameters. Gender and age influenced the absorption parameter, K_a.	These statements are acceptable based on covariate analysis using the Applicant's model. None of the other covariates were deemed significant.
	Extrinsic factor	NA	NA. Reviewed previously (Original NDA 210854 review).
Derive exposure metrics for exposure-response analyses	AUC, C_{max}, C_{24}, C_{72}		The Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses.

Source: Reviewer's Analysis
Abbreviations: AUC, area under the concentration time curve; CL/F, apparent clearance; C_{max}, maximum plasma concentration; C_{24}, plasma concentration at 24 hours; C_{72}, plasma concentration 72 hours; K_a, absorption rate constant; NA, not applicable; PK, pharmacokinetics; Q/F, intercompartmental clearance; Vc/F, apparent central volume; Vp/F, apparent peripheral volume

14.2.1.2. Introduction

Primary Objectives of Applicant's Analysis

- Characterize the structural PK model and quantify the population variability in the PK parameters of baloxavir
- Describe the effects of intrinsic factors on baloxavir exposure
- Generate individual PK parameter (e.g., AUC, C_{max}, C_{24} and C_{72}) estimates for patients in Trial CP40563 that can be used for subsequent exposure-response analyses

14.2.1.3. Model development

Data

The analyses was based on PK data from six studies. The study design, study population, and timing of blood samples varied among the six clinical studies. Brief descriptions of the studies included are presented in Table 60.

The final NONMEM data file for analysis contained 6399 PK observations from 179 subjects. Table 61 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 60. Studies With PK Sampling Included in Population PK Analysis

Region	Study No.	Study Objectives	Study Population	Dosage Regimen	Number of Patients (n)
Global	CP40563	Randomized, double-blind active-controlled efficacy, safety, and PK study	Otherwise healthy pediatric patients 1 to <12 years of age with influenza	Baloxavir marboxil 2% granules suspension, single dose: 2 mg/kg <20 kg 40 mg ≥20 kg Oseltamivir (BID dose based on body weight) for 5 days	176 (bxm=117, oselt.=59)
Global	1601T0831	Randomized, double-blind placebo-controlled efficacy, safety, and PK study	Otherwise healthy adults and adolescents ≥12 years with influenza	Baloxavir marboxil tablets, single dose: 40 mg <80 kg 80 mg ≥80 kg Placebo Oseltamivir: 75 mg BID for 5 days	1436 (bxm=612, pbo=310, oselt.=514)
Global	1602T0832	Randomized, double-blind placebo- and active-controlled efficacy, safety and PK study	High-risk adults and adolescents ≥12 years with influenza	Baloxavir marboxil tablets, single dose: 40 mg <80 kg 80 mg ≥80 kg Placebo Oseltamivir: 75 mg BID for 5 days	2184 (bxm=730, Pbo=729 oselt.=725)
Japan	1618T0822	Open-label safety, PK, and efficacy study	Otherwise healthy pediatric patients aged 6 months to <12 years with influenza	Baloxavir marboxil tablets, single dose: 5 to <10 kg 5 mg, 10 to <20 kg 10 mg, 20 to <40 kg 20 mg, ≥40 kg 40 mg	108
Japan	1705T0833	Open-label safety, PK, and efficacy study	Otherwise healthy pediatric patients <20 kg and aged <12 years	Baloxavir marboxil 2% granules, single dose by weight: <10 kg 1 mg/kg, 10 to <20 kg 10 mg	33
Japan	1518T0821	Randomized, double-blind, placebo-controlled efficacy, safety, and PK study	Otherwise healthy adults with influenza	Baloxavir marboxil: 10 mg, 20 mg, 40 mg or placebo	400 (100 per group)

Source: Applicant's Population PK report, Table 1
Abbreviations: BID, twice a day; bxm, baloxavir marboxil; pbo, placebo; oselt., oseltamivir; PK, pharmacokinetic

Table 61. Demographic Data (Continuous Covariates)

Covariate Study	N	Mean	SD	Median	Min	Max
Age (years)						
ALL	1795	37.1	19.9	37.0	0.12	85
CP40563	105	6.17	2.88	6	1	11
T0822	107	7.29	2.69	8	1	11
T0833	33	2.53	1.73	2	0.12	6
T0831	586	33.5	13.2	32	12	64
T0832	664	51.4	17.1	53	12	85
T0821	300	37.7	10.9	37	20	63
Body weight (kg)						
ALL	1795	65.7	25.5	65.7	4	217
CP40563	105	26.1	12.0	23.6	7.6	64.4
T0822	107	25.2	8.95	24.3	9	51
T0833	33	12.1	3.92	11.8	4	19.2
T0831	586	68.1	16.5	65.55	40.1	131
T0832	664	80.1	22.9	76.1	40.1	217
T0821	300	63.5	13.4	62.6	36	110
Body mass index (kg/m^2)						
ALL	1795	24.8	7.0	23.6	9.7	69.4
CP40563	105	17.3	3.42	16.4	11.4	28.3
T0822	107	16.1	2.19	15.6	9.7	24
T0833	33	15.3	1.74	14.8	12.9	21.6
T0831	586	24.5	5.12	23.1	15.3	51.2
T0832	664	29.1	7.29	27.8	15.8	69.4
T0821	300	22.8	3.75	22.2	16.7	36.6
Body surface area (m^2)						
ALL	1795	1.67	0.406	1.73	0.220	3.02
CP40563	105	0.918	0.28	0.875	0.39	1.68
T0822	107	0.925	0.229	0.93	0.41	1.51
T0833	33	0.537	0.148	0.52	0.22	0.8
T0831	586	1.753	0.225	1.73	1.32	2.45
T0832	664	1.866	0.269	1.84	1.23	3.02
T0821	300	1.702	0.202	1.71	1.19	2.27

Source: Applicant's Population PK report, Table 5
Abbreviations: N, Number of subjects; PK, pharmacokinetic; SD, Standard deviation

Table 62. Demographic Data (Categorical Covariates)

Covariate Category	ALL (N=1795) n (%)	CP40563 (N=105) n (%)	T0822 (N=107) n (%)	T0833 (N=33) n (%)	T0831 (N=586) n (%)	T0832 (N=664) n (%)	T0821 (N=300) n (%)
Race							
0: Asian	985 (54.9)	1 (1.0)	107 (100)	33 (100)	359 (61.3)	186 (28.0)	299 (99.7)
1: Non-Asian	810 (45.1)	104 (99.0)	0 (0.00)	0 (0.00)	227 (38.7)	478 (72.0)	1 (0.3)
Patient type							
0: OwH	1131 (63.0)	105 (100)	107 (100)	33 (100)	586 (100)	0 (0.00)	300 (100)
1: HR	664 (37.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	664 (100)	0 (0.00)
Gender							
0: Male	894 (49.8)	51 (48.6)	56 (52.3)	11 (33.3)	287 (49.0)	303 (45.6)	186 (62.0)
1: Female	901 (50.2)	54 (51.4)	52 (47.7)	22 (66.7)	299 (51.0)	361 (54.4)	114 (38.0)
Formulation							
1. 2% granule suspension	105 (5.80)	105 (100)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2. 2% granules	33 (1.80)	0 (0.00)	0 (0.00)	33 (100)	0 (0.00)	0 (0.00)	0 (0.00)
3. 10-mg film-coated tablet	100 (5.60)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	100 (33.3)
4. 10-mg tablet (uncoated)	33 (1.80)	0 (0.00)	33 (30.8)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5. 20-mg film-coated tablet	200 (11.1)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	200 (66.7)
6. 20-mg film-coated tablet	1324 (73.8)	0 (0.00)	74 (69.2)	0 (0.00)	584 (100)	664 (100)	0 (0.00)
Region							
0. Asia	955 (53.2)	0 (0.00)	300 (100)	300 (100)	350 (59.7)	165 (24.9)	300 (100)
1. North America / Europe	808 (45.0)	103 (98.1)	0 (0.00)	0 (0.00)	236 (40.3)	469 (70.6)	0 (0.00)
2. Others	32 (1.8)	2 (1.90)	0 (0.00)	0 (0.00)	0 (0.00)	30 (4.5)	0 (0.00)

Source: Applicant's Population PK report, Table 6
Abbreviations: HR, high risk subjects; PK, pharmacokinetic; N, number of subjects; OwH, otherwise healthy subjects; SD, standard deviation

Table 63. Laboratory Values at Baseline

Covariate Study	N	Mean	SD	Median	Min	Max
Albumin concentration (g/L)						
ALL	1795	44.8	3.03	45.0	28.0	55.0
CP40563	105	46.6	2.457	47	41	55
T0822	107	45.4	2.351	46	39	52
T0833	33	45.8	2.701	46	39	50
T0831	586	45.3	2.839	45	35	53
T0832	664	44.2	3.32	44	28	55
T0821	300	44.2	2.67	44	36	52
Aspartate aminotransferase (U/L)						
ALL	1795	26.2	19.8	22.0	10	428
CP40563	105	32.2	8.92	31	17	66
T0822	107	29.6	5.92	29	15	45
T0833	33	39.6	8.30	37	26	66
T0831	586	22.0	10.0	19	10	137
T0832	664	27.2	24.4	22	11	355
T0821	300	27.4	26.5	23	13	428
Alanine aminotransferase (U/L)						
ALL	1795	23.7	24.2	18	6	552
CP40563	105	15.7	6.68	14	6	61
T0822	107	15.6	5.86	14	7	47
T0833	33	18.4	8.07	16	9	49
T0831	586	20.7	14.7	16	6	115
T0832	664	27.7	32.5	20	6	552
T0821	300	26.9	24.7	19.5	8	320
Bilirubin (total) (mg/dL)						
ALL	1795	0.444	0.253	0.400	0.100	2.70
CP40563	105	0.27	0.18	0.2	0.1	1.1
T0822	107	0.443	0.189	0.4	0.2	1.1
T0833	33	0.494	0.46	0.3	0.1	2.6
T0831	586	0.44	0.246	0.4	0.2	2.7
T0832	664	0.422	0.255	0.4	0.1	2.6
T0821	300	0.556	0.224	0.5	0.2	1.8
Creatinine clearance (mL/min)						
ALL	1795	113	38.5	109	21.7	438
CP40563	105	109	18.9	109	75.2	184
T0822	107	119	15.0	118	75.7	166
T0833	33	117	20.6	116	72.1	174
T0831	586	116	34.7	110	51.3	375
T0832	664	111	49.9	102	21.7	438
T0821	300	108	26.4	105	57.3	226

Source: Applicant's Population PK report, Table 7
Abbreviations: N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Base Model

The final base model was a two-compartment PK model with lag time, first-order absorption, and first-order elimination from the central compartment. Interindividual variability was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Additive models on ln-transformed dependent variable were investigated as well. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a

decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate Analysis

The influence of baseline covariates was tested on CL/F, Vc/F, Q/F, K_a, and T_{LAG}. Due to limited number of patients in some of the covariate categories (e.g., formulation and region) their influence on the PK parameters of baloxavir was investigated only using graphical summaries. Clinical judgment, physiologic relevance, and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Additionally, collinearity of covariates was assessed to ensure that no collinear covariates were added to the model. Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change.

Final Model

The parameter estimates for the final covariate model are listed in Table 64. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 8. The Visual Predictive Check plot for the final covariate model with all data are shown in Figure 9.

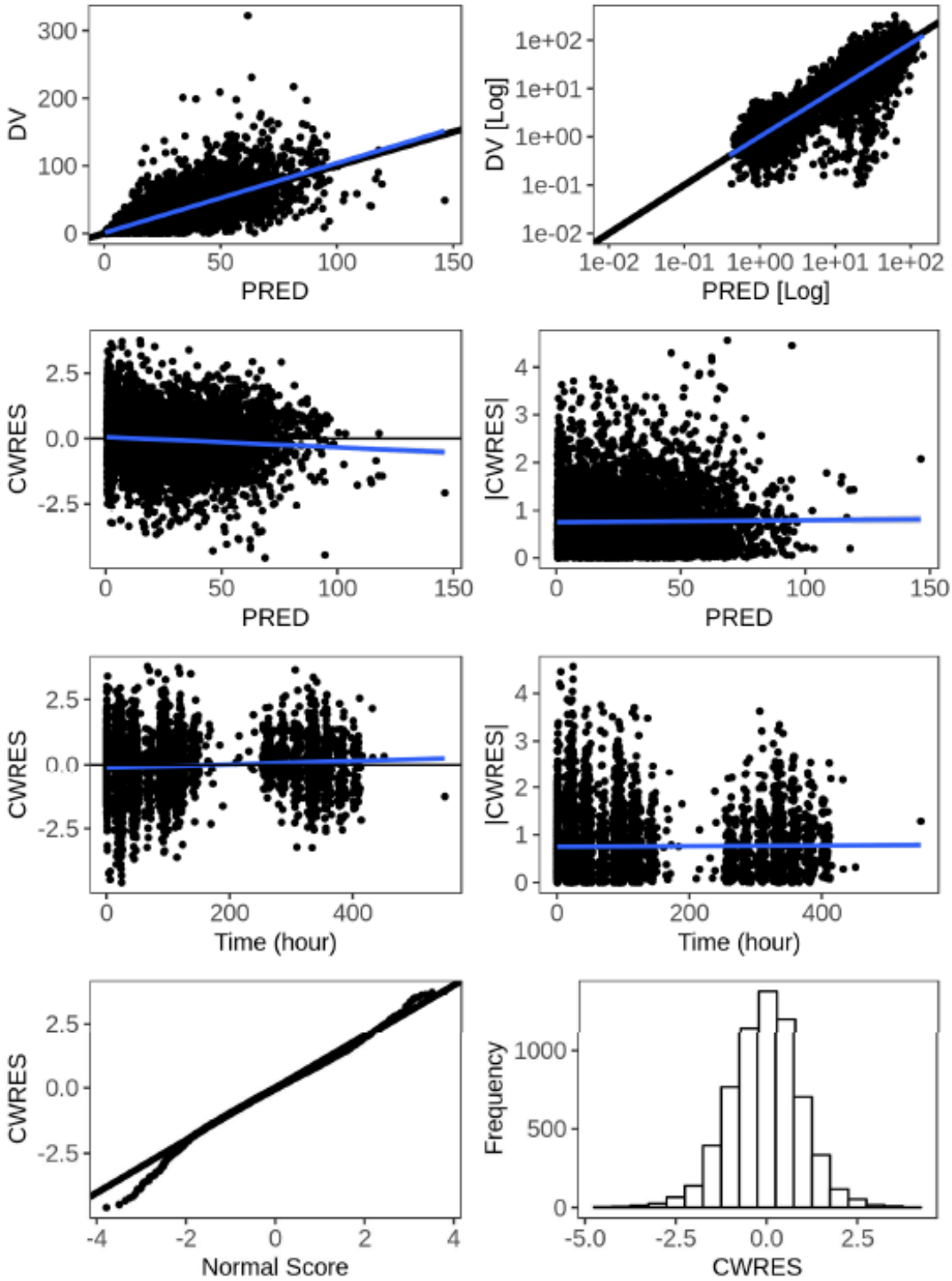
Table 64. Parameter Estimates (RSE) for Final Model

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
Fixed effects[1] CL/F	L/hr	11.02	1.87	
Vc/F	L	735	2.12	
Q/F	L/hr	2.12	5.20	
Vp/F	L	260	6.68	
K_a	1/hr	1.39	14.6	
T_{LAG}	hr	0.223	39.6	
Random effects BPV CL/F	CV%	45.6%	4.23[2]	3.22
Vc/F	CV%	45.7%	5.55[2]	6.04
Q/F	CV%	48.6%	23.0[2]	13.1
Vp/F	CV%	15% (fixed)	-	32.3
K_a	CV%	113%	8.91[2]	41.8
T_{LAG}	CV%	62.6%	80.4[2]	92.3
Correlations				
Correlation CL/F-V/F	-	0.860	1.38[3]	
Correlation CL/F-Q/F	-	0.700	6.79[3]	
Correlation CL/F-K_a	-	0.218	25.9[3]	
Correlation V/F-Q/F	-	0.899	13.6[3]	
Correlation V/F-K_a	-	0.224	27.9[3]	
Correlation Q/F-K_a	-	0.369	30.9[3]	
Correlation K_a-T_{LAG}	-	-0.733	16.5[3]	
Correlation CL/F-T_{LAG}	-	-0.032	316[3]	
Correlation V/F-T_{LAG}	-	-0.085	159[3]	
Correlation Q/F-T_{LAG}	-	-0.121	124[3]	
Covariate effects				
Effect of BW on CL/F, Q/F	–	0.467	5.61	
Effect of BW on Vc/F, Vp/F	–	0.887	4.09	
Effect of race (Asian) on CL/F	-	0.504	2.40	
Effect of race (Asian) on V/F	-	0.335	5.28	
Effect of race (Asian) on Q/F	-	0.391	7.21	
Effect of gender (female) on K_a	-	0.205	36.4	
Effect of age on K_a	-	0.242	21.4	

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
Error model				
σ_1 (additive)	ng/mL	0.257	10.5	
σ_2 (proportional)	%	14.9	4.09	

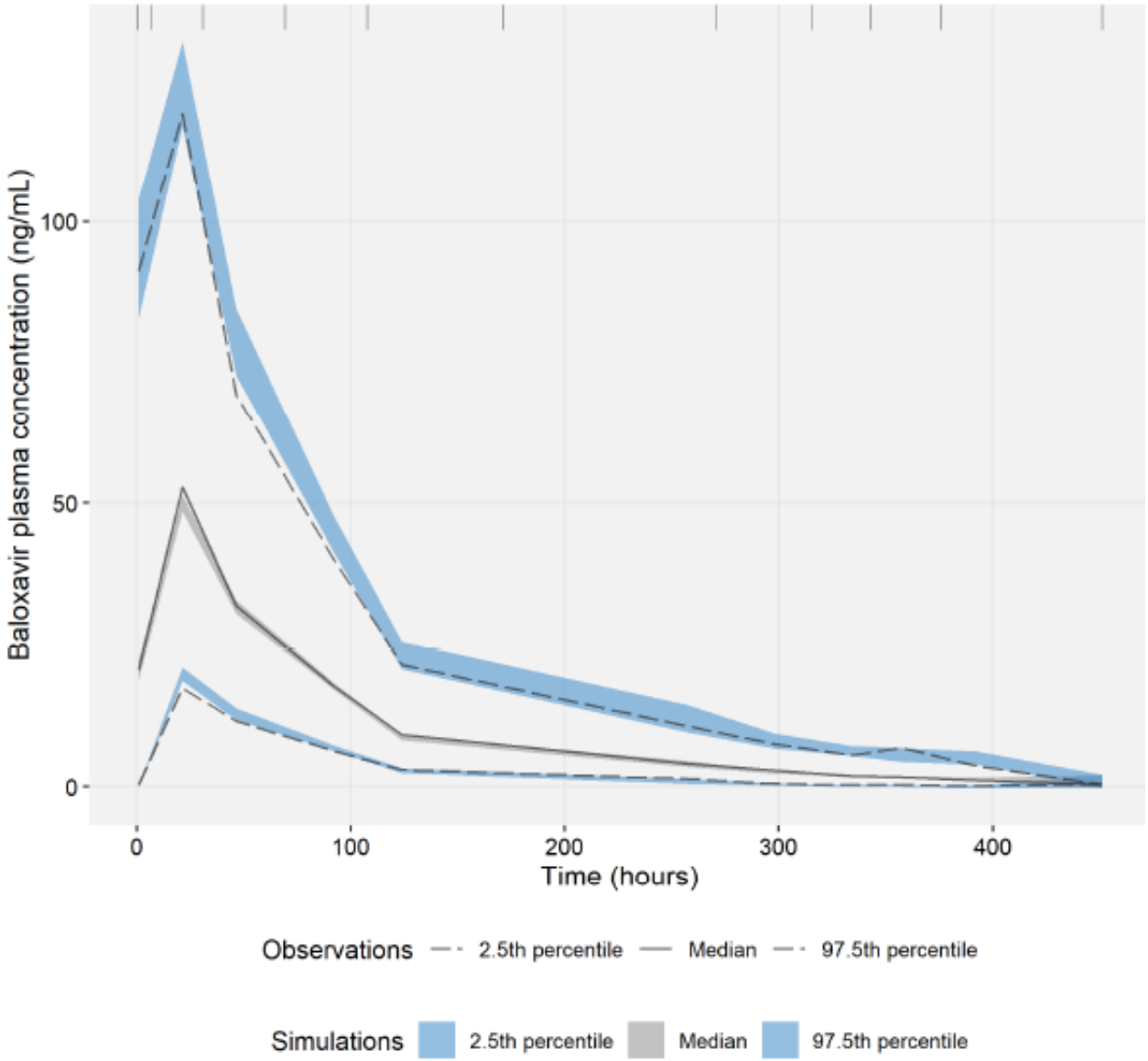
Source: Applicant's Population PK Report, Table 11
[1] exponential value of the NONMEM estimates of the typical population value
[2] RSE computed for the corresponding variance
[3] RSE computed for the corresponding covariance
$CL/F=11.02 \times (\text{body weight}/70)^{0.467} \times (1-0.504 \times \text{Asian})$; $Vc/F=735 \times (\text{body weight}/70)^{0.887} \times (1-0.335 \times \text{Asian})$;
$Q/F=2.12 \times (\text{body weight}/70)^{0.467} \times (1-0.391 \times \text{Asian})$; $Vp/F=260 \times (\text{body weight}/70)^{0.887}$;
$K_a=1.39 \times (1-0.205 \times \text{female}) \times (\text{age}/37)^{0.242}$
Abbreviations: BPV, between-patient variability; BW, body weight; CL/F, apparent clearance; CV, coefficient of variation; K_a, absorption rate constant; T_{LAG}, lag time; OFV, objective function value; Q/F, intercompartmental clearance; RSE, relative standard error of estimate; V/F, volume of distribution; Vc/F, apparent central volume; Vp/F, apparent peripheral volume; σ, residual error

Figure 8. Goodness-of-Fit Plots for Final Baloxavir PK Model Using Patient Data From Studies CP40563, T0822, T0833, T0831, T0832, and T0821 – I



Source: Applicant's Population PK Report, Figure 7
Blue line = linear smooth of the dots, black line, identity line or line y=0.
Abbreviations: DV, observed baloxavir concentration [ng/mL; CWRES (IWRES), conditional (individual) weighted residual values; PK, pharmacokinetics; PRED (IPRED), NONMEM predicted baloxavir concentrations [µg/mL] based on population (individual); TIME, time after first drug intake [hour]

Figure 9. Prediction-Corrected Visual Predictive Check for All Patients Receiving Baloxavir Marboxil and Included in Population PK Database From Studies CP40563, T0822, T0833, T0831, T0832, and T0821



Source: Applicant's Population PK Report, Figure 10
Abbreviation: PK, pharmacokinetics

15. Trial Design: Additional Information and Assessment

15.1. Clinical Study Report Synopsis for Trial CP40563

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final CSR Study CP40563, (miniSTONE-2) A Multicenter, Randomized, Double-Blind, Active (Oseltamivir)-Controlled Study to assess the Safety, Pharmacokinetics, and Efficacy of Baloxavir Marboxil in Otherwise Healthy Pediatric Patients 1 to < 12 Years of Age with Influenza-Like Symptoms. Report No. 1095408 October, 2019
CENTERS AND COUNTRIES	USA (54 centers), South Africa (6), Argentina (4), Poland (4), Russia (4), Mexico (3), Spain (3), Costa Rica (1), Israel (1), and Panama (1).
PUBLICATION (REFERENCE)	Baker J, Macutkiewicz L, Dimonaco S, et al. Single-Dose Baloxavir is Well Tolerated and Effective for Treatment of Influenza in Otherwise Healthy Children Aged 1 to < 12 Years: A Randomized, Double-Blinded, Active-Controlled Study (miniSTONE-2). OPTIONS X 2019:abstract 11756
PERIOD OF TRIAL	First patient enrolled: 20-Nov-2018 Last patient last visit: 03-Apr-2019 End of study: 27-Aug-2019
CLINICAL PHASE	III
OBJECTIVES	• The primary objective was to compare the safety of a single dose of baloxavir marboxil with 5 days of oseltamivir administered twice daily. • The pharmacokinetic (PK) objective was to evaluate the PK of baloxavir marboxil after single-dose administration. • The secondary objectives were to evaluate the clinical efficacy and virological activity of baloxavir marboxil compared with oseltamivir. • The exploratory objectives were to evaluate polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, and PB2 genes and drug susceptibility and to evaluate extended PK parameters of baloxavir marboxil after single-dose administration.
STUDY DESIGN	This was a global, multicenter, randomized, double-blind, active-controlled study to compare baloxavir marboxil with oseltamivir in pediatric patients with influenza-like symptoms. Patients received either a single dose of baloxavir marboxil or oseltamivir for 5 days. During the 5-day treatment period, each randomized patient also received the corresponding placebo of its comparator. With a 24-day safety follow-up period after treatment, the total study duration for each patient was 29 days.

NUMBER OF SUBJECTS	Approximately 120 patients were planned to be enrolled and randomized in a 2:1 ratio to one of two treatment groups. A total of 199 patients were screened, of which 23 failed screening, and 176 were randomized (117 patients in the baloxavir marboxil group and 59 in the oseltamivir group).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Otherwise healthy pediatric patients (i.e., 1 to < 12 years of age) with influenza.
EXPLORATORY	The exploratory endpoints were: • Polymorphic and treatment-emergent amino acid substitutions in the PA, PB1, and PB2 genes, drug susceptibility in patients with evaluable virus, and non-compartmental PK parameters (intensive PK).
STATISTICAL METHODS	The primary safety analyses was based on the safety population (defined as patients who received any portion of a single dose). The study was not powered for a comparison between baloxavir marboxil and oseltamivir. All comparisons were descriptive. The PK analysis population comprised all patients who had at least one post-dose drug concentration measurement at a scheduled visit timepoint. The efficacy analysis was based on the intent-to-treat infected (ITTI) population. This included all patients who received any portion of a single dose and who had a laboratory confirmation of influenza infection (RT-PCR result) from any swab sample collected at baseline or during the study. The statistical analyses of efficacy endpoints were descriptive. Virology analyses were based on the ITTI population.

Source: Clinical Study Report Synopsis

15.2. Protocol Synopsis for Trial T0834

Study Title:

A phase 3 randomized, double-blind, placebo-controlled study to confirm the efficacy of a single dose of baloxavir marboxil in the prevention of influenza virus infection

Study Number:

1719T0834

Study Phase: 3

Primary Objective:

- To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection in subjects who are household members (hereinafter referred to as "subjects") of influenza-infected patients (hereinafter referred to as "index patients"). The primary efficacy endpoint is the proportion of subjects who are infected with influenza virus (reverse transcription polymerase chain reaction [RT-PCR] positive), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10.

Secondary Objectives:

- To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo in the prevention of influenza virus infection by measuring the secondary endpoints in subjects.
- To determine the pharmacokinetics (PK) of the active form of baloxavir marboxil, ie, S-033447 in subjects treated with baloxavir marboxil for prophylaxis.
- To evaluate the safety of a single oral dose of baloxavir marboxil for prophylaxis.

Study Design:

This is a randomized, double-blind, multicenter, parallel-group, placebo-controlled comparative study enrolling approximately 750 subjects who are household members of influenza-infected index patients. Subjects are randomly assigned with the stochastic minimization method in a 1:1 ratio to receive a single, oral dose of baloxavir marboxil or placebo.

Study Population:

Subjects who live with an influenza-infected index patient

Criteria for Inclusion and Exclusion

Inclusion criteria for patients with influenza virus infection (index patients)

Patients who fulfill all of the following criteria will be included in the study as index patients:

1. For adult patients, written informed consent must be obtained from the patients prior to Screening who participate voluntarily in the study. For patients under legal age, written informed consent must be obtained from the parent/legal representative of the patients; written informed assent must also be provided in the case of patients aged ≥ 12 years, and should be provided in the case of patients aged < 12 years when feasible.

2. The first patient in a household with influenza virus infection in the 2018-2019 influenza season (November 2018 to April 2019).
3. Patients diagnosed as having influenza with positive rapid influenza diagnostic test (RIDT) by nasopharyngeal (if difficult, nasal or throat) swabs.
4. Patients with onset of symptoms within 48 hours or less at informed consent. The onset of symptoms is defined as the time when body temperature first rises to 37.5°C or higher.
5. Patients who will receive any treatment with anti-influenza drugs after informed consent.
6. Patients with body weight of at least 10 kg at Screening.

Inclusion criteria for household members of index patients (subjects)

Subjects who fulfill all of the following criteria will be included in the study:

1. For adult subjects, written informed consent must be obtained from the subjects prior to Screening who participate voluntarily in the study. For subjects under legal age, written informed consent must be obtained from the parent/legal representative of the subjects; written informed assent must also be provided in the case of subjects aged ≥ 12 years, and should be provided in the case of subjects aged < 12 years when feasible.
2. Subjects who had lived with the index patient for 48 hours or more prior to informed consent.
3. Subjects who meet all of the following criteria and are judged not to have influenza virus infection by the investigator or subinvestigator.
   - Subjects who have a body temperature (axillary) < 37.0°C at Screening
   - Subjects who have no influenza like symptoms (cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) at Screening
4. Subjects 12 years of age or older, or subjects under 12 years of age whose guardian is capable of evaluating influenza symptoms by using a subject diary.
5. Subjects who are able to provide informed consent within 48 hours or less from onset of symptoms in index patients and within 24 hours or less from informed consent in index patients.
6. Women of childbearing potential who agree to use a highly effective method of contraception for 3 months after study drug administration.

Exclusion criteria for household members of index patients (subjects)

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects who have been diagnosed with influenza during the 2018-2019 influenza season (November 2018 to April 2019).
2. Subjects who are unable to live with the index patient from Screening until Day 10.

3. Subjects who live with a household member who has any influenza like symptom(s) (body temperature of ≥ 37.5°C, cough, sore throat, headache, nasal discharge/nasal congestion, feverishness or chills, muscle or joint pain, or fatigue) other than the index patient on the day of Screening.
4. Subjects with household members other than the index patient that was diagnosed with or strongly suspected to have influenza during the 2018-2019 influenza season (November 2018-April 2019).
5. Subjects who have any underlying diseases requiring systemic (oral or injection), or nasal treatment of antipyretics/analgesics, corticosteroids, or immunosuppressive agents.
6. Subjects who are immunocompromised (including subjects receiving systemic immunosuppressant agents or subjects with human immunodeficiency virus [HIV] infection).
7. Subjects who have received baloxavir marboxil (Xofluza®), peramivir (Rapiacta®), laninamivir (Inavir®), oseltamivir (Tamiflu®), zanamivir (Relenza®) or amantadine (Symmetrel®) within 30 days prior to Screening (including prophylaxis).
8. Subjects with known allergy and/or history of significant intolerance against baloxavir marboxil.
9. Subjects with severe (Grade 3 or higher of Common Terminology Criteria for Adverse Events [CTCAE] ver. 5) underlying diseases.
10. Subjects who have been exposed to an investigational drug within 30 days or 5 half-lives of the drug prior to Screening.
11. Women who are pregnant or lactating.
12. Subjects with any condition or circumstance that, in the opinion of the investigator or subinvestigator, would compromise the safety of the subject or the quality of the study data.

Test Drug, Control drug, Dose, and Mode of Administration:

A single oral dose of baloxavir marboxil (S-033188) 20-mg tablet/placebo tablet or S-033188 2% granule/placebo granule will be administered on Day 1 at a dose depending on the subject's age and body weight at Screening.
(Administration [for subjects ≥ 12 years of age])

Subject's body weight at Screening	Dose	Test drug Control drug
Weight < 80 kg	40 mg	2 S-033188 20-mg tablets or 2 placebo tablets
Weight ≥ 80 kg	80 mg	4 S-033188 20-mg tablets or 4 placebo tablets

(Administration [for subjects < 12 years of age])

Subject's body weight at Screening	Dose	Test drug Control drug
Weight < 10 kg	1 mg/kg	S-033188 2% granule 1 mg/kg (50 mg/kg[a]) or placebo granule (50 mg/kg[a])
Weight 10 to < 20 kg	10 mg	S-033188 2% granule 10 mg (0.5 g[a] [1packet]) or 1 placebo granule packet
Weight 20 to < 40 kg	20 mg	1 S-033188 20-mg tablet or 1 placebo tablet
Weight ≥ 40 kg	40 mg	2 S-033188 20-mg tablets or 2 placebo tablets

a: Amount of drug/placebo granules

Duration of Treatment:

1 day

Prohibited Concomitant Therapy:

The use of the following drugs and over-the-counter drugs with equivalent efficacy will be prohibited from the time of informed consent until completion of assessments on Day 11 (or until completion of assessments at study discontinuation). The use of anti-influenza drugs and antipyretics/analgesics will be permitted when a subject is diagnosed with influenza virus infection, has influenza-like symptoms, or experiences adverse event(s) and the investigator or subinvestigator judges its necessity.

- Antipyretics/analgesics [a]
- Anti-influenza drugs [b]
- Corticosteroids [a]
- Immunosuppressive agents [a]
- Influenza vaccines
- Other study drugs

a Only systemic (oral, injection, rectal or enema) and nasal formulations are prohibited

b Including herbal medicines with indication for influenza virus infection such as Mao-to

Restricted Concomitant Therapy:

Treatment which a subject is using for underlying diseases prior to informed consent is permitted (except for use of prohibited concomitant therapy). However, changes in the dosage and administration will not be permitted from the time of informed consent until completion of assessments on Day 11 (or until completion of assessments at study discontinuation). Use of a new treatment for underlying diseases of the subject during the study is not permitted during the study unless there is aggravation of the underlying disease and the investigator or subinvestigator judges its necessity.

Efficacy Assessments:

For subjects ≥ 12 years of age at Screening, the subject will self-assess 7 symptoms associated with 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, Absent; 1, Mild; 2, Moderate; 3, Severe).

For subjects < 12 years of age at Screening, the subject's guardian will assess 2 symptoms associated with influenza (cough, nasal discharge/nasal congestion) on a 4-point rating scale (0, Absent; 1, Mild; 2, Moderate; 3, Severe).

Primary Endpoint:

- Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10.
  - Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C, having symptom of "cough" or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positive assessed by RT-PCR.

Secondary Endpoints:

- Time from study treatment to the time when fever, at least one respiratory symptom, and influenza virus infection were observed.
  - Defined as the later timepoint of the following (1) and (2):
    (1) Timepoint when body temperature (axillary) rises first to ≥ 37.5°C
    (2) Timepoint when symptom of "cough" or "nasal discharge/nasal congestion" was first assessed as "2, Moderate" or "3, Severe" in the subject diary

  If a subject does not have a body temperature (axillary) of ≥37.5°C or respiratory symptom was not assessed as "2, Moderate" or "3, Severe" in the period from Day 1 to Day 10, the subject will be handled as a censored case.
- Proportion of subjects who are infected with influenza virus (RT-PCR positive), and present with fever or at least one influenza symptom (respiratory symptom or systemic symptom) in the period from Day 1 to Day 10.
  - Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C or having at least one symptom of influenza with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus positive assessed by RT-PCR.
- Time from study treatment to the time when fever or at least one influenza symptom (respiratory symptom or systemic symptom), and influenza virus infection are observed.
  - Defined as the timepoint of the following (1) and (2), whichever is earlier:
    (1) Timepoint when body temperature (axillary) rises first to ≥ 37.5°C
    (2) Timepoint when an influenza symptom was first assessed as "2, Moderate" or "3, Severe" in the subject diary

  If a subject does not have a body temperature (axillary) of ≥37.5°C and influenza symptoms (respiratory symptoms and systemic symptoms) were not assessed as "2, Moderate" or "3, Severe" in the period from Day 1 to Day 10, the subject will be handled as a censored case.
- Proportion of asymptomatic influenza-infected (RT-PCR positive) subjects in the period from Day 1 to Day 10

  - Defined as the proportion of subjects having body temperature (axillary) < 37.5°C, influenza symptoms all assessed as "0, Absent" or "1, Mild", and influenza virus positive assessed by RT-PCR.
- Proportion of subjects with influenza virus infection in the period from Day 1 to Day 10
  - Defined as the proportion of subjects having influenza virus positive assessed by RT-PCR regardless of body temperature or influenza symptoms.

Other Endpoints:

- Serum influenza antibody titer
- Proportion of subjects who are not infected with influenza virus (RT-PCR negative), and present with fever and at least one respiratory symptom in the period from Day 1 to Day 10
  - Defined as the proportion of subjects having body temperature (axillary) ≥ 37.5°C, having symptom of "cough" or "nasal discharge/nasal congestion" with a severity of "2, Moderate" or "3, Severe" assessed in the subject diary, and influenza virus negative at all time points assessed by RT-PCR.

Pharmacokinetic Assessments:

Plasma S-033447 concentrations

Safety Assessments:

Adverse events (AEs), Treatment-related AEs, serious AEs, and clinical laboratory tests

Statistical Methods:

The modified intention-to-treat population (mITT population) will be the primary efficacy analysis population in this study. The per-protocol set (PPS) will be used for supportive analysis of the primary analyses of efficacy. All statistical testing will be performed at the two-sided significance level of 0.05 unless stated otherwise.

Primary efficacy analysis of primary endpoint

In mITT population, the risk ratio of baloxavir marboxil group versus the placebo group, its 95% confidence interval (CI) and P value will be calculated using the modified Poisson regression approach (ie, Poisson regression with sandwich estimator as a robust error variance) of a binary response (whether all of the following are confirmed for a subject or not; occurrence of fever, at least one respiratory symptom, and influenza virus infection) on a study treatment for the subject with randomization factors (time from onset of influenza in the index patient to informed consent of the subject, treatment for influenza virus infection in the index patient, age of the subject) as covariates. P value will be calculated for the null hypothesis that the true risk ratio is 1. In this primary analysis, the proportion of influenza-infected subjects with fever and at least one respiratory symptom, which is the primary endpoint, in the baloxavir marboxil group will be compared with that in the placebo group.

Efficacy analyses of secondary endpoints

In mITT population, an influenza infection proportion curve based on time length from the study treatment to the first time point when fever, at least one respiratory symptom

and influenza virus infection are all confirmed will be plotted for each treatment group, using the Kaplan-Meier method. Restricted mean survival time (RMST) up to Day 10 will be estimated for each treatment group. In addition, difference in RMST will be estimated between the treatment groups.

For each of other secondary efficacy endpoints given as a proportion of subjects, similar analysis for the primary efficacy endpoint will be performed and the proportion will be compared between the treatment groups.

For each of the remaining other secondary efficacy endpoints given as time to influenza infection, the influenza infection proportion curve will be plotted and the treatment group difference in RMST up to Day 10 will be estimated as described above.

Safety analyses

In safety population, the numbers of events and subjects with AEs will be counted for each treatment group. The percentage of subject will be calculated for each treatment group. Treatment-related AEs will be summarized in the same way as AEs for overall summary. The numbers and percentage of subjects with AEs/treatment-related AEs will be counted by system organ class (SOC) and preferred term (PT) for each treatment group.

For quantitative data, observed measurements and changes from baseline will be summarized at each planned time point for each treatment group using descriptive statistics. For qualitative data, the number of subjects will be counted for each pair of categories at baseline and at each planned time point in the form of 2-way layout contingency table for each treatment group.

Study Duration:

Study duration for individual subjects: the maximum duration of study participation for an individual subject is for 15 days from the time of Screening (Day 1) to the follow-up assessment (14 days after study drug administration).

Planned duration of the study: from September 2018 to June 2019

Date of Original: 26 July 2018

Date of Latest Amendment: 15 October 2018 (Amendment 1)

Source: Section 16.1.1 of the Clinical Study Report, Study Protocol (2nd version)

16. Efficacy: Additional Information and Assessment

16.1. Trial CP40563

Approximately 10 to 15% of the subjects were censored, leaving 73/80 (91%) of the baloxavir marboxil subjects and 36/43 (84%) of the oseltamivir subjects with observed event times for the primary endpoint. The 25th percentile was a little higher for oseltamivir (95 hours) than for baloxavir marboxil (89 hours) while the 75th percentile was a little higher for baloxavir marboxil (189 hours) than for oseltamivir (184 hours). However the 95% CIs for the 25th and 75th percentiles in the two treatment arms had a substantial amount of overlap (results for the median were presented in Section 6).

Table 65. Additional Summary Statistics for Time to Alleviation of Influenza Signs and Symptoms, Trial CP40563 (ITTI Population)

Treatment Group	N	Number (%) of Patients With Alleviated Signs and Symptoms	25th Percentile (95% CI) (hours)	75th Percentile (95% CI) (hours)
Baloxavir marboxil	80	73 (91%)	89 (67, 115)	189 (164, 225)
Oseltamivir	43	36 (84%)	95 (63, 118)	184 (158, 248)

Source: Statistics Reviewer's analysis
Hodges-Lehmann estimator and asymptotic 95% confidence interval
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected

The statistics reviewer estimated the restricted mean survival time (RMST) for each treatment group along with the difference in mean time to alleviation of influenza signs and symptoms between the two arms as shown in the following table. Follow-up time was restricted to 346.3 hours, which was the minimum observed follow-up time (observed in the oseltamivir treatment group). Compared to subjects in the oseltamivir arm, the estimated mean time to alleviation of influenza signs and symptoms was reduced by 8 hours (95% CI: -24, +40 hours) for subjects in the baloxavir marboxil treatment group in the first 346 hours of the trial.

Table 66. Restricted Mean Survival Time to Alleviation of Influenza Signs and Symptoms, Trial CP40563

Treatment Group	N	RMST up to 346 hours (hours)	Standard Error (hours)	95% CI (hours)
Baloxavir marboxil	80	147.5	8.97	(130, 165)
Oseltamivir	43	155.3	13.5	(129, 182)
Oseltamivir		7.8	16.2	(-24, +40)

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; RMST, restricted mean survival time

Subgroup Analysis by Age

The percentage of subjects who had an observed time to alleviation of influenza signs and symptoms was between 80% and 90% including for subjects <5 years of age and for subjects from 5 to <12 years of age, although there were a relatively small number of subjects <5 years of age in the study. The following table shows time to alleviation of influenza signs and symptoms by age. There was no significant difference in time to alleviation of influenza signs and

symptoms between treatment arms in subjects <5 years of age or in those between 5 and 12 years old.

Table 67. Time to Alleviation of Influenza Signs and Symptoms by Age, Trial CP40563

Age Range Parameter	Baloxavir Marboxil		Oseltamivir
Subjects <5 years	N=20		N=10
Subjects with observed TTAS, n (%)	17		9
Median (hours)	121		159
95% CIs	88, 189		46, 248
P-value oseltamivir vs. baloxavir		0.25	
Subjects 5 to <12 years	N=60		N=33
Subjects with observed TTAS, n (%)	56 (93%)		27 (82%)
Median (hours)	138		126
95% CIs	117, 163		95, 166
P-value oseltamivir vs. baloxavir		0.83	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; TTAS, time to alleviation of influenza signs and symptoms

Additional Subgroup Analyses

Analyses of time to alleviation of influenza signs and symptoms did not reveal any significant treatment group differences in any of the following demographic subgroups (sex, race, ethnicity). The Blacks/African Americans subgroup had sample sizes that were too small to make any meaningful comparisons.

Table 68. Time to Alleviation of Influenza Signs and Symptoms by Gender, Trial CP40563

Gender Parameter	Baloxavir Marboxil		Oseltamivir
Females	N=43		N=23
Responders, n (%)	41 (95)		19 (83)
Median (hours)	135		154
95% CIs	91, 163		71, 214
P-value oseltamivir vs. baloxavir		0.38	
Males	N=37		N=20
Responders, n (%)	32 (86)		17 (85)
Median (hours)	139		126
95% CIs	117, 175		96, 164
P-value oseltamivir vs. baloxavir		0.63	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval

Table 69. Time to Alleviation of Influenza Signs and Symptoms by Race, Trial CP40563

Race Parameter	Baloxavir Marboxil	Oseltamivir
Whites	N=72	N=38
Responders, n (%)	65 (90)	31 (82)
Median (hours)	132	154
95% CIs	116, 149	118, 183
P-value oseltamivir vs. baloxavir	0.28	
Blacks/African Americans	N=2	N=4
Responders, n (%)	2 (100)	4 (100)
Median (hours)	237	100
95% CIs	225, 249	71, 152
P-value oseltamivir vs. baloxavir	0.08	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval

Table 70. Time to Alleviation of Influenza Signs and Symptoms by Ethnicity, Trial CP40563

Ethnicity Parameter	Baloxavir Marboxil	Oseltamivir
Hispanic or Latino	N=37	N=19
Responders, n (%)	31 (84)	14 (74)
Median (hours)	164	154
95% CIs	122, 192	96, 246
P-value oseltamivir vs. baloxavir	0.88	
Other	N=43	N=24
Responders, n (%)	42 (98)	22 (92)
Median (hours)	117	123
95% CIs	88, 139	71, 166
P-value oseltamivir vs. baloxavir	0.57	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval

Analyses of time to alleviation of influenza signs and symptoms did not reveal any significant treatment group differences in any influenza virus subtype subgroups. The influenza virus subtype B subgroup had sample sizes that were too small to make any meaningful comparisons.

Table 71. Median Time to Alleviation of Influenza Signs and Symptoms by Virus Subtype, Trial CP40563

Virus Subtype Parameter	Baloxavir Marboxil		Oseltamivir
A/H1N1	N=18		N=10
Responders, n (%)	17 (94)		6 (60)
Median (hours)	116		207
95% CIs	77, 166		63, --
P-value oseltamivir vs. baloxavir		0.08	
A/H3N2	N=47		N=28
Responders, n (%)	44 (94)		26 (93)
Median (hours)	127		118
95% CIs	99, 163		88, 158
P-value oseltamivir vs. baloxavir		0.76	
B	N=5		N=2
Responders, n (%)	4 (80)		1 (50)
Median (hours)	147		--
95% CIs	119, 238		150, --
P-value oseltamivir vs. baloxavir		0.43	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval

Secondary Endpoint Analysis

Duration of Fever in Trial CP40563

- Defined as the time to return to afebrile state (tympanic temperature ≤37.2°C) and remaining so for at least 21.5 hours.
- Patients who did not return to afebrile state were censored at the last observation timepoint.

As shown in the following table, there was no significant difference between baloxavir and oseltamivir groups in median time to afebrile state.

Table 72. Applicant's Analysis of Duration of Fever, Trial CP40563

Duration of Fever (Hours)

	Baloxavir Marboxil (N=81)	Oseltamivir (N=43)
Patients with CARIFS Assessment	80	43
Patients with event (%)	80 (100.0%)	41 (95.3%)
Patients Censored (%)	0	2 (4.7%)
Time to event (hours) (a)		
Median (b)	41.2	46.8
95% CI	(24.5, 45.7)	(30.0, 53.5)
Min - Max	4 - 269	2 - 126

Source: Table 15 of the Clinical Study Report
(a) Time from start of treatment to return to afebrile state (tympanic temperature ≤37.2 °C) and remaining so for at least 21.5 hours
(b) Median time was estimated from the Kaplan-Meier curve.
Abbreviations: CARIFS, Canadian Acute Respiratory Illness and Flu Scale; CI, confidence interval

16.2. Trial T0834

In the first two columns of the following table, results for the same index patient could be used for each treatment group as contact cases within the same household received different treatments. Therefore the number of subjects for each treatment group sum to 759 while the overall number of index patients in the last column is only 545. In addition results summarized by contact cases were similar to results summarized for index patients. Therefore, only the results for index patients (Total column) will be described here.

The mean age of index patients was only 11 years old, with the majority (62%) of the index patients <10 years old, followed by 29% who were at least 10 to <20 years of age, followed by 4% who were between 20 and <40 years old, 4% who were between 40 and <65 years of age and only 1% who were at least 65 years of age. All subjects were Asian, and slightly more than half were male. Only 1% of index patients were current smokers and 31% had received the influenza vaccine within the prior 6 months.

Table 73. Index Patient Demographics and Characteristics by Treatment Group of Index Patient's Household Contacts and for All Index Patients, Trial T0834 (mITT Population)

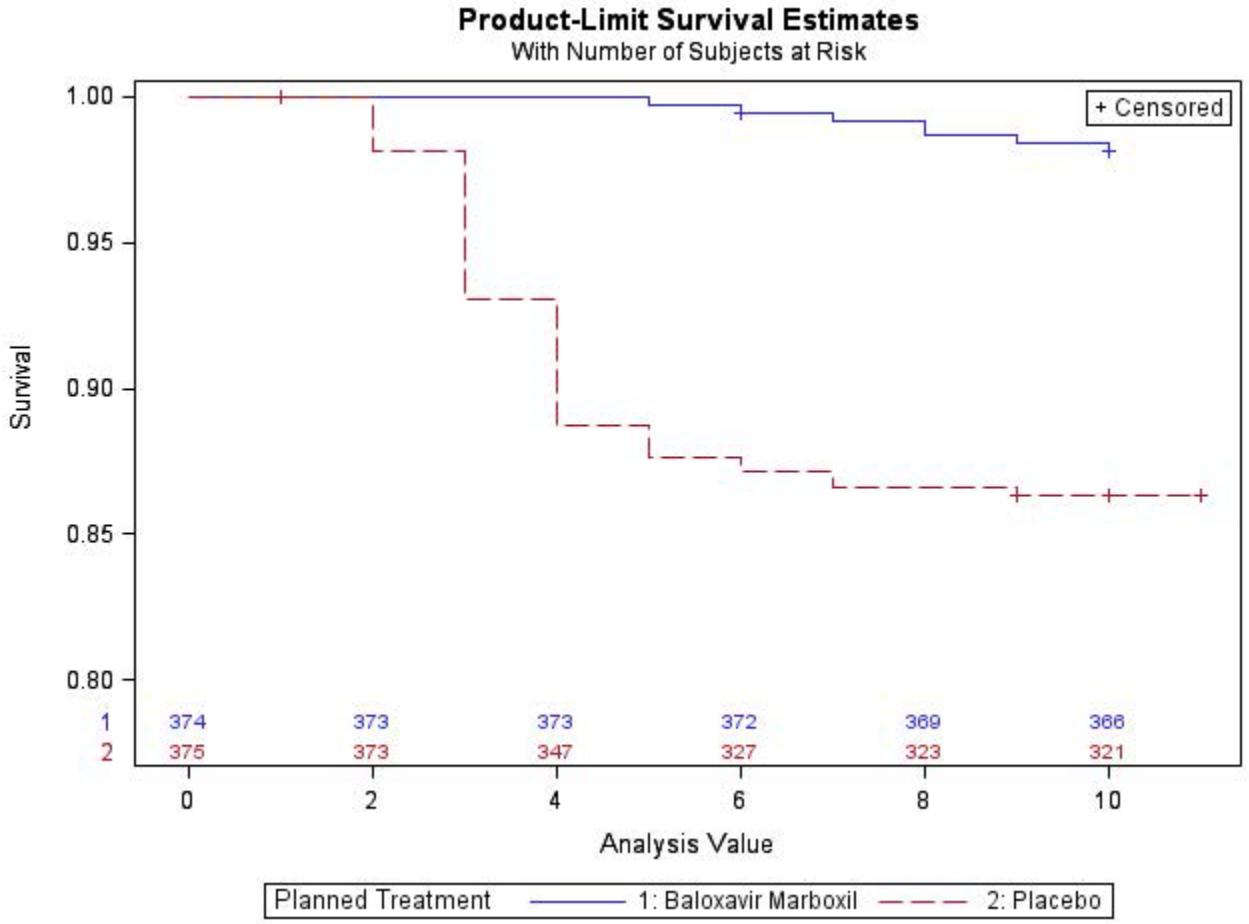
Parameter	Baloxavir Marboxil N=374	Placebo N=375	Total N=545
Mean age (range)	10.2 (1-81)	11.3 (0-80)	11.3 (0-81)
<10 years	249 (67)	226 (60)	336 (62)
≥10 to <20 years	98 (26)	113 (30)	158 (29)
≥20 to <40 years	16 (4)	16 (4)	23 (4)
≥40 to <65 years	9 (2)	14 (4)	20 (4)
≥65 years	2 (1)	6 (2)	8 (1)
Race: Asian	374 (100)	375 (100)	545 (100)
Female	173 (46)	177 (47)	255 (47)
Male	201 (54)	198 (53)	290 (53)
Current smoker	7 (2)	6 (2)	8 (1)
Influenza vaccine in prior 6 months	110 (29)	115 (31)	170 (31)

Source: Summaries by treatment group from Table 11-3 of the Clinical Study Report and total summary by the Statistics Reviewer
Data is expressed as n (%) unless otherwise specified.
Abbreviations: mITT, modified intent-to-treat

Secondary Efficacy Analyses

A secondary efficacy analysis of the time from commencement of study treatment to the time when the primary efficacy endpoint was reached also shows a large separation of the Kaplan-Meier curves for the two treatment groups in favor of baloxavir marboxil compared to placebo. Kaplan-Meier estimates of influenza infection rates for the primary efficacy endpoint were 13.7% for baloxavir marboxil and 1.9% for placebo and the log-rank, Wilcoxon, Peto and modified Peto statistical tests had p-values that were <0.0001.

Figure 10. Kaplan-Meier Plot of Time From Study Treatment to Time When Fever, at Least One Respiratory Symptom, and Influenza Virus Symptom (RT-PCR positive) Were Observed, Trial T0834



Source: Statistics Reviewer's analysis
Abbreviations: RT-PCR, reverse transcription-polymerase chain reaction

The distribution of times to influenza infections in household contacts for the primary efficacy endpoint are shown in the table below. None of the household contacts in the baloxavir marboxil group met the primary efficacy endpoint in the first 4 days of the trial and approximately one subject met the primary efficacy endpoint in each of the remaining 10 days. Household contacts in the placebo arm met the primary efficacy endpoint as early as the second day when 7/51 or 4% of the household contacts were reported as reaching the primary efficacy endpoint. The highest percentage of placebo subjects meeting the primary efficacy endpoint occurred on study Days 3 and 4. The last observed primary efficacy endpoint in subjects in the baloxavir marboxil arm occurred on study Day 10 and on study Day 9 in placebo subjects.

Table 74. Distribution of Event Times to Contact Cases for Primary Efficacy Endpoint, Trial T0834

Time (Days)	Baloxavir Marboxil N=7 n (%)	Placebo N=51 n (%)
2	0	7 (14)
3	0	19 (37)
4	0	16 (31)
5	1 (14)	4 (8)
6	1 (14)	2 (4)
7	1 (14)	2 (4)
8	2 (29)	0
9	1 (14)	1 (2)
10	1 (14)	0

Source: Statistics Reviewer's analysis

Since very few events occurred in either treatment group the median time to event was not estimable. Instead, the Applicant and statistics reviewer estimated the RMST for each treatment group along with the difference between the two arms. Follow-up time was restricted to 10 days and the estimated mean and standard error only changed for the placebo subjects (from 8.28 and 0.0985 without RMST to 9.14 and 0.116 using RMST) since the last placebo event occurred prior to study Day 10 on study Day 9. Compared to placebo subjects, the mean time to event for the primary efficacy endpoint in household contacts in the first 10 days was increased by 0.8 days in subjects treated with baloxavir marboxil.

Table 75. Restricted Mean Survival Time to Event in Contact Cases up to First 10 days of PEP Trial for Primary Efficacy Endpoint, Trial T0834

Treatment Group	N	RMST up to Day 10	Standard Error (Days)	95% CI (Days)
Baloxavir marboxil	374	9.95	0.022	(9.9, 10.0)
Placebo	375	9.14	0.116	(8.9, 9.4)
Placebo - Baloxavir		0.81	0.118	(0.6, 1.0)

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; PEP, postexposure prophylaxis; RMST, restricted mean survival time

Pediatric Subgroup Analysis

The proportion of subjects <12 years of age who met the primary endpoint (PCR + symptomatic influenza) was lower in those who received baloxavir compared to those who received placebo (p=0.02).

- Results in youngest age group were consistent with all patients
- Large sample size in this age group (71 subjects <12 years of age in the baloxavir marboxil arm)
- Insufficient number of adolescent subjects 12 to <18 years of age but results in younger and in adult subjects had similar trends

Table 76. Primary Efficacy Endpoint by Age for Pediatric Subjects, Trial T0834

Age Range Parameter	Baloxavir Marboxil	Placebo
1 to <12 years old	N=71	N=71
Subjects with RT-PCR-confirmed influenza, n (%)	3 (4)	11 (15)
95% CI	1, 12	8, 26
P-value placebo vs. baloxavir	0.02	
12 to <18 years	N=12	N=21
Subjects with RT-PCR-confirmed influenza, n (%)	0	1 (5)
95% CI	0, 36	0, 24
P-value placebo vs. baloxavir	0.51	

Source: Statistics Reviewer's analysis
Abbreviations: CI, confidence interval; RT-PCR , reverse transcription-polymerase chain reaction

As shown in the previous table, the proportion of subjects 1 to <12 years of age who met the primary endpoint (PCR+ symptomatic influenza) was lower in those who received baloxavir compared to those who received placebo (p=0.02). There were too few subjects enrolled who were 18 to <30, to <65 and ≥65 years of age to reach conclusions regarding efficacy.

Table 77. Primary Efficacy Endpoint by Age, Trial T0834

Age Range	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
<12 years old	3/71 (4)	11/71 (15)
12 to <18 years	0/12	1/21 (5)
18 to <30 years	0/22	1/16 (6)
30 to <40 years	1/108 (1)	27/108 (25)
40 to <50 years	2/131 (2)	11/130 (8)
50 to <65 years	1/22 (5)	0/14
≥65 years	0/8	0/15

Source: Statistics Reviewer's analysis

Table 78. Primary Efficacy Endpoint in PEP Trial by Gender, Trial T0834

Gender	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
Female	5/297 (2)	38/290 (13)
Male	2/77 (3)	13/85 (15)

Source: Statistics Reviewer's analysis
Abbreviations: PEP, postexposure prophylaxis

Table 79. Primary Efficacy Endpoint by Time From Onset of Influenza in Index Patient to Informed Consent in Contact Case, Trial T0834

Time From Onset of Influenza	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
0 to <24 hours	6/272 (2)	34/271 (13)
≥24 hours	1/102 (1)	17/104 (16)

Source: Statistics Reviewer's analysis

Table 80. Primary Efficacy Endpoint by Intended Treatment for Index Patient, Trial T0834

Intended Treatment	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
Baloxavir	5/198 (3)	22/198 (11)
Laninamivir	0/34	7/35 (20)
Oseltamivir	1/115 (1)	19/114 (17)
Peramivir	1/11 (9)	1/13 (8)
Zanamivir	0/16	2/15 (13)

Source: Statistics Reviewer's analysis

Table 81. Primary Efficacy Endpoint[1] by Influenza Drug Taken by Index Patient, Trial T0834

Influenza Drug Taken	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
Baloxavir	5/195 (3)	21/197 (11)
Other than baloxavir	2/179 (1)	30/178 (17)

Source: Statistics Reviewer's analysis
[1] Primary endpoint – PCR positive for influenza, febrile and at least one respiratory symptom
Abbreviations: PCR, polymerase chain reaction

Table 82. Primary Efficacy Endpoint by High Risk Factor at Baseline for Contact Case, Trial T0834

Parameter	Baloxavir Marboxil n/N (%)	Placebo n/N (%)
High risk factor		
Present	1/46 (2)	8/52 (15)
Absent	6/328 (2)	43/323 (13)
Vaccination within 6 months		
Yes	3/131 (2)	21/124 (17)
No	4/243 (2)	30/251 (12)
Smoker		
Yes	1/38 (3)	5/37 (14)
No	6/336 (2)	46/338 (14)

Source: Statistics Reviewer's analysis

17. Clinical Safety: Additional Information and Assessment

Safety data from two Phase 3 trials were analyzed separately. Trial CP40563 was a Phase 3, randomized, double-blind, active-controlled trial in pediatric patients >1 year of age to <12 years of age with acute, uncomplicated influenza. Trial T0834 was a Phase 3, randomized, double-blind, placebo-controlled trial to prevent influenza infection in patients >1 year of age and older who were household contacts of index cases with influenza. Data from the trials could not be pooled because of the different study populations; Trial CP40563 was conducted in subjects with influenza while Trial T0834 was conducted in subjects without influenza.

Clinical trial data were analyzed by the Clinical Data Scientist using Python software. The medical officer analyzed data in JMP. All the safety assessments and conclusions are those of the FDA reviewer unless otherwise specified. Safety tables include calculated percentages with decimal places; therefore, some percentages may be different compared to labeled safety information which rounds to whole numbers.

The Applicant submitted a safety update report (SUR) 4 months after the original NDA and supplemental NDAs were submitted. The SUR included only postmarketing data. The majority of data were from the interim period (August 23, 2019, to February 22, 2020) since the last SUR was submitted in 2019; other data were included the entire period of baloxavir marboxil marketing.

There were no deaths and no serious adverse events in any patients who received baloxavir marboxil in Trials CP40563 or T0834. Treatment-emergent adverse events by System Organ Class for Trial CP40563 are provided Table 83.

Table 83. Treatment-Emergent Adverse Events by System Organ Class and Baloxavir Marboxil Dose, Safety Population, Trial CP40563

System Organ Class Preferred Term[1]	2 mg/kg BXM[2] N=47 n (%)	40 mg BXM N=68 n (%)	Total BXM N=115 n (%)	OST 30 mg/5 mL N=58 n (%)	Risk Difference[3] (95% CI)
Injury, poisoning and procedural complications	8 (17.0)	4 (5.9)	12 (10.4)	3 (5.2)	5.3 (-2.7, 13.2)
Medication error	5 (10.6)	0	5 (4.3)	2 (3.4)	0.9 (-5.1, 6.9)
Accidental overdose	1 (2.1)	2 (2.9)	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Accidental underdose	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Contusion	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Incorrect dose administered	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Product dispensing error	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Respiratory, thoracic and mediastinal disorders	4 (8.5)	7 (10.3)	11 (9.6)	3 (5.2)	4.4 (-3.4, 12.2)
Rhinorrhea	1 (2.1)	3 (4.4)	4 (3.5)	1 (1.7)	1.8 (-3.0, 6.5)
Rhinitis allergic	1 (2.1)	1 (1.5)	2 (1.7)	0	1.7 (-0.7, 4.1)
Cough	2 (4.3)	1 (1.5)	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Allergic cough	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Epistaxis	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Oropharyngeal pain	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Upper-airway cough syndrome	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Asthma	0	1 (1.5)	1 (0.9)	1 (1.7)	-0.9 (-4.6, 2.9)
Pharyngeal erythema	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Skin and subcutaneous tissue disorders	3 (6.4)	2 (2.9)	5 (4.3)	1 (1.7)	2.6 (-2.4, 7.6)
Rash	2 (4.3)	0	2 (1.7)	0	1.7 (-0.7, 4.1)
Dermatitis	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Petechiae	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Rash morbilliform	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Dermatitis diaper	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Blood and lymphatic system disorders	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Anemia	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
General disorders and administration site conditions	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Pyrexia	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Vascular disorders	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Flushing	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Nervous system disorders	0	2 (2.9)	2 (1.7)	2 (3.4)	-1.7 (-7.0, 3.6)
Headache	0	2 (2.9)	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Febrile convulsion	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Psychiatric disorders	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Sleep terror	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)

System Organ Class Preferred Term[1]	2 mg/kg BXM[2] N=47 n (%)	40 mg BXM N=68 n (%)	Total BXM N=115 n (%)	OST 30 mg/5 mL N=58 n (%)	Risk Difference[3] (95% CI)
Ear and labyrinth disorders	1 (2.1)	0	1 (0.9)	2 (3.4)	-2.6 (-7.6, 2.4)
Ear pain	1 (2.1)	0	1 (0.9)	2 (3.4)	-2.6 (-7.6, 2.4)
Infections and infestations	8 (17.0)	10 (14.7)	18 (15.7)	11 (19.0)	-3.3 (-15.4, 8.8)
Upper respiratory tract infection	3 (6.4)	2 (2.9)	5 (4.3)	2 (3.4)	0.9 (-5.1, 6.9)
Bronchitis	2 (4.3)	1 (1.5)	3 (2.6)	1 (1.7)	0.9 (-3.6, 5.3)
Bronchiolitis	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Conjunctivitis	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Ear infection	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Gastritis viral	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Influenza	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Nasopharyngitis	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Pneumonia	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Sinusitis	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Viral infection	1 (2.1)	0	1 (0.9)	0	0.9 (-0.8, 2.6)
Viral rash	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Pharyngitis streptococcal	1 (2.1)	1 (1.5)	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Croup infectious	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Gastroenteritis viral	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Otitis media acute	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Respiratory syncytial virus bronchiolitis	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Otitis media	2 (4.3)	1 (1.5)	3 (2.6)	4 (6.9)	-4.3 (-11.4, 2.9)
Metabolism and nutrition disorders	0	1 (1.5)	1 (0.9)	3 (5.2)	-4.3 (-10.2, 1.6)
Decreased appetite	0	1 (1.5)	1 (0.9)	0	0.9 (-0.8, 2.6)
Dehydration	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Vitamin D deficiency	0	0	0	2 (3.4)	-3.4 (-8.1, 1.2)
Gastrointestinal disorders	6 (12.8)	9 (13.2)	15 (13.0)	12 (20.7)	-7.6 (-19.8, 4.5)
Diarrhea	1 (2.1)	5 (7.4)	6 (5.2)	1 (1.7)	3.5 (-1.8, 8.8)
Nausea	1 (2.1)	1 (1.5)	2 (1.7)	0	1.7 (-0.7, 4.1)
Abdominal pain	1 (2.1)	1 (1.5)	2 (1.7)	1 (1.7)	0.0 (-4.1, 4.1)
Feces soft	0	0	0	1 (1.7)	-1.7 (-5.1, 1.6)
Vomiting	3 (6.4)	4 (5.9)	7 (6.1)	9 (15.5)	-9.4 (-19.7, 0.9)

Source: adae.xpt; Software: Python
[1] Terms included are those that occurred in at least one subject.
[2] Includes four subjects who received underdose of 4 mg (0.06 to 0.19 mg/kg; CP40563-(b) (6), CP40563-(b) (6), CP40563-(b) (6)) or 34 mg (1.53 mg/kg; CP40563-(b) (6)
[3] Risk differences are comparisons of the total BXM group with the OST group.
Abbreviations: BXM, baloxavir marboxil; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; OST, oseltamivir

More treatment-emergent adverse events (TEAEs) were reported in baloxavir marboxil arm compared to the oseltamivir arm for Injury, Poisoning, and Procedural Complications; Respiratory, Thoracic, and Mediastinal Disorders; and Skin and Subcutaneous Tissue Disorders. In the Injury, Poisoning, and Procedural Complications System Organ Class (SOC), the differences were largely due to medication errors observed in subjects who received baloxavir marboxil at a dose of 2 mg/kg. Dosing errors at one site resulted in five medication errors.

Three additional TEAEs in the baloxavir arm were overdoses, but of the oseltamivir placebo not of baloxavir marboxil. In the opinion of this reviewer, the dosing errors resulting in more TEAEs in this SOC were not related to baloxavir marboxil. TEAEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC were also more commonly reported in subjects who received baloxavir marboxil (11 subjects, 9.6%) compared to those who received oseltamivir (three subjects or 5.2%). Cough and rhinitis were more common in the baloxavir marboxil arm than in the oseltamivir arm. Study participants had to have either cough or nasal congestion to participate in the trial; therefore, the reason that cough and rhinitis were reported as TEAEs more often in the baloxavir marboxil arm compared to the oseltamivir arm is unclear. Skin and Subcutaneous Tissue Disorders were reported in five patients (4.3%) in the baloxavir marboxil arm and in one (1.7%) in the oseltamivir arm. There were three TEAEs of rash (two rash AEs and one morbilliform rash) in the baloxavir marboxil arm. All were Grade 1. Rash is known to occur with baloxavir marboxil and is included in the product labeling. One subject in the baloxavir marboxil arm reported petechiae, but this AE occurred on Day 22 and was not due to baloxavir marboxil.

There was a substantial difference in the percentage of subjects who had medication errors and who received an incorrect dose for subjects who received 2 mg/kg of baloxavir (12.8%) compared to a single 40-mg dose (zero subjects). Calculation of dose by weight resulted in dosing errors in this trial.

Treatment-emergent adverse events by SOC for Trial T0834 are shown in Table 84. Treatment-emergent adverse events are shown for the pediatric and adult/adolescent population; TEAEs are shown by dose for the pediatric patients.

Table 84. Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial T0834

	>1 Year to <12 Years of Age					≥12 Years of Age	
System Organ Class Preferred Term[1]	**10 mg BXM N=19 n (%)**	**20 mg BXM[2] N=48 n (%)**	**40 mg BXM[3] N=5 n (%)**	**Total BXM N=72 n (%)**	**Placebo N=71 n (%)**	**Total BXM N=302 n (%)**	**Placebo N=304 n (%)**
Infections and infestations	6 (31.6)	4 (8.3)	0	10 (13.9)	10 (14.1)	32 (10.6)	35 (11.5)
Nasopharyngitis	3 (15.8)	3 (6.2)	0	6 (8.3)	6 (8.5)	18 (6.0)	19 (6.2)
Bronchitis	1 (5.3)	0	0	1 (1.4)	0	2 (0.7)	0
Upper respiratory tract infection	1 (5.3)	0	0	1 (1.4)	0	1 (0.3)	2 (0.7)
Rhinitis	1 (5.3)	0	0	1 (1.4)	0	0	1 (0.3)
Gastroenteritis viral	1 (5.3)	0	0	1 (1.4)	0	0	0
Bacterial infection	0	1 (2.1)	0	1 (1.4)	0	1 (0.3)	0
Viral infection	0	0	0	0	2 (2.8)	0	0
Beta hemolytic streptococcal infection	0	0	0	0	1 (1.4)	0	1 (0.3)
Enteritis infectious	0	0	0	0	1 (1.4)	0	0
Pharyngitis	0	0	0	0	0	4 (1.3)	1 (0.3)
Gastroenteritis	0	0	0	0	0	2 (0.7)	1 (0.3)
Acute sinusitis	0	0	0	0	0	1 (0.3)	3 (1.0)
Gingivitis	0	0	0	0	0	1 (0.3)	2 (0.7)
Otitis media acute	0	0	0	0	0	1 (0.3)	1 (0.3)
Hordeolum	0	0	0	0	0	1 (0.3)	0
Laryngitis	0	0	0	0	0	1 (0.3)	0
Oral herpes	0	0	0	0	0	1 (0.3)	0
Sinusitis	0	0	0	0	0	0	2 (0.7)
Herpes zoster	0	0	0	0	0	0	1 (0.3)
Mycoplasma infection	0	0	0	0	0	0	1 (0.3)
Otitis media	0	0	0	0	0	0	1 (0.3)
Tonsillitis	0	0	0	0	0	0	1 (0.3)
Vulvovaginal candidiasis	0	0	0	0	0	0	1 (0.3)

	>1 Year to <12 Years of Age					≥12 Years of Age	
System Organ Class Preferred Term[1]	10 mg BXM N=19 n (%)	20 mg BXM[2] N=48 n (%)	40 mg BXM[3] N=5 n (%)	Total BXM N=72 n (%)	Placebo N=71 n (%)	Total BXM N=302 n (%)	Placebo N=304 n (%)
Investigations	1 (5.3)	1 (2.1)	0	2 (2.8)	2 (2.8)	13 (4.3)	7 (2.3)
Alanine aminotransferase increased	1 (5.3)	0	0	1 (1.4)	0	3 (1.0)	1 (0.3)
Neutrophil count decreased	1 (5.3)	0	0	1 (1.4)	0	0	0
Blood urine present	0	1 (2.1)	0	1 (1.4)	0	5 (1.7)	1 (0.3)
Protein urine present	0	1 (2.1)	0	1 (1.4)	0	1 (0.3)	0
Blood uric acid increased	0	0	0	0	1 (1.4)	1 (0.3)	0
Platelet count increased	0	0	0	0	1 (1.4)	0	0
Glucose urine present	0	0	0	0	0	2 (0.7)	2 (0.7)
Aspartate aminotransferase increased	0	0	0	0	0	1 (0.3)	1 (0.3)
Gamma-glutamyl transferase increased	0	0	0	0	0	1 (0.3)	0
Protein total decreased	0	0	0	0	0	1 (0.3)	0
C-reactive protein increased	0	0	0	0	0	0	2 (0.7)
Neutrophil count increased	0	0	0	0	0	0	1 (0.3)
White blood cell count increased	0	0	0	0	0	0	1 (0.3)
General disorders and administration site conditions	1 (5.3)	1 (2.1)	0	2 (2.8)	0	0	3 (1.0)
Pyrexia	1 (5.3)	1 (2.1)	0	2 (2.8)	0	0	1 (0.3)
Chills	0	0	0	0	0	0	1 (0.3)
Feeling abnormal	0	0	0	0	0	0	1 (0.3)
Skin and subcutaneous tissue disorders	1 (5.3)	0	0	1 (1.4)	4 (5.6)	4 (1.3)	0
Dermatitis contact	1 (5.3)	0	0	1 (1.4)	0	0	0
Eczema	0	0	0	0	3 (4.2)	1 (0.3)	0
Miliaria	0	0	0	0	1 (1.4)	0	0
Acne	0	0	0	0	0	1 (0.3)	0
Dermatitis	0	0	0	0	0	1 (0.3)	0
Rash	0	0	0	0	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	0	3 (6.2)	0	3 (4.2)	0	4 (1.3)	2 (0.7)
Cough	0	2 (4.2)	0	2 (2.8)	0	1 (0.3)	0
Rhinitis allergic	0	1 (2.1)	0	1 (1.4)	0	0	0
Oropharyngeal pain	0	0	0	0	0	1 (0.3)	1 (0.3)
Upper respiratory tract inflammation	0	0	0	0	0	1 (0.3)	1 (0.3)
Rhinorrhea	0	0	0	0	0	1 (0.3)	0
Productive cough	0	0	0	0	0	1 (0.3)	0

	>1 Year to <12 Years of Age					≥12 Years of Age	
System Organ Class Preferred Term[1]	10 mg BXM N=19 n (%)	20 mg BXM[2] N=48 n (%)	40 mg BXM[3] N=5 n (%)	Total BXM N=72 n (%)	Placebo N=71 n (%)	Total BXM N=302 n (%)	Placebo N=304 n (%)
Nervous system disorders	0	2 (4.2)	0	2 (2.8)	0	8 (2.6)	10 (3.3)
Headache	0	2 (4.2)	0	2 (2.8)	0	6 (2.0)	6 (2.0)
Dizziness	0	0	0	0	0	2 (0.7)	0
Migraine	0	0	0	0	0	0	3 (1.0)
Hypoesthesia	0	0	0	0	0	0	1 (0.3)
Injury, poisoning and procedural complications	0	0	1 (20.0)	1 (1.4)	1 (1.4)	1 (0.3)	0
Contusion	0	0	1 (20.0)	1 (1.4)	1 (1.4)	0	0
Superficial injury of eye	0	0	0	0	0	1 (0.3)	0
Gastrointestinal disorders	0	0	0	0	1 (1.4)	8 (2.6)	6 (2.0)
Vomiting	0	0	0	0	1 (1.4)	0	0
Nausea	0	0	0	0	0	3 (1.0)	1 (0.3)
Diarrhea	0	0	0	0	0	2 (0.7)	1 (0.3)
Abdominal pain upper	0	0	0	0	0	1 (0.3)	2 (0.7)
Abdominal discomfort	0	0	0	0	0	1 (0.3)	0
Constipation	0	0	0	0	0	1 (0.3)	0
Enterocolitis	0	0	0	0	0	0	1 (0.3)
Gastroesophageal reflux disease	0	0	0	0	0	0	1 (0.3)
Hepatobiliary disorders	0	0	0	0	1 (1.4)	1 (0.3)	0
Hepatic function abnormal	0	0	0	0	1 (1.4)	1 (0.3)	0
Metabolism and nutrition disorders	0	0	0	0	0	1 (0.3)	1 (0.3)
Hyperuricemia	0	0	0	0	0	1 (0.3)	0
Glucose tolerance impaired	0	0	0	0	0	0	1 (0.3)
Reproductive system and breast disorders	0	0	0	0	0	0	2 (0.7)
Dysmenorrhea	0	0	0	0	0	0	2 (0.7)
Blood and lymphatic system disorders	0	0	0	0	0	0	1 (0.3)
Granulocytopenia	0	0	0	0	0	0	1 (0.3)
Immune system disorders	0	0	0	0	0	0	1 (0.3)
Seasonal allergy	0	0	0	0	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (0.3)
Pain in jaw	0	0	0	0	0	0	1 (0.3)

	>1 Year to <12 Years of Age					≥12 Years of Age	
System Organ Class Preferred Term[1]	10 mg BXM N=19 n (%)	20 mg BXM[2] N=48 n (%)	40 mg BXM[3] N=5 n (%)	Total BXM N=72 n (%)	Placebo N=71 n (%)	Total BXM N=302 n (%)	Placebo N=304 n (%)
Psychiatric disorders	0	0	0	0	0	0	1 (0.3)
Psychotic disorder	0	0	0	0	0	0	1 (0.3)
Renal and urinary disorders	0	0	0	0	0	0	1 (0.3)
Renal glycosuria	0	0	0	0	0	0	1 (0.3)

Source: adae.xpt; Software: Python
[1] Terms included are those that occurred in at least one subject.
[2] Includes one subject (1719T0834 (b) (6)) aged 12 years with a planned dosage of 40 mg and an actual dosage of 20 mg.
[3] Includes one child subject (1719T0834 (b) (6)) with a body weight of 21.8 kg with a planned dosage of 20 mg and an actual dosage of 40 mg.
[4] Includes one adult subject (1719T0834) with a body weight of 96.8 kg with a planned dosage of 80 mg and an actual dosage of 40 mg.
Abbreviations: BXM, baloxavir marboxil; N, number of subjects in treatment arm; n, number of subjects with at least one event

Although the same number of TEAEs in the SOC investigations were reported in the baloxavir marboxil arm and the placebo arm, there were more TEAEs in Investigations SOC in adults and adolescents who received baloxavir marboxil (13 or 4.3%) compared to placebo (7 or 2.3%). This was primarily due to abnormalities in urine dipstick testing. In the baloxavir marboxil arm blood in urine was reported in five subjects, glucose in the urine was reported in two subjects, and proteinuria was reported in one subject. In the placebo arm, blood in urine was reported in one subject and glucose in the urine was reported in two subjects. Baloxavir marboxil has not been associated with renal toxicity and the reason for this difference is unclear. However, laboratory values were reported at the investigator's discretion, and this could have introduced bias. There were also more TEAEs in the Respiratory, Thoracic, and Mediastinal in the baloxavir marboxil arm (7 or 1.8%) compared to the placebo arm (2 or 0.5%); but the overall number of TEAEs in both arms was small and the types of TEAEs were varied.

The incidence of TEAEs by SOC was similar in the pediatric and adult/adolescent population with no TEAEs by SOC with a difference of 3% or more between the two age groups.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Baloxavir marboxil (S-033188) is a prodrug that is hydrolyzed to the active compound, baloxavir, which selectively inhibits the endonuclease activity of the influenza virus PA polymerase complex subunit. Hence, the virus is prevented from generating the 5' 7-methylguanosine (m^7G) cap-containing oligomers from host messenger ribonucleic acid (mRNA) that are required for viral gene expression (Krug et al. 1976). Evidence supporting the mechanism of action includes inhibition of PA endonuclease activity in influenza virus ribonucleoprotein complexes, lack of specific activity against RNA-dependent RNA polymerase primer extension activity, and the mapping of determinants of resistance to the endonucleolytic site of the PA protein. Reduced susceptibility to baloxavir in cell culture is conferred by amino acid substitutions at positions 23, 37, 38, and 199 in the PA protein (Genentech 2018).[1]

19. Other Drug Development Considerations: Additional Information and Assessment

19.1. Clinical Virology

19.1.1. Supportive Nonclinical Studies

Table 85. Nonclinical Studies Submitted to Support This Efficacy Supplement

Study Report	Title	Summary
S-033188-EB-301-N	Prophylactic Effect of S-033447[1] against Lethal Infection with Influenza A Virus in Mice	A 1.6 mg/kg subcutaneous dose of baloxavir resulted in 100% survival when mice were lethally challenged with A/Puerto Rico/8/34 (H1N1; EC_{50} value =1.07nM) up to 96 hours after dosing.
S-033188-EB-303-N	Prophylactic Effect of S-033447[1] against Lethal Infection with Influenza A Virus in Mice	A 1.6 mg/kg subcutaneous dose of baloxavir resulted in 50% survival when mice were lethally challenged with B/Hong Kong/5/72 (EC_{50} value =4.33nM) up to 96 hours after dosing. 6.4 mg/kg baloxavir was 100% protective after 96 hours.
S-033188-EB-326-N	Inhibitory Effect of S-033447 in Combination with Neuraminidase Inhibitor on Cytopathic Effect in Cultured Cells Infected with Influenza B Virus	Antagonism was not detected in cell culture when baloxavir was combined with oseltamivir, zanamivir, laninamivir or peramivir (active forms) over concentration ranges encompassing their respective EC_{50} values.
S-033188-EB-337-N	Competitive Fitness of Reverse Genetics-derived Influenza Viruses with Amino Acid Substitutions in Cultured Cells Study	PA variants I38T or F in A/H1N1, I38T or M in A/H3N2, and I38T in B were outcompeted by their wild-type counterparts by passage 3 in cell culture; however, proportions were assessed by Sanger sequencing chromatogram peak height, which is only semiquantitative.
S-033188-EB-287-N	Effect of Delayed Treatment with S-033188[1] on Pathological Changes of Lungs in Mice Lethally Infected with Influenza A Virus	Mice infected with A/Puerto Rico/8/34 (H1N1; EC_{50} value =1.07nM) and orally treated at 96 hours post infection with 15 mg/kg of baloxavir marboxil ± oseltamivir for 3 to 5 days had reduced lung inflammation and pathology. Oseltamivir alone had no apparent effect. Dosing with 0.5 mg/kg baloxavir marboxil + oseltamivir had a limited effect, but better than monotherapy of the same doses.
S-033188-EB-346-N	Competitive Fitness of Influenza Virus Derived from Patients in S-033188 Clinical Study in Primary Human Nasal Epithelial Cells	A/H3N2 clinical isolates with or without a PA I38T substitution from trial T0831 were competed in cell culture. Wild-type outcompeted I38T variants by passage 3; however, the starting proportion of the I38T variant was <50%.

Study Report	Title	Summary
S-033188-EB-356-N	Drug Susceptibility Testing of Reverse Genetics-derived Influenza Viruses with Amino Acid Substitutions to S−033447 (6)	Recombinant molecular clone-derived viruses with selected PA, PB1, or PB2 amino acid substitutions identified in clinical studies were evaluated for susceptibility to baloxavir in MDCK cells. Cumulative results of these studies are described in Table 86.

Source: Virology Reviewer analysis of data from the indicated study report.
[1] S-033447 = baloxavir, the active metabolite of the prodrug baloxavir marboxil.
Abbreviations: EC_{50}, half maximal effective concentration; MDCK, Madin-Darby Canine Kidney; PA, polymerase acidic

Table 86. Cumulative Evaluations of Baloxavir Susceptibility of Molecular Clone-Derived PA/PB1/PB2 Variants Identified in Clinical Studies

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
A/H1N1	rgA/WSN/33-PA/A20S	PA	20	A20S	0.5	0.27	1.19	S-033188-EB-301-N
A/H1N1	rgA/WSN/33- PA/A20S+I38T	PA	20	A20S+I38T	11.43	2.6	27.38[2]	
A/H1N1	rgA/WSN/33- PA/A20S+I38F	PA	20	A20S+I38F	3.38	1.16	8.1[2]	S-033188-EB-303-N
A/H1N1	rgA/WSN/33-PA/E23K	PA	23	E23K	1.98	0.48	4.74[2]	
A/H1N1	rgA/WSN/33 PA/E23K	PA	23	E23K	1.232	0.69	3.1391[2]	S-033188-EB-326-N
A/H1N1	rgA/WSN/33 PA/E23G	PA	23	E23G	0.691	0.15	1.7593	
A/H1N1	rgA/WSN/33 PA/E23R	PA	23	E23R	1.502	0.61	3.8230[2]	S-033188-EB-337-N
A/H1N1	rgA/WSN/33-PA/Y24H	PA	24	Y24H	0.545	0.08	1.3880	
A/H1N1	rgA/WSN/33 PA/Y24H+V122A	PA	24	Y24H+V122A	0.454	0.03	1.1551	S-033188-EB-287-N
A/H1N1	rgA/WSN/33-PA/A36V	PA	36	A36V	1.5	0.37	3.59[2]	
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	11.37	1.85	27.24[2]	S-033188-EB-346-N
A/H1N1	rgA/WSN/33-PA/I38F	PA	38	I38F	4.43	1.95	10.61[2]	
A/H1N1	rgA/WSN/33-PA/I38M	PA	38	I38M	4.07	1.84	13.15[2]	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PA/I38V	PA	38	I38V	0.97	0.8	2.18[2]	S-033188-EB-301-N
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	20.53	5.13	43.92[2]	
A/H1N1	rgA/WSN/33-PA/I38T+PB1/K757N	PA	38	PA/I38T+PB1/K757N	20.75	13.15	44.39[2]	S-033188-EB-303-N
A/H1N1	rgA/WSN/33-PA/I38T+PB2/Q288L	PA	38	PA/I38T+PB2/Q288L	11.48	3.21	24.55[2]	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PA/I38T+PB1/K757N+PB2/Q288L	PA	38	PA/I38T+PB1/K757N +PB2/Q288L	21.90	5.23	46.85[2]	S-033188-EB-326-N
A/H1N1	rgA/WSN/33-PA/ I38T	PA	38	I38T	6.9	2.94	19.16[2]	S-033188-EB-335-N
A/H1N1	rgA/WSN/33-PA/I38N	PA	38	I38N	8.52	2.87	23.66[2]	S-033188-EB-337-N
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	16.71	9.30	26.30[2]	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PA/I38S	PA	38	I38S	7.90	3.90	12.43[2]	S-033188-EB-287-N
A/H1N1	rgA/WSN/33-PA/I38L	PA	38	I38L	4.02	3.51	6.33[2]	S-033188-EB-356-N
A/H1N1	rgB/Maryland/1/59-PB2/G76R	PB2	76	G76R	9.90	4.20	0.95	S-033188-EB-346-N
A/H1N1	rgA/WSN/33-PB1/M92T	PB1	92	M92T	0.33	0.05	0.79	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/E119D	PA	119	E119D	2.7	1.5	6.46[2]	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PB2/A221T	PB2	221	A221T	0.38	0.06	0.9	S-033188-EB-301-N
A/H1N1	rgA/WSN/33-NA/H274Y	NA	274	H274Y	0.32	0.06	0.77	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/Q288L	PB2	288	Q288L	0.64	0.21	1.36	S-033188-EB-303-N
A/H1N1	rgA/WSN/33-PB2/Q288L+I638V	PB2	288	Q288L+I638V	0.48	0.08	1.03	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PB2/I310M	PB2	310	I310M	0.29	0.08	0.71	S-033188-EB-326-N
A/H1N1	rgA/WSN/33-PB2/T333I	PB2	333	T333I	0.24	0.02	0.58	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/R356K	PA	356	R356K	0.38	0.07	1.07	S-033188-EB-337-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
A/H1N1	rgA/WSN/33-PA/E397G	PA	397	E397G	0.33	0.08	0.92	S-033188-EB-335-N
A/H1N1	rgA/WSN/33 PA/W406G	PA	406	W406G	0.275	0.09	0.7000	S-033188-EB-287-N
A/H1N1	rgA/WSN/33-PB1/V418I	PB1	418	V418I	0.3	0.1	0.71	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/I465M	PA	465	I465M	0.29	0.05	0.93	S-033188-EB-346-N
A/H1N1	rgA/WSN/33-PA/V545T	PA	545	V545T	0.31	0.11	0.73	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/I638V	PB2	638	I638V	0.46	0.16	0.99	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PB1/K757N	PB1	757	K757N	0.47	0.1	1	S-033188-EB-301-N
A/H1N1	rgA/WSN/33				0.31	0.11		S-033188-EB-276-N
A/H1N1	rgA/WSN/33				0.45	0.22		S-033188-EB-303-N
A/H1N1	rgA/WSN/33				0.47	0.05		S-033188-EB-319-N
A/H1N1	rgA/WSN/33				0.36	0.03		S-033188-EB-326-N
A/H1N1	rgA/WSN/33				0.393	0.12		S-033188-EB-329-N
A/H1N1	rgA/WSN/33				0.64	0.35		S-033188-EB-337-N
A/H1N1	rgA/WSN/33				0.42	0.12		S-033188-EB-235-N
A/H1N1	rgB/Maryland/1/59				10.40	1.95		S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75- PB2/S12L	PB2	12	S12L	0.91	0.3	0.86	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/E23K	PA	23	E23K	6.2	2.86	5.5[2]	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75-PA/E23G	PA	23	E23G	2.75	1.48	2.39[2]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E23G+C_{24}1F	PA	23	E23G+C_{24}1F	2.04	1.35	1.77	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/L28P	PA	28	L28P	2.15	0.13	2.58[2]	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/L28P+V63I	PA	28	L28P+V63I	2.4	0.32	2.88[2]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/L28V	PA	28	L28V	1.47	0.78	2.02[2]	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/K34E	PA	34	K34E	1.43	1.6	1.96	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/A36V	PA	36	A36V	6.87	2.76	6.09[2]	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/A37T	PA	37	A37T	6.78	4.04	8.13[2]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	63.8	3.4	56.59[2]	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/I38F	PA	38	I38F	22.69	10.82	20.13[2]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75-PA/I38T*	PA	38	I38T*	40.76	11.94	48.9[2]	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+E623K	PA	38	I38T+E623K	35.34	16.12	42.41[2]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I38M	PA	38	I38M	11.48	1.43	13.77[2]	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	57.33	6.81	49.76[2]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+S60P	PA	38	I38T+S60P	55.55	4.64	48.21[2]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/D60G	PA	38	I38T+PB2/D60G	49.37	19.05	42.85[2]	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/K197R	PA	38	I38T+PB2/K197R	23.12	20.73	20.07[2]	S-033188-EB-290-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
A/H3N2	rgA/Victoria/3/75-PA/I38V	PA	38	I38V	2.11	0.81	1.83	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+I201T	PA	38	I38T+I201T	39.09	5.29	33.92[2]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	26.18	7.76	24.85[2]	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	14.8	5.86	20.33[2]	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	45.74	8.66	25.489[2]	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/I38M	PA	38	I38M	6.561	1.71	3.6561[2]	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I38M+I201T	PA	38	I38M+I201T	16.40	7.92	9.1406[2]	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	55.97	7.99	33.97[2]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38N	PA	38	I38N	17.01	9.37	10.32[2]	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75-PA/I38S	PA	38	I38S	9.63	5.93	5.85[2]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38L	PA	38	I38L	3.57	2.51	2.17[2]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/S60P	PA	60	S60P	0.46	0.22	0.4	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PB2/D60G	PB2	60	D60G	1.06	0.15	0.92	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V63I	PA	63	V63I	1.44	0.33	1.73	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/P68L	PA	68	P68L	0.89	0.4	1.23	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/L71M	PA	71	L71M	0.46	0.08	0.64	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/V90A	PA	90	V90A	0.83	0.45	1.14	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/T98N	PA	98	T98N	0.38	0.08	0.52	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/G99E	PA	99	G99E	0.71	0.28	0.61	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PB2/R101G	PB2	101	R101G	0.85	0.14	0.8	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75-PB2/V105M	PB2	105	V105M	0.67	0.18	0.58	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/E119D	PA	119	E119D	5.09	2.48	4.51[2]	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75- PA/D160G	PA	160	D160G	0.59	0.16	0.81	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/T162A	PA	162	T162A	1.96	0.3	1.7	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/A183V	PA	183	A183V	0.59	0.4	0.51	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/G186D	PA	186	G186D	0.21	0.13	0.18[2]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/R192H	PA	192	R192H	0.62	0.1	0.85	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PB2/K197R	PB2	197	K197R	1.56	0.69	1.36	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E199G	PA	199	E199G	3.72	1.37	4.46[2]	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75- PA/E199G	PA	199	E199G	2.95	0.3	2.8[2]	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/E199G+PB2/S12L	PA	199	E199G+PB2/S12L	2.87	0.41	2.73[2]	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/I201T	PA	201	I201T	1.26	0.61	1.1	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I201T	PA	201	I201T	1.438	0.48	0.8013	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75- PB2/M202L	PB2	202	M202L	1.8	0.36	1.7	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PB1/I205M	PB1	205	I205M	0.73	0.17	0.63	S-033188-EB-346-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
A/H3N2	rgA/Victoria/3/75- PB2/R209K	PB2	209	R209K	0.55	0.15	0.53	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/R212C	PA	212	R212C	0.79	0.33	0.68	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/S224F	PA	224	S224F	0.9	0.84	0.78	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/A231V	PA	231	A231V	0.67	0.3	0.58	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/C_{24}1F	PA	241	C_{24}1F	0.65	0.17	0.56	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/P271S	PA	271	P271S	0.6	0.22	0.52	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PB1/M290T	PB1	290	M290T	0.39	0.24	0.34	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/G299R	PA	299	G299R	1.54	0.77	1.34	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/G316R	PA	316	G316R	0.3	0.07	0.26	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/G316R+E630K	PA	316	G316R+E630K	0.41	0.18	0.36	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PB2/K353R	PB2	353	K353R	0.84	0.22	0.73	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75- PA/R356K	PA	356	R356K	0.8	0.49	0.96	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/T357A	PA	357	T357A	1.07	0.86	0.93	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75-PA/K362R	PA	362	K362R	1.05	0.66	1.25	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PB2/I385V	PB2	385	I385V	0.74	0.13	0.64	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/R385K	PA	385	R385K	1.22	0.46	1.06	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/S395N	PA	395	S395N	0.7	0.44	0.6	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/E397K	PA	397	E397K	0.56	0.39	0.77	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/S405C	PA	405	S405C	0.8	0.62	0.69	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/N412D	PA	412	N412D	0.45	0.02	0.54	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/I421T	PA	421	I421T	1.26	1.14	1.1	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PB2/M475I	PB2	475	M475I	1.38	0.37	1.31	S-033188-EB-337-N
A/H3N2	rgA/Victoria/3/75-PA/L482I	PA	482	L482I	0.6	0.06	0.52	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E493G	PA	493	E493G	0.51	0.39	0.44	S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75-PA/V517A	PA	517	V517A	0.43	0.22	0.52	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75- PB1/I517M	PB1	517	I517M	1.02	0.18	0.97	S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75-PA/I545M	PA	545	I545M	0.49	0.17	0.43	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/M561I	PA	561	M561I	1.05	0.23	0.91	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/V602I	PA	602	V602I	1.31	0.76	1.14	S-033188-EB-301-N
A/H3N2	rgA/Victoria/3/75-PA/E623K	PA	623	E623K	1	0.29	1.2	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/E623G	PA	623	E623G	1.2	0.72	1.04	S-033188-EB-303-N
A/H3N2	rgA/Victoria/3/75-PA/E630K	PA	630	E630K	0.46	0.19	0.4	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/S632P	PA	632	S632P	0.61	0.28	0.74	S-033188-EB-326-N
A/H3N2	rgA/Victoria/3/75-PA/L649M	PA	649	L649M	0.47	0.1	0.41	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V668I	PA	668	V668I	0.93	0.48	0.81	S-033188-EB-337-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
A/H3N2	rgA/Victoria/3/75				1.13	0.51		S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75				0.83	0.28		S-033188-EB-287-N
A/H3N2	rgA/Victoria/3/75				1.15	0.59		S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75				1.05	0.35		S-033188-EB-346-N
A/H3N2	rgA/Victoria/3/75				0.73	0.41		S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75				1.795	0.66		S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75				1.65	0.69		S-033188-EB-301-N
B	rgB/Maryland/1/59- PA/R7K	PA	7	R7K	9.45	3.43	1.24	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/E23K	PA	23	E23K	8.73	0.56	0.81	S-033188-EB-303-N
B	rgB/Maryland/1/59- PA/S25G	PA	25	S25G	7.2	1.8	0.95	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/F36A	PA	36	F36A	8.46	0.88	0.79	S-033188-EB-326-N
B	rgB/Maryland/1/59-PA/F36V	PA	36	F36V	8.6	3.17	0.8	S-033188-EB-235-N
B	rgB/Maryland/1/59-PA/I38T	PA	38	I38T	61.79	9.17	5.76[2]	S-033188-EB-337-N
B	rgB/Maryland/1/59-PA/I38F	PA	38	I38F	25.59	0.54	2.39[2]	S-033188-EB-235-N
B	rgB/Maryland/1/59- PA/I38M	PA	38	I38M	41.71	14.71	8.04[2]	S-033188-EB-287-N
B	rgB/Maryland/1/59-PA/I38T	PA	38	I38T	86.80	58.48	8.72[2]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38N	PA	38	I38N	>240.23	N/C	>24.14[2]	S-033188-EB-346-N
B	rgB/Maryland/1/59-PA/I38S	PA	38	I38S	>169.02	N/C	>16.99[2]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38V	PA	38	I38V	23.29	14.32	2.34[2]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38L	PA	38	I38L	26.33	18.68	2.65[2]	S-033188-EB-301-N
B	rgB/Maryland/1/59- PA/T60V	PA	60	T60V	8.63	3.28	0.86	S-033188-EB-290-N
B	rgB/Maryland/1/59- PA/T62K	PA	62	T62K	3.67	1.25	0.48	S-033188-EB-303-N
B	rgB/Maryland/1/59- PA/D112N	PA	112	D112N	6.17	3.22	0.61	S-033188-EB-290-N
B	rgB/Maryland/1/59-PA/E120D	PA	120	E120D	21.1	11.06	1.97	S-033188-EB-326-N
B	rgB/Maryland/1/59- PA/D201E	PA	201	D201E	7.58	1.89	1	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/D201G	PA	201	D201G	10.32	1.08	1.36	S-033188-EB-337-N
B	rgB/Maryland/1/59- PA/E333K	PA	333	E333K	7.08	1.88	0.7	S-033188-EB-290-N
B	rgB/Maryland/1/59- PA/E333G	PA	333	E333G	9.58	2.7	1.26	S-033188-EB-287-N
B	rgB/Maryland/1/59- PA/N354K	PA	354	N354K	10.58	2.31	1.39	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/Y361H	PA	361	Y361H	10.42	3.7	1.03	S-033188-EB-346-N
B	rgB/Maryland/1/59- PA/S415G	PA	415	S415G	9.3	2.45	1.22	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/S415N	PA	415	S415N	11.91	0.72	1.57	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/G548R	PA	548	G548R	12.17	1.88	1.13	S-033188-EB-301-N
B	rgB/Maryland/1/59-PA/E680K	PA	680	E680K	8.786	1.05	0.7789	S-033188-EB-329-N
B	rgB/Maryland/1/59				10.73	5.52		S-033188-EB-303-N
B	rgB/Maryland/1/59				5.19	1.29		S-033188-EB-276-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position[1]	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold Change	Study Report
B	rgB/Maryland/1/59				10.07	5.45		S-033188-EB-326-N
B	rgB/Maryland/1/59				7.6	5.22		S-033188-EB-335-N
B	rgB/Maryland/1/59				11.29	3.82		S-033188-EB-337-N
B	rgB/Maryland/1/59				9.95	2.92		S-033188-EB-356-N

Source: Virology Reviewer analysis of data from the indicated study report.
[1] Amino acid numbering is virus type/subtype-specific.
[2] Fold change >2
Abbreviations: EC_{50}, half maximal effective concentration; PA, polymerase acidic; SD, standard deviation

19.1.2. Clinical Virology Methods

All clinical virologic assay methodologies have been previously described in Original NDA review and Supplement 1.[1,2] The identity of the vender and performance characteristics (where applicable) for each assay used in the respective clinical trials are summarized in (Table 87). Assays were performed in central labs (b) (4)

Notable limitations for certain virologic assays are as follows:

- Nucleotide sequence analyses were carried out by Sanger sequencing, which, compared to newer sequencing technologies, may lack sensitivity for detecting minor populations of potentially resistant viral variants often selected as mixtures with wild-type within patient samples
- The Virospot assay employed for baseline screening for reduced virus susceptibility to baloxavir may not have adequate sensitivity to detect small fold-changes (i.e., <5 fold)[1] in susceptibility by direct analysis of virus in patient samples, which may limit its utility in screening for the presence of reduced susceptibility at baseline for substitutions that only confer a small fold change but that may impact response to treatment.
- The neuraminidase gene Sanger-based sequencing assay may not be adequate to detect subpopulations of resistant virus, which are often selected as mixtures with wild-type during neuraminidase inhibitor treatment.
- Influenza virus type/subtype was based on HA gene-specific reverse transcription-polymerase chain reaction (RT-PCR) assays; NA targets were not included.

Table 87. Clinical Virology Assay Identity, Central Lab and Performance Characteristics

Trial	Assay	Central Lab	SOPs and Validation Reports	LLOQ	LOD
T0822	Confirmatory RT-PCR	[redacted] (b) (4)		flu A: 2.18 (log_{10} vp/mL) flu B: 2.93 (log_{10} vp/mL)	flu A: 2.05 (log_{10} vp/mL) flu B: 2.83 (log_{10} vp/mL)
	Subtyping RT-PCR			N/A	Ct <32
	Quantitative infectivity ($TCID_{50}$)			0.7 (log_{10} $TCID_{50}$/mL)	0.7 (log_{10} $TCID_{50}$/mL)
	PA/PB1/PB 2 genotyping			N/A	N/A
	Drug susceptibility phenotyping			N/A	N/A
	Influenza antibody titration			HI ≥10	HI ≥10
T0833	Confirmatory RT-PCR			flu A: 2.18 (log_{10} vp/mL) flu B: 2.93 (log_{10} vp/mL)	flu A: 2.05 (log_{10} vp/mL) flu B: 2.83 (log_{10} vp/mL)
	Subtyping RT-PCR			N/A	Ct <32
	Quantitative infectivity ($TCID_{50}$)			0.7 (log_{10} $TCID_{50}$/mL)	0.7 (log_{10} $TCID_{50}$/mL)
	PA/PB1/PB2 genotyping			N/A	N/A
	Drug susceptibility phenotyping			N/A	N/A
	Influenza antibody titration			HI ≥10	HI ≥10

Trial	Assay	Central Lab	SOPs and Validation Reports	LLOQ	LOD
CP40563	Confirmatory RT-PCR	(b) (4)		flu A: 2.18 (log_{10} vp/mL) flu B: 2.93 (log_{10} vp/mL)	flu A: 2.05 (log_{10} vp/mL) flu B: 2.83 (log_{10} vp/mL)
	Subtyping RT-PCR			N/A	Ct <32
	Quantitative infectivity ($TCID_{50}$)			0.75 (log_{10} $TCID_{50}$/mL)	0.75 (log_{10} $TCID_{50}$/mL)
	PA/PB1/PB2[/NA] genotyping			N/A	N/A
	Drug susceptibility phenotyping			N/A	N/A
	Influenza antibody titration	N/A	N/A	N/A	N/A

Trial	Assay	Central Lab	SOPs and Validation Reports	LLOQ	LOD
T0834	Confirmatory RT-PCR	[redacted]	(b) (4)	N/A	Ct <40
	Subtyping RT-PCR			N/A	Ct <40
	Quantitative infectivity ($TCID_{50}$)			N/A	N/A
	PA genotyping			N/A	N/A
	PA next-generation sequencing			To determine a frequency threshold for variant calling [based on Sanger sequencing], an influenza A virus stock will be run twice and a calculated risk % for calling false positive variants, insertions and deletions will be calculated at a variant frequency cut-off of 1%.	N/A
	PB1/PB2 genotyping			N/A	N/A
	HA/NA genotyping			N/A	N/A
	Influenza antibody titration			HI ≥10	HI ≥10

Source: Applicant
[1] Webpage is no longer active. Assay information is reviewed in the Original NDA Clinical Virology Review
Abbreviations: HI, hemagglutination inhibition; LLOQ, lower limit of quantitation; LOD, limit of detection; PA, polymerase acidic; RT-PCR, reverse transcription-polymerase chain reaction; N/A, not applicable

19.1.3. FDA Virology Endpoint Analysis of PEP Trial

In an independent FDA virology analysis, further evaluations were carried out with regard to infection events inferred to have occurred postbaseline (after prophylaxis initiation) within the reporting period of Days 1 through 10 (Table 88 and Table 89). Across event categories, there was a statistically significant impact of baloxavir marboxil prophylaxis on infection events in subjects overall and across influenza A virus subtypes; there was inadequate representation of influenza type B virus infections in this study to evaluate the impact of treatment on prevention of type B virus infections.

Table 88. Postexposure Prophylaxis Outcomes

	Baloxavir		Placebo		
Event category	**N**	**% of N**	**N**	**% of N**	**P-value[5]**
mITT total	374		375		
RT-PCR-positive at baseline[1]	26	7	36	9.6	0.2325
RT-PCR-positive postbaseline only[2]	37	9.9	87	23.2	<0.0001
Primary endpoint met	7	1.9	51	13.6	<0.0001
Primary endpoint met (post baseline RT-PCR positive only)[3]	5	1.4	39	11.5	<0.0001
Asymptomatic RT-PCR positive (postbaseline only)[4]	22	6.3	23	6.8	>0.9999
Total infection events	63	16.8	123	32.8	

Source: FDA Virology analysis
[1] Zero and two subjects type/subtype mismatch index in baloxavir and placebo arms, respectively.
[2] Four and seven subjects type/subtype mismatch index in baloxavir and placebo arms, respectively.
[3] One and two subjects type/subtype mismatch index in baloxavir and placebo arms, respectively. The percentages in this analysis are based on all subjects who were RT-PCR negative at baseline: 348 and 339 subjects in the baloxavir and placebo arms, respectively.
[4] Two and one subjects type/subtype mismatch index in baloxavir and placebo arms, respectively. The percentages in this analysis are based on all subjects who were RT-PCR negative at baseline: 348 and 339 subjects in the baloxavir and placebo arms, respectively.
[5] Fisher's exact test.
Abbreviations: mITT, modified intent-to-treat; RT-PCR, reverse transcription-polymerase chain reaction

Table 89. Postexposure Prophylaxis Outcomes for Subjects by Associated Index Patient Virus Type/Subtype

	Baloxavir		Placebo		
Virus Type/Subtype Event Category[1]	**N**	**% of N**	**N**	**% of N**	**P-value[3]**
A/H1N1					
mITT total	176		176		
RT-PCR-positive at baseline	7	4	10	5.7	0.6203
RT-PCR-positive postbaseline only	14	8	32	18.2	0.0067
Primary endpoint met	2	1.1	17	9.7	0.0005
Primary endpoint met (post baseline RT-PCR pos only)[2]	2	1.1	14	8	0.0034
Asymptomatic RT-PCR positive (postbaseline only)[2]	9	5.1	9	5.1	>0.9999
Total infection events	21	11.9	42	23.9	
A/H3N2					
mITT total	178		181		
RT-PCR-positive at baseline	18	10.1	23	12.7	0.5079
RT-PCR-positive postbaseline only	19	10.7	47	26	0.0002
Primary endpoint met	4	2.2	32	17.7	<0.0001
Primary endpoint met (post baseline RT-PCR pos only)[b]	2	1.1	23	12.7	<0.0001
Asymptomatic RT-PCR positive (postbaseline only)[b]	11	6.2	13	7.2	0.8333
Total infection events	37	20.8	70	38.7	

Virus Type/Subtype Event Category[1]	Baloxavir N	 % of N	Placebo N	 % of N	 P-value[3]
B					
mITT total	1		2		
Total infection events	0	0	0	0	

Source: FDA Virology analysis
[1] Events by index patient virus type/subtype. Index-subject type/subtype mismatches and subjects with mixed infections were excluded.
[2] The percentages in this analysis are based on all subjects who were RT-PCR negative at baseline.
[3] Fisher's exact test.
Abbreviations: mITT, modified intent-to-treat; RT-PCR, reverse transcription-polymerase chain reaction

Additional subset analyses (FDA virology analyses) were carried out based on subject age (≥12 versus <12 years of age), index patient age (≥12 versus <12 years of age), subject vaccination status, index vaccination status, subject hemagglutinin inhibition titer (≤10 versus >10), index patient baseline virus titer (<5 versus ≥5 $\log_{10}$ $TCID_{50}$/mL), and index patient treatment (baloxavir marboxil versus neuraminidase inhibitor). In all subsets, the rate of total infection events were reduced in the baloxavir marboxil prophylaxis arm compared to placebo; however, based on numerical trends, a diminished impact of baloxavir marboxil prophylaxis on the primary endpoint compared to placebo and relative to the overall symptomatic infection rate (1.9% versus 13.6% met the primary endpoint in baloxavir marboxil and placebo arms, respectively; Table 26) was notable for subjects <12 years of age (4.2% versus 15.5%), subjects associated with index patients treated with baloxavir marboxil (2.1% versus 10.5%), and subjects with hemagglutination inhibition (HI) titer ≤10 (3.5% versus 17%) (Table 90).

Table 90. Subset Analyses of Infection Events

Subset Category Subset Parameter	Baloxavir N	 % of N	Placebo N	 % of N
Subject Age				
<12				
mITT total	71		71	
RT-PCR-positive at baseline	4	5.6	11	15.50
RT-PCR-positive postbaseline only	13	18.3	14	19.70
Primary endpoint met	3	4.2	11	15.50
Primary endpoint met (post baseline RT-PCR pos only)	2	2.8	7	9.9
Asymptomatic RT-PCR positive (postbaseline only)	8	11.3	0	0
Total events	17	23.9	25	35.2
>12				
mITT total	303		304	
RT-PCR-positive at baseline	22	7.3	25	8.2
RT-PCR-positive postbaseline only	24	7.9	73	24
Primary endpoint met	4	1.3	40	13.2
Primary endpoint met (post baseline RT-PCR pos only)	3	1	32	10.5
Asymptomatic RT-PCR positive (postbaseline only)	14	4.6	23	7.6
Total events	46	15.2	98	32.2

Subset Category Subset Parameter	Baloxavir N	Baloxavir % of N	Placebo N	Placebo % of N
Age index (mismatch excluded)				
<12				
mITT total	281		273	
RT-PCR-positive at baseline	23	8.2	29	10.6
RT-PCR-positive postbaseline only	28	10	59	21.6
Primary endpoint met	6	2.1	43	15.8
Primary endpoint met (post baseline RT-PCR pos only)	4	1.4	32	11.7
Asymptomatic RT-PCR positive (postbaseline only)	18	6.4	13	4.8
Total events	51	18.1	88	32.2
≥12				
mITT total	87		95	
RT-PCR-positive at baseline	1	1.1	7	7.4
RT-PCR-positive postbaseline only	5	5.7	21	22.1
Primary endpoint met	0	0	6	6.3
Primary endpoint met (post baseline RT-PCR pos only)	0	0	5	5.3
Asymptomatic RT-PCR positive (postbaseline only)	2	2.3	9	9.5
Total events	6	6.9	28	29.5
Vaccination subject				
No				
mITT total	243		251	
RT-PCR-positive at baseline	19	7.8	22	8.8
RT-PCR-positive postbaseline only	18	7.4	59	23.5
Primary endpoint met	4	1.6	30	12
Primary endpoint met (post baseline RT-PCR pos only)	3	1.2	25	10
Asymptomatic RT-PCR positive (postbaseline only)	8	3.3	14	5.6
Total events	37	15.2	81	32.3
Yes				
mITT total	131		124	
RT-PCR-positive at baseline	7	5.3	14	11.3
RT-PCR-positive postbaseline only	19	14.5	29	23.4
Primary endpoint met	3	2.3	21	16.9
Primary endpoint met (post baseline RT-PCR pos only)	2	1.5	14	11.3
Asymptomatic RT-PCR positive (postbaseline only)	14	10.7	9	7.3
Total events	26	19.8	43	34.7
Vaccination index (mismatch excluded)				
No				
mITT total	259		254	
RT-PCR-positive at baseline	16	6.2	25	9.8
RT-PCR-positive postbaseline only	18	6.9	58	22.8
Primary endpoint met	4	1.5	28	11
Primary endpoint met (post baseline RT-PCR pos only)	3	1.2	22	8.7
Asymptomatic RT-PCR positive (postbaseline only)	8	3.1	17	6.7
Total events	34	13.1	83	32.7
Yes				
mITT total	109		114	
RT-PCR-positive at baseline	8	7.3	11	9.6
RT-PCR-positive postbaseline only	15	13.8	22	19.3
Primary endpoint met	2	1.8	21	18.4
Primary endpoint met (post baseline RT-PCR pos only)	1	0.9	15	13.2
Asymptomatic RT-PCR positive (postbaseline only)	12	11	5	4.4
Total events	23	21.1	33	28.9

Subset Category Subset Parameter	Baloxavir N	Baloxavir % of N	Placebo N	Placebo % of N
Baseline virus titer index (mismatch excluded)				
<5 log_{10} $TCID_{50}$/mL				
mITT total	150		160	
RT-PCR-positive at baseline	10	6.7	14	8.8
RT-PCR-positive postbaseline only	10	6.7	33	20.6
Primary endpoint met	0	0	16	10
Primary endpoint met (post baseline RT-PCR pos only)	0	0	13	8.1
Asymptomatic RT-PCR positive (postbaseline only)	5	3.3	8	5
Total events	20	13.3	47	29.4
≥5				
mITT total	218		208	
RT-PCR-positive at baseline	14	6.4	22	10.6
RT-PCR-positive postbaseline only	23	10.6	47	22.6
Primary endpoint met	6	2.8	33	15.9
Primary endpoint met (post baseline RT-PCR pos only)	4	1.8	24	11.5
Asymptomatic RT-PCR positive (postbaseline only)	15	6.9	14	6.7
Total events	37	17	69	33.2
Treatment in the Index (mismatch excluded)				
Baloxavir				
N (subjects)	191		191	
RT-PCR-positive at baseline	9	4.7	17	8.9
RT-PCR-positive postbaseline only	16	8.4	39	20.4
Primary endpoint met	4	2.1	20	10.5
Primary endpoint met (post baseline RT-PCR pos only)	3	1.6	14	7.3
Asymptomatic RT-PCR positive (postbaseline only)	10	5.2	13	6.8
Total events	25	13.1	56	29.3
Neuraminidase inhibitor				
N (subjects)	177		177	
RT-PCR-positive at baseline	15	8.50	19	10.70
RT-PCR-positive postbaseline only	17	9.6	41	23.2
Primary endpoint met	2	1.1	29	16.4
Primary endpoint met (post baseline RT-PCR pos only)	1	0.6	23	13
Asymptomatic RT-PCR positive (postbaseline only)	10	5.6	9	5.1
Total events	32	18.1	60	33.9
HI titer to Index type A subtype (mismatch excluded, index type B and mixed infections excluded)				
≤10				
N (subjects)	144		159	
RT-PCR-positive at baseline	13	9	19	11.9
RT-PCR-positive postbaseline only	14	9.7	49	30.8
Primary endpoint met	5	3.5	27	17
Primary endpoint met (post baseline RT-PCR pos only)	4	2.8	21	13.2
Asymptomatic RT-PCR positive (postbaseline only)	5	3.5	13	8.2
>10				
N (subjects)	207		197	
RT-PCR-positive at baseline	10	6.9	16	10.1
RT-PCR-positive postbaseline only	19	13.2	30	18.9
Primary endpoint met	1	0.7	22	13.8
Primary endpoint met (post baseline RT-PCR pos only)	0	0	16	10.1
Asymptomatic RT-PCR positive (postbaseline only)	15	10.4	9	5.7

Source: FDA Virology analysis
Abbreviations: HI, hemagglutination inhibition; mITT, modified intent-to-treat; RT-PCR, reverse transcription-polymerase chain reaction

19.1.3.1. Conclusion: FDA Virology Endpoint Analysis for PEP Trial

Overall, baloxavir marboxil had a clear impact on the reduction of the incidence of both symptomatic and asymptomatic cases of influenza virus infection when administered to household contacts of identified index cases. Baloxavir marboxil had a greater impact on prevention of symptomatic cases (defined by the primary endpoint) compared to asymptomatic cases. The prophylaxis effect was similar for prevention of A/H1N1 and A/H3N2 infections; however, there were too few index cases infected with type B virus to allow an evaluation of the impact of prophylaxis against this influenza virus type, which, because of the reduced activity of baloxavir against type B virus, raises the concern that prophylaxis may not be as effective against type B virus as was demonstrated for type A virus. Additional data regarding the prophylactic effect of baloxavir marboxil against type B virus should be collected.

19.1.4. Resistance in PEP Trial

The Applicant carried out PA gene sequencing for all RT-PCR-positive subjects and baseline samples from index patients with at least one household contact who was RT-PCR-positive.

PA Amino Acid Sequence Variability Associated With Baloxavir Marboxil Prophylaxis in Subjects

In an initial analysis to identify amino acid substitutions relative to consensus that were associated with baloxavir prophylaxis of subjects, polymorphic sites in the inferred PA protein sequence were evaluated for imbalance in variants between arms in subjects who were successfully sequenced (prior to initiation of baloxavir marboxil rescue therapy, if received). Of all variable sites (>1 variant; 26 and 24 sites among H1N1 an H3N2 virus PA sequences, respectively) only E23K and I38M/T, previously identified as resistance-associated substitutions (RAS), were statistically significantly over-represented in one arm; prior to rescue therapy, substitutions at these sites were only observed in subjects in the baloxavir marboxil arm (Table 91).

Table 91. Subject Virus Amino Acid Polymorphisms Associated With Baloxavir Marboxil or Placebo Treatment in Trial T0834

Subtype	PA Amino Acid Position	Subject Sequence Consensus	Subject Sequence	Baloxavir (n)	Placebo (n)	Fisher's Exact Test: WT vs. Variant Representation in Baloxavir vs. Placebo Arms[1]
A/H1N1	8	C	C	11	31	
A/H1N1	8	C	S	2	10	0.7079
A/H1N1	23	E	E	9	41	
A/H1N1	23	E	K	4	0	0.0023
A/H1N1	38	I	I	10	41	
A/H1N1	38	I	T	3	0	0.0115
A/H1N1	55	D	D	13	39	
A/H1N1	55	D	N	0	2	
A/H1N1	85	I	I	13	40	
A/H1N1	85	I	V	0	1	
A/H1N1	104	K	K	13	37	
A/H1N1	104	K	N	0	4	
A/H1N1	158	K	K	13	39	
A/H1N1	158	K	Q	0	2	

Subtype	PA Amino Acid Position	Subject Sequence Consensus	Subject Sequence	Baloxavir (n)	Placebo (n)	Fisher's Exact Test: WT vs. Variant Representation in Baloxavir vs. Placebo Arms[1]
A/H1N1	186	S	S	13	40	
A/H1N1	186	S	G	0	1	
A/H1N1	212	R	R	13	38	
A/H1N1	212	R	H	1	3	
A/H1N1	258	E	E	12	40	
A/H1N1	258	E	K	0	1	
A/H1N1	259	P	P	11	41	
A/H1N1	259	P	L	1	0	
A/H1N1	266	R	R	12	40	
A/H1N1	266	R	H	0	1	
A/H1N1	279	R	R	12	40	
A/H1N1	279	R	K	0	1	
A/H1N1	283	L	L	11	41	
A/H1N1	283	L	M	1	0	
A/H1N1	296	S	S	11	36	
A/H1N1	296	S	N	0	1	
A/H1N1	305	Y	Y	11	36	
A/H1N1	305	Y	H	0	1	
A/H1N1	322	I	I	10	36	
A/H1N1	322	I	T	1	1	
A/H1N1	325	P	P	11	35	
A/H1N1	325	P	Q	0	2	
A/H1N1	351	E	E	11	36	
A/H1N1	351	E	D	0	1	
A/H1N1	357	T	T	11	35	
A/H1N1	357	T	A	0	2	
A/H1N1	379	V	V	10	37	
A/H1N1	379	V	M	1	0	
A/H1N1	437	H	H	11	36	
A/H1N1	437	H	Y	0	1	
A/H1N1	595	M	M	11	40	
A/H1N1	595	M	I	1	0	
A/H1N1	603	K	K	12	39	
A/H1N1	603	K	R	0	1	
A/H1N1	677	E	E	11	40	
A/H1N1	677	E	D	1	0	
A/H1N1	696	N	N	12	38	
A/H1N1	696	N	S	0	2	
A/H3N2	38	I	I	20	60	
A/H3N2	38	I	M	1	0	
A/H3N2	38	I	T	5	0	0.0005
A/H3N2	65	L	L	26	59	
A/H3N2	65	L	P	0	1	
A/H3N2	158	R	R	21	47	
A/H3N2	158	R	K	5	12	
A/H3N2	185	R	R	25	55	
A/H3N2	185	R	I	0	1	
A/H3N2	185	R	K	1	3	>0.9999
A/H3N2	238	P	P	25	59	
A/H3N2	238	P	L	0	1	
A/H3N2	251	K	K	25	58	
A/H3N2	251	K	R	0	1	
A/H3N2	253	V	V	24	59	

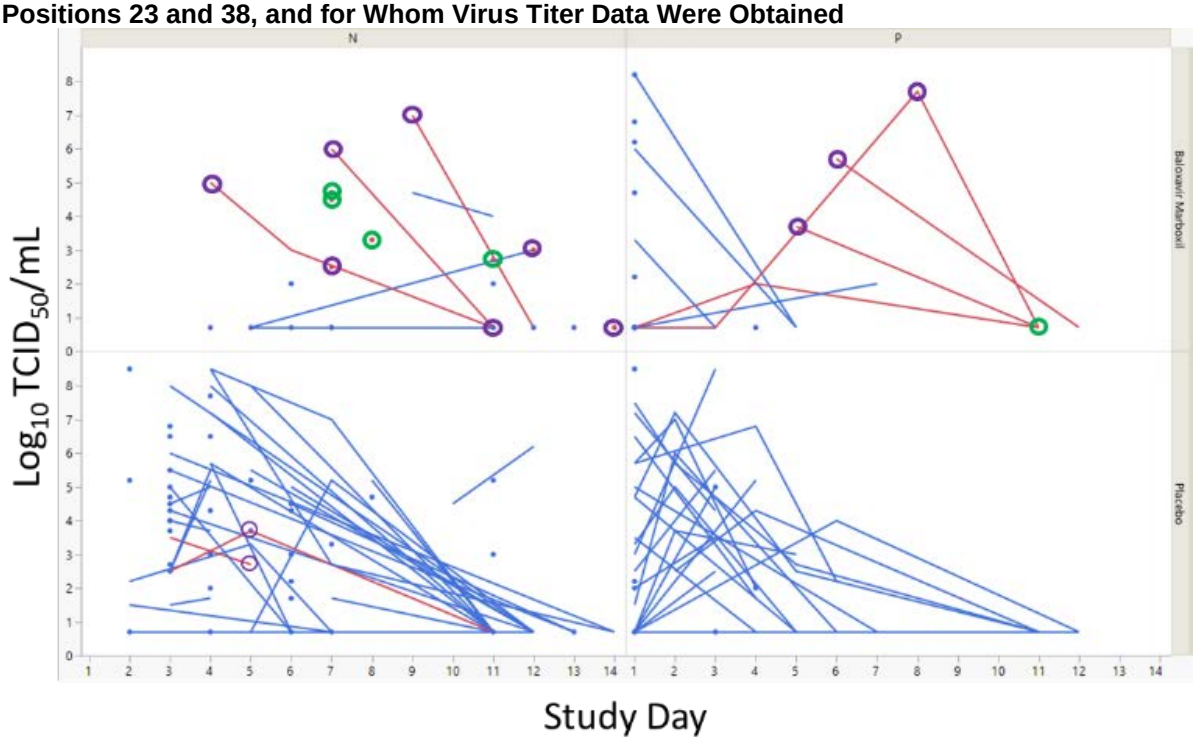
Subtype	PA Amino Acid Position	Subject Sequence Consensus	Subject Sequence	Baloxavir (n)	Placebo (n)	Fisher's Exact Test: WT vs. Variant Representation in Baloxavir vs. Placebo Arms[1]
A/H3N2	253	V	M	1	0	
A/H3N2	256	Q	Q	25	57	
A/H3N2	256	Q	K	0	2	
A/H3N2	274	P	P	25	56	
A/H3N2	274	P	L	0	2	
A/H3N2	322	I	I	19	52	
A/H3N2	322	I	V	1	1	
A/H3N2	341	V	V	20	52	
A/H3N2	341	V	I	0	1	
A/H3N2	354	I	I	21	53	
A/H3N2	354	I	T	0	1	
A/H3N2	361	K	K	20	53	
A/H3N2	361	K	R	1	1	
A/H3N2	379	V	V	20	54	
A/H3N2	379	V	I	1	0	
A/H3N2	397	E	E	20	52	
A/H3N2	397	E	G	0	2	
A/H3N2	400	L	L	19	53	
A/H3N2	400	L	I	0	1	
A/H3N2	400	L	S	1	0	
A/H3N2	421	V	V	19	53	
A/H3N2	421	V	I	1	1	
A/H3N2	441	M	M	20	52	
A/H3N2	441	M	T	0	2	
A/H3N2	461	K	K	20	53	
A/H3N2	461	K	R	0	1	
A/H3N2	551	R	R	15	53	
A/H3N2	551	R	K	1	0	
A/H3N2	554	I	I	16	50	
A/H3N2	554	I	L	0	3	>0.9999
A/H3N2	614	N	N	15	49	
A/H3N2	614	N	D	2	4	
A/H3N2	614	N	T	0	1	
A/H3N2	617	E	E	17	53	
A/H3N2	617	E	D	0	1	
A/H3N2	626	K	K	17	53	
A/H3N2	626	K	R	0	1	

Source: FDA Virology analysis derived from T0834_SV. Based on first sequence time point.
[1] All positions represented by three or more variants were evaluated for statistically significant differences between treatment arms.
Abbreviations: PA, polymerase acidic; WT, wildtype

RAS Detection and Virus Shedding in Subjects

Subjects with RAS variants detected postbaseline generally cleared virus by Day 12. For subjects who were positive at baseline, RAS variants were detected at later time points that likely coincided with virus rebound in most cases and was often associated with prolonged shedding in these subjects; however, it is not clear if subjects with prolonged shedding were identified earlier in the infection cycle and thus in whom there was more time to select for resistant virus (Figure 11).

Figure 11. Virus Shedding in 139 Subjects for Whom PA Sequencing Included PA Amino Acid Positions 23 and 38, and for Whom Virus Titer Data Were Obtained



Source: Virus titer data are from T0834SH_SN0007, genotypic data are from T0834SV_SN0000
Subjects are grouped according to whether they were RT-PCR positive postbaseline (left panels) or at baseline only (right panels) and whether they were in the baloxavir marboxil (top panels) or placebo (bottom panel) arms. Subjects who were identified as having a RAS variant (E23K or I38M/T) are indicated in red. Circles indicate the first time point of detection of E23K (green) or I38M/T (purple).
Abbreviations: PA, polymerase acidic; RAS, resistance-associated substitution; RT-PCR, reverse transcription-polymerase chain reaction.

RAS Detection by Age in Trial T0834

There was no statistically significant difference in the frequency of RAS detection in subjects <12 years of age versus ≥12 years of age who received prophylaxis with baloxavir marboxil, RT-PCR positive post-baseline, and evaluated for resistance (P=0.2852, Fisher's exact test) (Table 92). The frequency of RAS detection was numerically lower in subjects <12 years of age, although the numbers were too small to draw a strong conclusion. The index patient age did not appear to be associated with the frequency of resistance in household contacts who became infected, although numbers of subjects were small and the frequency of infections overall was higher among households with index patients <12 years of age (Table 92).

Table 92. RAS Detection Frequency by Subject and Index Patient Age

	Overall			Subjects <12 Years of Age			Subjects ≥12 Years of Age		
Parameter	Total	Subjects With RAS	% With RAS	Total	Subjects With RAS	% With RAS	Total	Subjects With RAS	% With RAS
RT-PCR+ post-baseline	31	15	48.4	14	5	35.7	17	10	58.8
Primary endpoint met	7	7	100.0	3	3	100.0	4	4	100.0
RT-PCR + post-baseline primary endpoint not met	24	8	33.3	11	2	18.2	13	6	46.2
RT-PCR + positive and associated w/ index patient <12	27	14	51.9	13	5	38.5	14	9	64.3
RT-PCR + and associated w/index patient ≥12	4	1	25.0	1	0	0.0	3	1	33.3

Source: FDA Virology analysis
Abbreviations: RAS, resistance-associated substitution; RT-PCR, reverse transcription-polymerase chain reaction

19.1.2.1 Conclusion: Resistance in PEP Trial

Most cases (86%) of baloxavir marboxil prophylactic primary endpoint failures were associated with the detection of RAS variants, indicating that resistance reduced the effectiveness of prophylaxis; however, subjects receiving baloxavir marboxil prophylaxis were clearly less likely to become infected, thus treatment demonstrated efficacy overall in spite of the significant contribution of resistance to prophylaxis failure. There were seven cases of resistance in subjects associated with index patients treated with baloxavir marboxil, and five cases among these households represent likely transmission of a baloxavir-resistant variant; however, transmission of resistance could not be conclusively demonstrated nor ruled out given the design of the study, and thus the risk of transmitted resistance could not be adequately assessed. Additional data from an ongoing transmission prevention study (NIH 2019) will provide more conclusive data. Type B virus infections were not adequately represented in this study, and thus the efficacy of baloxavir marboxil prophylaxis against type B virus remains unknown.

Of note, non-I38X RAS (E23K) constituted approximately 30% of cases of resistance and were detected more frequently in A/H1N1 versus A/H3N2 viruses; I38X substitutions were detected more frequently in A/H3N2 viruses, although the association was not statistically significant. In treatment studies, non-I38X RAS have typically constituted <10% of RAS, although these studies were dominated by A/H3N2 viruses (Ince et al. 2020).[1,2]

19.1.5. FDA Virology Analysis of Endpoints in Pediatric Trials

Baseline demographics for Trials CP40563, T0822, and T0833 are displayed in Table 93. Median ages in the intent-to-treat-infected (ITTI) population in Trials CP40563, T0822, and T0833 were 7, 8, and 2; most subjects were unvaccinated in Trials CP40563 and T0833; and the most common virus type/subtype was A/H3N2 in Trials CP40563 and T0822 and A/H1N1 in Trial T0833. Type B viruses represented 5.8%, 7.7% and 36.3% of the ITTI populations in Trials CP40563, T0822, and T0833, respectively.

Table 93. Key Baseline Characteristics of ITTI Populations of Pediatric Trials

	CP40563			T0822	T0833
Parameter Characteristic	**Baloxavir N=81**	**Oseltamivir N=43**	**All N=124**	**Baloxavir N=104**	**Baloxavir N=33**
Age (years)					
Median	7	7	7	8	2
Interquartile range	4.5-9	5-9	5-9	6-10	1-4
Weight (kg)					
Median	26	27	26.4	24.8	11.8
Range	19.0-34.5	19.7-39.5	19.2-35.4	19.1-31.1	8.6-15.1
Vaccination in last 6 months, n (%)					
Y	25 (31)	11 (26)	36 (30)	76 (73)	25 (76)
N	54	32	86	28	8

Parameter Characteristic	CP40563 Baloxavir N=81	CP40563 Oseltamivir N=43	CP40563 All N=124	T0822 Baloxavir N=104	T0833 Baloxavir N=33
Virus subtype/subtype, n (%)[1]					
Type B	5 (6.3)	2 (4.8)	7 (5.8)	8 (7.7)	12 (36.3)
Type A	69 (87.3)	40 (95.2)	109 (90.1)	92 (88.5)	20 (60.6)
A/H1N1	20 (25.3)	11 (26.1)	31 (25.6)	2 (1.92)	11 (33.3)
A/H3N2	49 (62.0)	29 (69.0)	78 (64.4)	87 (83.6)	9 (27.2)
A/H1N1 / A/H3N2	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
A/H1N1 / B	1 (1.26)	0 (0)	1 (0.82)	0 (0)	0 (0)
A/H3N2 / B	0 (0)	0 (0)	0 (0)	2 (1.9)	0 (0)
A/B	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
A/Unknown	0 (0)	0 (0)	0 (0)	3 (2.9)	0 (0)
Unknown	4 (5.1)	0 (0)	4 (3.3)	0 (0)	1 (3)

Source: FDA Virology analysis
[1] CP40563: Type/subtype numbers differ from the Applicant's numbers by a total of five subjects because FDA analysis of virus type/subtype included subjects for whom no STYPPCR result was reported but for whom a type/subtype was inferred based on PA sequence data (of eight subjects in the ITTI who had missing or "unknown" type/subtype information). This included an additional two A/H1N1 (subject IDs (b) (6) and one A/H3N2 (subject ID (b) (6) in the baloxavir marboxil arm and an additional one A/H1N1 (subject ID (b) (6) and one A/H3N2 (subject ID (b) (6) in the oseltamivir arm. Note that one UNKNOWN subject had successful sequencing for A/H3N2 (baloxavir marboxil arm; subject ID (b) (6)), and two remaining subjects in the baloxavir marboxil arm with neither baseline type/subtype data nor sequencing data were typed as A/H1N1 (subject ID (b) (6) and A/H3N2 (subject ID (b) (6)). One subject categorized as type B had successful sequencing for type B at baseline and for A/H1N1 at Day 2 (baloxavir marboxil arm; subject ID (b) (6) . The reported STYPPCR/MBORRES parameter result was used for subsequent analyses for subjects (b) (6)
Abbreviations: ITTI, intent-to-treat-infected

Clinical Endpoint Response

In pivotal Trial CP40563, there was no clear differences in the time to alleviation of influenza signs and symptoms (TTAS) between the baloxavir marboxil and oseltamivir arms (Table 94; FDA virology analysis included subjects who had not achieved alleviation within the defined observation period; see summary of Applicant analysis, above). Times to alleviation were shorter in the T0822 and T0833 trials compared with the TTAS in CP40563, likely do to the overall shorter TTAS observed for subjects enrolled at Japanese sites (Ince et al. 2020). Importantly, there was no clear difference in the TTAS between type A and B virus infections across studies, although the numbers of type B virus-infected subjects were limited.

Table 94. Times to Alleviation of Symptoms by Virus Type/Subtype Across Trials CP40563, T0822, and T0833

Virus Type/Subtype Time to Alleviation of Symptoms[a]	CP40563 Baloxavir	CP40563 Oseltamivir	T0822 Baloxavir	T0833 Baloxavir
All				
N	80	43	103	33
Median (hours)	138.1	126.1	44.55	45.27
95% CI lower limit	116.2	96.8	314.3	28.45
95% CI upper limit	163.2	163.5	317.3	68.38
P-value baloxavir vs. oseltamivir	0.8213			
A/H1N1				
N	20	11	2	11
Median (hours)	116.4	165.7	164.2	58.93
95% CI lower limit	86.9	30.5	151.4	17.5
95% CI upper limit	188.5	314.7	177.1	170.2
P-value baloxavir vs. oseltamivir	0.4511			

Virus Type/Subtype Time to Alleviation of Symptoms[a]	CP40563 Baloxavir	 Oseltamivir	T0822 Baloxavir	T0833 Baloxavir
A/H3N2				
N	48	29	86	9
Median (hours)	131.1	115	45.16	26.75
95% CI lower limit	99.4	88.3	314	21.67
95% CI upper limit	163.4	158.1	318.1	199.3
P-value baloxavir vs. oseltamivir	0.5254			
B				
N	5	2	8	12
Median (hours)	147	162.2	44.68	41.67
95% CI lower limit	119.3	150	81.7	26.42
95% CI upper limit	238.3	174.3	321.5	86.87
P-value baloxavir vs. oseltamivir	0.5714			
P vs. type A	0.3321	0.5226	0.3853	0.5778

Source: FDA Virology analysis
[a] Time to alleviation of symptoms is a composite of similar endpoints from each study; the definition of time to alleviation of symptoms or illness differed slightly between studies. Analyses includes all subjects in the ITTI set including those who did not achieve alleviation within the defined observation period; the reported time to event value was used for each subject. Type/subtype subset analysis excludes co-infected subjects and subjects with missing type/subtype information. All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected

Virologic Endpoint Response

Changes from baseline in virus shedding were relatively consistent across trials (Table 95). Baloxavir marboxil treatment resulted in a substantial and statistically significant reduction in virus shedding in Trial CP40563 compared to oseltamivir at Day 2 (24 hours post-treatment initiation) (Table 95), an effect that was also reflected in viral RNA shedding (median Day 2 viral RNA changes from baseline in baloxavir marboxil and oseltamivir arms were -1.80 $\log_{10}$ copies/mL versus -1.08 $\log_{10}$ copies/mL; P =0.0008, Mann-Whitney [Appendix M]). There was no consistent difference in the change from baseline in virus shedding at Day 2 between type A and B virus infections among subjects treated with baloxavir; however, the treatment effect against type B virus was statistically significantly reduced in Trial T0822, and there was a trend toward reduced activity in Trial T0833, but not CP40563 based on virus shedding. Adult/adolescent studies have demonstrated a more consistent difference in the antiviral activity of baloxavir between type A and B virus infections based on change from baseline in virus shedding (Ince et al. 2020).[1,2]

Oseltamivir also exhibited reduced antiviral activity against type B virus infections as assessed by Day 2 virus shedding in Trial CP40563 (although only two subjects were type B virus infected in the oseltamivir arm), consistent with previous observations in adults/adolescent studies.[1,2] Day 2 change from baseline in viral RNA shedding mirrored the changes observed in virus shedding across studies and virus type (Table 96).

Table 95. Change From Baseline at Day 2 (24 Hours Post-Treatment Initiation) in Virus Shedding in Pediatric Trials

Virus Type/Subtype	CP40563		T0822	T0833
Day 2 Virus Shedding Change From Baseline (Subjects positive at baseline)	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
All				
N	64	37	101	32
Median (log_{10} $TCID_{50}$/mL)	-4	-1.75	-4	-4.75
95% CI lower limit	-4.501	-2.5	-4.8	-5.3
95% CI upper limit	-3.251	-1.25	-3.8	-3.8
P-value baloxavir vs. oseltamivir	<0.0001			
A/H1N1				
N	17	9	2	10
Median (log_{10} $TCID_{50}$/mL)	-4.501	-1.5	-5.65	-4.6
95% CI lower limit	-5.001	-3.5	-6.5	-6.8
95% CI upper limit	-2.751	-0.001	-4.8	-2.8
P-value baloxavir vs. oseltamivir	0.0055			
A/H3N2				
N	44	26	87	9
Median (log_{10} $TCID_{50}$/mL)	-3.751	-2.25	-4	-4.8
95% CI lower limit	-4.251	-2.75	-5	-6.3
95% CI upper limit	-3.251	-1.251	-3.7	-4
P-value baloxavir vs. oseltamivir	<0.0001			
B				
N	2	2	8	12
Median (log_{10} $TCID_{50}$/mL)	-4.126	0.5	-2.35	-4.1
95% CI lower limit	-4.251	-0.5	-5.5	-5
95% CI upper limit	-4.001	1.5	0	-3
P-value baloxavir vs. oseltamivir	0.3333			
P-value vs. type A	0.745	0.0465	0.0316	0.2228

Source: FDA Virology analysis
Analyses includes all subjects in the ITTI set who were virus-positive at baseline.
All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-exposed

Table 96. Change From Baseline at Day 2 (24 Hours Post-Treatment Initiation) in Viral RNA Shedding in Pediatric Trials

Virus Type/Subtype	CP40563		T0822	T0833
Day 2 Viral RNA Shedding Change From Baseline (Subjects Positive at Baseline)	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
All				
N	70	39	104	33
Median (log_{10} copies/mL)	-1.802	-1.084	-1.98	-1.6
95% CI lower limit	-2.209	-1.499	-2.23	-2.1
95% CI upper limit	-1.526	-0.7689	-1.6	-1.15
P-value baloxavir vs. oseltamivir	0.0008			
A/H1N1				
N	17	9	2	11
Median (log_{10} copies /mL)	-1.903	-0.8534	-2.865	-1.83
95% CI lower limit	-2.447	-1.472	-3.23	-2.74
95% CI upper limit	-1.625	0.729	-2.5	-0.71
P-value baloxavir vs. oseltamivir	0.0029			
A/H3N2				
N	45	28	87	9
Median (log_{10} copies /mL)	-2.018	-1.121	-2.03	-2.17
95% CI lower limit	-2.312	-1.582	-2.3	-3.06
95% CI upper limit	-1.445	-0.9074	-1.73	-1.15
P-value baloxavir vs. oseltamivir	0.0113			
B				
N	4	2	8	12
Median (log_{10} copies /mL)	-0.8164	0.008528	-0.64	-1.2
95% CI lower limit	-2.28	-0.3219	-2.12	-2
95% CI upper limit	3.388	0.3389	0.71	-0.29
P-value baloxavir vs. oseltamivir	0.5333			
P-value vs. type A	0.0562	0.081	0.006	0.0172

Source: FDA Virology analysis
Analyses includes all subjects in the ITTI set who were viral RNA-positive at baseline.
All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected

The median time to sustained virus negativity was 24 hours in Trials CP40563 and T0822, and 192 hours in Trial T0833 (Table 97), which reflects the increased incidence of rebound observed in Trial T0833 (Table 98). In Trials CP40563 and T0822, there was a clear and consistent trend, although not statistically significant, of reduced activity of baloxavir marboxil treatment against type B virus compared to type A virus by this measure, which was also consistent with the increased incidence of rebound in type B virus compared to type A virus infections in these studies (Table 98). The rates of rebound in baloxavir marboxil arm of all three pediatric studies (26 to 69%) exceeded the overall rate of rebound in adult/adolescent studies (18% of subjects treated with baloxavir marboxil in Trials T0821, T0831, and T0832 (Table 101).

Table 97. Time to Sustained Virus Negativity in Pediatric Trials

Virus Type/Subtype	CP40563		T0822	T0833
Time to Sustained Virus Negativity[1]	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
All				
N	71	40	101	32
Median (hours)	24	96	24	192
95% CI lower limit	24	72	24	144
95% CI upper limit	72	120	48	216
P-value baloxavir vs. oseltamivir	0.0098			
A/H1N1				
N	18	11	2	10
Median (hours)	24	72	96	48
95% CI lower limit	24	24	24	24
95% CI upper limit	120	216	168	216
P-value baloxavir vs. oseltamivir	0.1021			
A/H3N2				
N	48	27	87	9
Median (hours)	24	96	24	192
95% CI lower limit	24	72	24	168
95% CI upper limit	72	120	48	240
P-value baloxavir vs. oseltamivir	0.0413			
B				
N	4	2	8	12
Median (hours)	144	192	144	192
95% CI lower limit	24	120	24	168
95% CI upper limit	240	264	168	192
P-value baloxavir vs. oseltamivir	0.8			
P vs. type A	0.1784	0.0833	0.1212	0.6331

Source: FDA Virology analysis
[1] TTSVN was defined by the last time point after which no positive time point was reported. For subjects who did not achieve negativity and who were not assessed at Day 11 or later, TTSVN was imputed as 264 hours (Day 12). Analysis includes all subjects in the ITTI set. All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected; TTSVN, time to sustained virus negativity

Table 98. Proportions of Subjects With Virus Rebound in Pediatric Trials

Virus Rebound	CP40563		T0822	T0833
n/N (%)[1]	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
All	19/67 (28)	7/38 (18)	26/101 (26)	22/32 (69)
A/H1N1	6/17 (35)	3/10 (30)	1/2 (50)	8/10 (80)
A/H3N2	12/46 (26)	3/26 (12)	21/87 (24)	8/9 (89)
Type B	1/3 (33)	1/2 (50)	3/8 (38)	11/12 (92)

Source: FDA Virology analysis
[1] Rebound was defined as any rise in virus titer relative to the previous time point. Analyses includes all subjects in the ITTI set.
Abbreviations: ITTI, intent-to-treat-infected

In a pooled analysis of pediatric subjects who experienced treatment-emergent resistance and virus rebound, the median virus shedding titer at the time of peak rebound was 2.75 $\log_{10}$ $TCID_{50}$/mL (n=31; interquartile range ±1.3 $\log_{10}$), compared to the median baseline titer of 5.7 $\log_{10}$ $TCID_{50}$/mL (n=39; ±1.75 $\log_{10}$).

19.1.5.1. Conclusion: FDA Virology Analysis of Endpoints in Pediatric Studies

Overall, baloxavir marboxil treatment had a significant impact on reduction in virus shedding across studies, similar to effects observe in adults; however, the impact on virus shedding was more variable for type B virus infections than for type A virus infections. The rate of virus rebound in pediatric studies exceeded that observed in adult studies, consistent with increased frequency of treatment-emergent resistance and a less developed immune system in young children (see Section 19.1.6). There was no clear and consistent difference in the impact of treatment on clinical outcomes between type A and type B virus infections in pediatric studies.

19.1.6. Resistance in Pediatric Studies

Baseline Susceptibility

The Applicant evaluated the susceptibility of clinical isolates obtained at baseline in Trials CP40563, T0822, and T0833 using the Virospot phenotypic assay. This assay may not be sensitive to small changes in half maximal effective concentration (EC_{50}) values,[1] which may be clinically relevant, and thus the adequacy of this assay for establishing the susceptibility of virus isolates in clinical trials may be limited for the purpose of evaluating the association between baseline EC_{50} value and endpoints.

Overall, median baseline normalized EC_{50} values (ratio to reference) varied by 5.6-fold, 2-fold, 4.6-fold between trials, for A/H1N1, A/H3N2, and type B virus subsets, respectively (Table 99). In addition, the baseline EC_{50} values measured by the Virospot assay in pediatric studies did not recapitulate the 5- to 10-fold differences observed in previous studies. Normalized baseline EC_{50} values did not appear to consistently correlate with baseline virus titer, change from baseline in virus titer at Day 2, time to sustained virus negativity, or time to alleviation of symptoms (Figure 12).

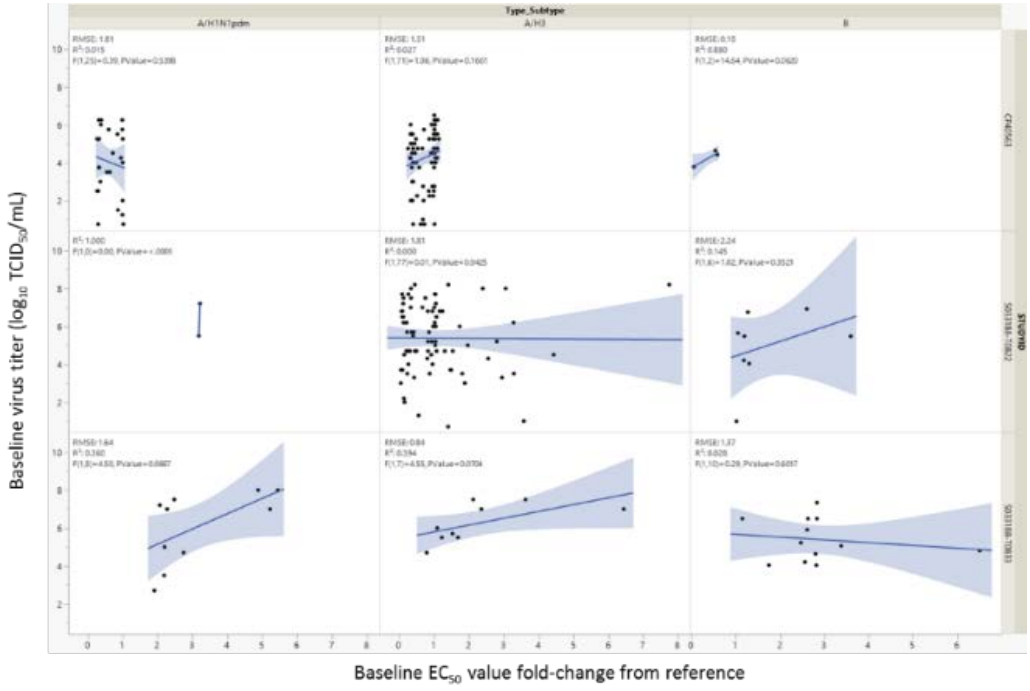
Table 99. Summary Statistics for Baseline EC_{50} Value Fold-Change Relative to Reference Across Trials and Virus Type/Subtype Obtained Using the Virospot Assay

				EC_{50} Value Normalized to Reference							
Trial	Type/ Subtype	Number of Values	EC_{50} value (Unadjusted)	25% Percentile	Median[1]	75% Percentile	Maximum	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit
CP40563	A/H1N1	28	3.24	0.3205	0.572	0.9775	1.016	0.7478	96.43%	0.328	0.8624
T0822	A/H1N1	2	17.96	3.178	3.195	3.212	3.212	0.03381	50.00%	3.178	3.212
T0833	A/H1N1	10	1.95	2.152	2.372	4.963	5.439	3.537	97.85%	2.061	5.22
CP40563	A/H3N2	75	4.87	0.3922	0.8604	1.005	1.136	0.8852	96.30%	0.5689	0.9894
T0822	A/H3N2	79	4.48	0.2598	0.8541	1.307	7.747	7.705	95.78%	0.4459	1.017
T0833	A/H3N2	9	1.93	1.153	1.683	2.988	6.439	5.653	96.09%	1.085	3.622
CP40563	B	5	5.64	0.2973	0.5829	0.5835	0.584	0.5299	93.75%	0.05411	0.584
T0822	B	8	18.67	1.083	1.234	2.278	3.595	2.579	99.22%	1.016	3.595
T0833	B	12	5.52	2.491	2.717	2.833	6.512	5.365	96.14%	2.468	2.833

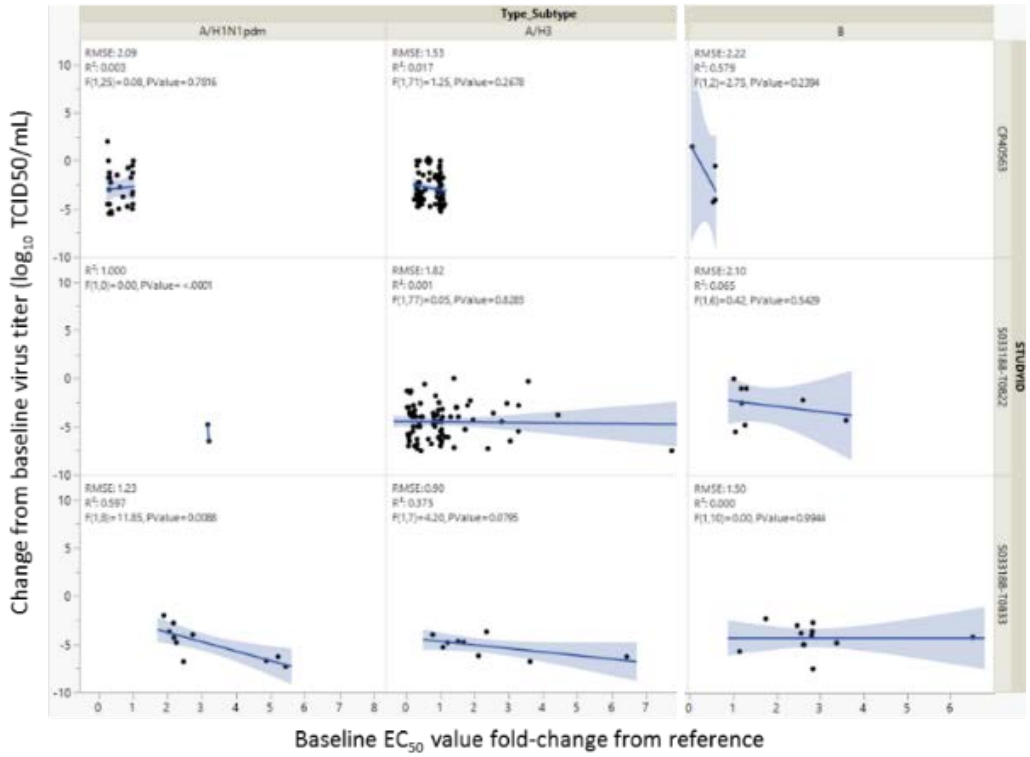
Source: FDA Virology analysis
[1] Color gradient indicates the high (red) and low (blue) range of normalized median EC_{50} values.
Abbreviations: EC_{50}, half maximal effective concentration

Figure 12. Association of Baseline EC_{50} Value With (A) Baseline Virus Shedding Titer, (B) Change From Baseline in Virus Shedding at Day 2, (C) Time to Sustained Virus Negativity, and (D) Time to Alleviation of Symptoms or Illness

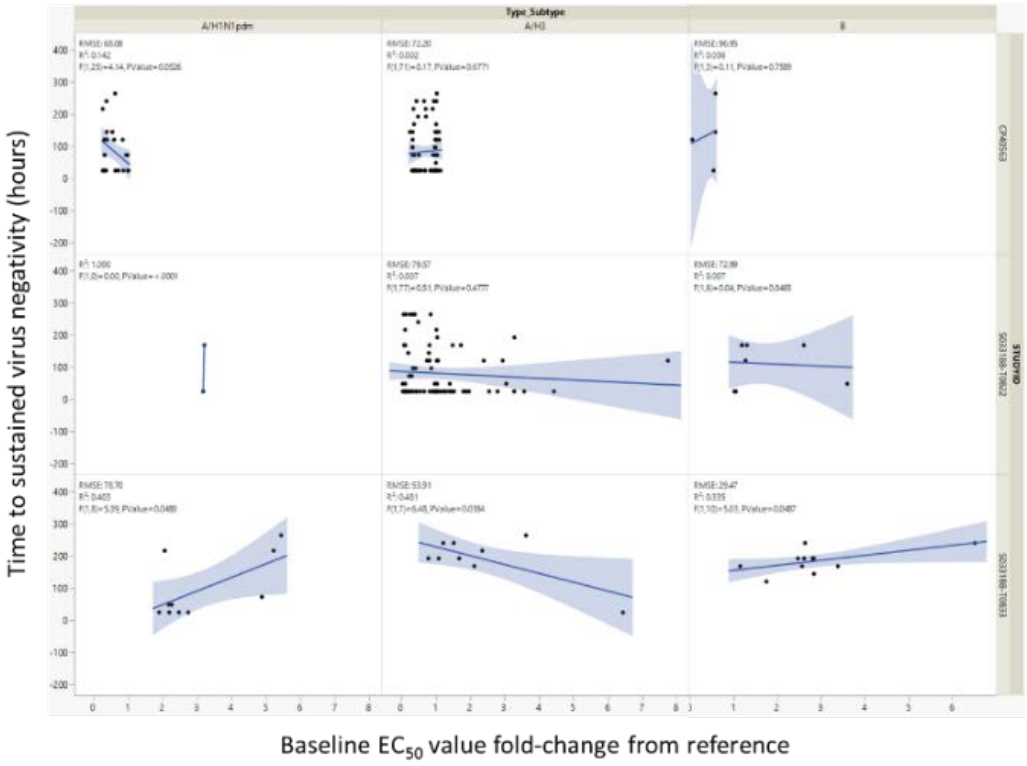
A.



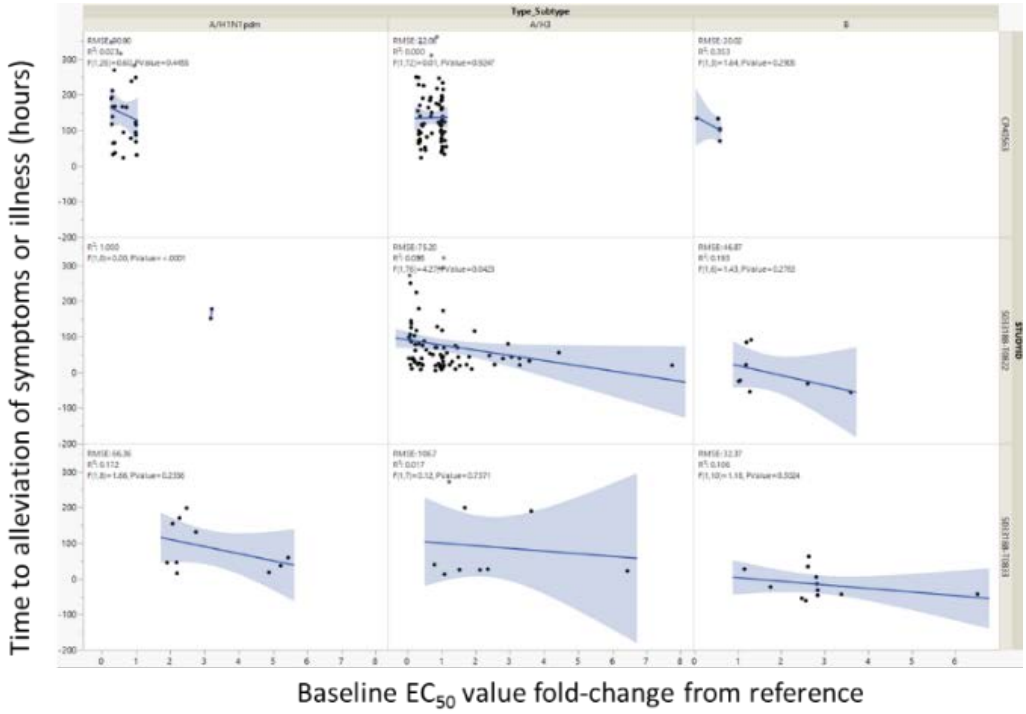
B.



C.



D.



Source: FDA Virology analysis
A/H1N1, A/H3N2, and type B virus subsets are represented in the left, middle, and right columns, respectively. Trials CP40563, T0822, and T0833 are represented in the top, middle and bottom rows, respectively.
Abbreviations: EC_{50}, half maximal effective concentration

Baseline Polymorphisms and Association With Selected Parameters

Nucleotide sequencing was carried out on PA, PB1 and PB2 at baseline and postbaseline time points in each pediatric study; however, PB1 and PB2 were only sequenced for subjects meeting the Applicant's criteria for virus rebound (T0822, rise in virus titer; T0833, rise in virus titer ≥0.6 log_{10}; CP40563, rise in titer ≥2 x the standard deviation for type A [0.68 log_{10}] or type B [0.86 log_{10}] virus) not attributable to an I38X substitution. In Trial CP40563, virus from subjects in the oseltamivir arm were subjected to NA sequence analysis.

Baseline Polymorphisms in PA and Baseline EC_{50} Value

The association of baseline EC_{50} values and PA genotype was evaluated for each polymorphic site to identify specific polymorphism associated with elevated EC_{50} values (Table 100). Note that the analysis does not take into account linked substitutions (i.e., haplotypes), but is intended to identify all sites linked to an elevated EC_{50} value. Overall, three as-yet unevaluated substitutions were identified as associated with a ≥3-fold increase in normalized EC_{50} value relative to the median EC_{50} value of the consensus variant for each site: A/H1N1 PA R269I, A/H1N1 PA V330I, and A/H3N2 PA I554V. These substitutions will be recommended for further evaluation.

Table 100. EC_{50} Values Associated With Baseline Polymorphic PA Variants

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
A/H1N1	13	V	3	0.3245	0.3598	0.3739	0.0493	75.00%	0.3245	0.3739	
A/H1N1	13	I	34	0.5079	0.9885	2.213	5.171	97.57%	0.6261	2.061	
A/H1N1	24	H	1	0.8466	0.8466	0.8466	0	5.000%			1.388
A/H1N1	24	Y	36	0.3765	0.9674	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	29	R	1	1	1	1	0	5.000%			
A/H1N1	29	K	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	61	V	1	2.061	2.061	2.061	0	5.000%			
A/H1N1	61	I	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1	
A/H1N1	100	M	1	0.8466	0.8466	0.8466	0	5.000%			
A/H1N1	100	I	36	0.3765	0.9674	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	196	G	1	0.3739	0.3739	0.3739	0	5.000%			
A/H1N1	196	R	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	225	G	2	0.9982	0.9991	1	0.0017	50.00%	0.9982	1	
A/H1N1	225	S	35	0.3739	0.8624	2.195	5.171	95.90%	0.5479	1.902	
A/H1N1	252	G	1	2.061	2.061	2.061	0	5.000%			
A/H1N1	252	E	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1	
A/H1N1	254	K	1	0.9982	0.9982	0.9982	0	5.000%			
A/H1N1	254	N	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	**269**	**I**	**2**	**2.195**	**3.537**	**4.878**	**2.683**	**50.00%**	**2.195**	**4.878**	
A/H1N1	269	R	35	0.3739	0.8624	2.061	5.171	95.90%	0.5479	0.9982	
A/H1N1	275	H	1	0.3104	0.3104	0.3104	0	5.000%			
A/H1N1	275	L	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	284	M	1	0.6314	0.6314	0.6314	0	5.000%			
A/H1N1	284	L	36	0.3765	0.9674	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	285	T	1	0.9965	0.9965	0.9965	0	5.000%			
A/H1N1	285	M	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	291	G	1	2.183	2.183	2.183	0	5.000%			
A/H1N1	291	S	36	0.3765	0.9048	2.162	5.171	97.12%	0.5479	1	
A/H1N1	322	T	1	0.3192	0.3192	0.3192	0	5.000%			
A/H1N1	322	I	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	**330**	**I**	**2**	**2.195**	**3.537**	**4.878**	**2.683**	**50.00%**	**2.195**	**4.878**	
A/H1N1	330	V	35	0.3739	0.8624	2.061	5.171	95.90%	0.5479	0.9982	
A/H1N1	335	F	1	0.388	0.388	0.388	0	5.000%			
A/H1N1	335	L	36	0.3765	0.9674	2.192	5.171	97.12%	0.5961	1.902	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
A/H1N1	343	T	4	1.994	2.506	4.765	3.537	87.50%	1.902	5.439	
A/H1N1	343	A	33	0.3668	0.8466	1.53	4.951	96.49%	0.388	0.9965	
A/H1N1	354	V	1	0.3122	0.3122	0.3122	0	5.000%			
A/H1N1	354	I	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	363	A	1	0.3122	0.3122	0.3122	0	5.000%			
A/H1N1	363	T	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	394	N	2	0.9894	0.9929	0.9965	0.0070	50.00%	0.9894	0.9965	
A/H1N1	394	D	35	0.3739	0.8624	2.195	5.171	95.90%	0.5479	1.902	
A/H1N1	400	S	2	0.9471	0.9683	0.9894	0.0423	50.00%	0.9471	0.9894	
A/H1N1	400	L	3	0.3245	0.3598	0.3739	0.0493	75.00%	0.3245	0.3739	
A/H1N1	400	P	32	0.428	0.9894	2.25	5.171	97.99%	0.5961	2.183	
A/H1N1	406	G/W	1	2.744	2.744	2.744	0	5.000%			0.7
A/H1N1	406	W	36	0.3765	0.9048	2.152	5.171	97.12%	0.5479	1	
A/H1N1	424	E/G	1	0.9965	0.9965	0.9965	0	5.000%			
A/H1N1	424	E	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	448	V	1	0.3598	0.3598	0.3598	0	5.000%			
A/H1N1	448	A	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	535	Y	1	0.328	0.328	0.328	0	5.000%			
A/H1N1	535	H	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	555	S	1	0.328	0.328	0.328	0	5.000%			
A/H1N1	555	G	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	560	S	1	0.328	0.328	0.328	0	5.000%			
A/H1N1	560	P	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H1N1	636	A	1	0.9894	0.9894	0.9894	0	5.000%			
A/H1N1	636	V	36	0.3765	0.9048	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	650	H	1	0.8466	0.8466	0.8466	0	5.000%			
A/H1N1	650	Y	36	0.3765	0.9674	2.192	5.171	97.12%	0.5479	1.902	
A/H1N1	710	L	1	0.328	0.328	0.328	0	5.000%			
A/H1N1	710	F	36	0.3854	0.9674	2.192	5.171	97.12%	0.5961	1.902	
A/H3N2	20	T	3	0.8025	0.872	1.016	0.2131	75.00%	0.8025	1.016	
A/H3N2	20	A	158	0.3663	0.9118	1.042	7.705	95.36%	0.6837	0.9912	
A/H3N2	28	P	1	7.747	7.747	7.747	0	5.000%			2.58
A/H3N2	28	L	160	0.3681	0.8909	1.04	6.397	95.22%	0.6979	0.9894	
A/H3N2	62	I	5	0.3611	0.7457	3.613	6.208	93.75%	0.2312	6.439	
A/H3N2	62	V	156	0.3681	0.9196	1.041	7.705	95.50%	0.6979	0.9912	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
A/H3N2	63	I	1	7.747	7.747	7.747	0	5.000%			1.73 (2.88+L28P)
A/H3N2	63	V	160	0.3681	0.8909	1.04	6.397	95.22%	0.6979	0.9894	
A/H3N2	65	F	1	0.9138	0.9138	0.9138	0	5.000%			
A/H3N2	65	L	160	0.3681	0.8909	1.041	7.705	95.22%	0.6979	0.9912	
A/H3N2	82	K	1	1.005	1.005	1.005	0	5.000%			
A/H3N2	82	R	160	0.3681	0.8909	1.041	7.705	95.22%	0.6979	0.9894	
A/H3N2	86	I	3	0.2606	0.3028	3.288	3.028	75.00%	0.2606	3.288	
A/H3N2	86	M	158	0.3732	0.9118	1.04	7.705	95.36%	0.7085	0.9912	
A/H3N2	98	A	1	0.5516	0.5516	0.5516	0	5.000%			0.52 (T98N)
A/H3N2	98	T	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	101	E	2	1.04	1.063	1.085	0.045	50.00%	1.04	1.085	
A/H3N2	101	G	159	0.3677	0.872	1.04	7.705	96.11%	0.6837	0.9894	
A/H3N2	105	Y	1	2.354	2.354	2.354	0	5.000%			
A/H3N2	105	F	160	0.3681	0.8909	1.04	7.705	95.22%	0.6979	0.9894	
A/H3N2	115	S	1	0.4448	0.4448	0.4448	0	5.000%			
A/H3N2	115	N	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	126	D	2	0.04804	0.0818	0.1157	0.0676	50.00%	0.04804	0.1157	
A/H3N2	126	E	159	0.3746	0.9138	1.041	7.705	96.11%	0.7085	0.9912	
A/H3N2	127	I	1	0.4459	0.4459	0.4459	0	5.000%			
A/H3N2	127	V	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	155	I	1	2.396	2.396	2.396	0	5.000%			
A/H3N2	155	M	160	0.3681	0.8909	1.04	7.705	95.22%	0.6979	0.9894	
A/H3N2	158	R	7	0.3092	1.466	1.878	2.245	98.44%	0.1083	2.354	
A/H3N2	158	K	154	0.3732	0.8909	1.033	7.705	95.64%	0.6979	0.9894	
A/H3N2	216	N	1	0.9541	0.9541	0.9541	0	5.000%			
A/H3N2	216	D	160	0.3681	0.8909	1.041	7.705	95.22%	0.6979	0.9912	
A/H3N2	221	L	1	0.3569	0.3569	0.3569	0	5.000%			
A/H3N2	221	P	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	268	V	6	0.5367	0.6846	0.9925	0.5565	96.88%	0.4399	0.9965	
A/H3N2	268	I	155	0.3622	0.9138	1.046	7.705	96.36%	0.6979	0.9912	
A/H3N2	269	R	2	0.9452	0.9876	1.03	0.0848	50.00%	0.9452	1.03	
A/H3N2	269	K	159	0.3677	0.872	1.041	7.705	96.11%	0.6837	0.9912	
A/H3N2	272	G	2	0.9254	0.9583	0.9912	0.0657	50.00%	0.9254	0.9912	
A/H3N2	272	N	6	0.1197	0.1759	0.6832	1.401	96.88%	0.08807	1.489	
A/H3N2	272	S	153	0.3754	0.9138	1.043	7.705	96.48%	0.7085	0.9965	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
A/H3N2	277	H	1	0.9912	0.9912	0.9912	0	5.000%			
A/H3N2	277	Y	160	0.3681	0.8909	1.041	7.705	95.22%	0.6979	0.9894	
A/H3N2	317	R/W	1	0.5516	0.5516	0.5516	0	5.000%			
A/H3N2	317	W	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	346	R	2	0.9894	1.002	1.014	0.0247	50.00%	0.9894	1.014	
A/H3N2	346	Q	159	0.3677	0.872	1.041	7.705	96.11%	0.6837	0.9912	
A/H3N2	350	I	1	0.6979	0.6979	0.6979	0	5.000%			
A/H3N2	350	N	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	354	T	1	0.3486	0.3486	0.3486	0	5.000%			
A/H3N2	354	I	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	356	K	1	7.747	7.747	7.747	0	5.000%			0.96
A/H3N2	356	R	160	0.3681	0.8909	1.04	6.397	95.22%	0.6979	0.9894	
A/H3N2	357	A	1	0.6608	0.6608	0.6608	0	5.000%			
A/H3N2	357	T	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	369	T	1	0.3286	0.3286	0.3286	0	5.000%			
A/H3N2	369	A	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	385	K	1	0.8165	0.8165	0.8165	0	5.000%			1.06
A/H3N2	385	R	160	0.3681	0.9118	1.041	7.705	95.22%	0.6979	0.9912	
A/H3N2	387	T	3	0.3428	0.9505	1.097	0.7544	75.00%	0.3428	1.097	
A/H3N2	387	I	158	0.3689	0.8909	1.04	7.705	95.36%	0.6979	0.9912	
A/H3N2	388	G	1	0.2598	0.2598	0.2598	0	5.000%			
A/H3N2	388	S	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	407	M	13	0.3887	0.6784	1.006	0.8245	97.75%	0.3852	1.009	
A/H3N2	407	I	148	0.3622	0.9196	1.06	7.705	96.05%	0.7085	0.9912	
A/H3N2	409	N	1	0.08185	0.0818	0.08185	0	5.000%			
A/H3N2	409	S	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	419	G	1	0.5106	0.5106	0.5106	0	5.000%			
A/H3N2	419	D	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	421	I	10	0.3594	1.009	2.366	4.391	97.85%	0.2598	3.571	
A/H3N2	421	V	151	0.3677	0.864	1.031	7.699	96.60%	0.6784	0.9912	
A/H3N2	492	R	12	0.339	0.6486	0.8581	0.8404	96.14%	0.3358	0.872	
A/H3N2	492	K	149	0.3719	0.9304	1.048	7.705	95.11%	0.7085	0.9965	
A/H3N2	535	Y	3	0.9304	0.9541	4.433	3.503	75.00%	0.9304	4.433	
A/H3N2	535	H	158	0.3663	0.868	1.04	7.705	95.36%	0.6837	0.9912	
A/H3N2	539	R	2	0.3693	0.7527	1.136	0.7668	50.00%	0.3693	1.136	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
A/H3N2	539	K	159	0.3677	0.9099	1.04	7.705	96.11%	0.6979	0.9912	
A/H3N2	543	I	1	0.2055	0.2055	0.2055	0	5.000%			
A/H3N2	543	L	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	548	I	1	1.524	1.524	1.524	0	5.000%			
A/H3N2	548	M	160	0.3681	0.8909	1.04	7.705	95.22%	0.6979	0.9894	
A/H3N2	**554**	**V**	**2**	**0.7864**	**3.613**	**6.439**	**5.653**	**50.00%**	**0.7864**	**6.439**	
A/H3N2	554	I	159	0.3677	0.9099	1.04	7.705	96.11%	0.6837	0.9912	
A/H3N2	594	N	1	0.3569	0.3569	0.3569	0	5.000%			
A/H3N2	594	S	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	608	A	1	0.872	0.872	0.872	0	5.000%			
A/H3N2	608	T	160	0.3681	0.9118	1.041	7.705	95.22%	0.6979	0.9912	
A/H3N2	614	D	1	0.3922	0.3922	0.3922	0	5.000%			
A/H3N2	614	N	160	0.3681	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	632	P/S	1	0.2598	0.2598	0.2598	0	5.000%			0.74
A/H3N2	632	S	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
A/H3N2	**668**	**V**	**16**	**0.8033**	**1.197**	**2.229**	**6.219**	**97.87%**	**0.7864**	**2.396**	
A/H3N2	668	I	145	0.3622	0.8604	1.026	7.705	95.41%	0.6608	0.9706	
A/H3N2	672	F	1	0.3269	0.3269	0.3269	0	5.000%			
A/H3N2	672	L	160	0.3706	0.9118	1.041	7.705	95.22%	0.7085	0.9912	
B	6	A	2	2.833	4.672	6.512	3.68	50.00%	2.833	6.512	
B	6	T	22	0.9332	1.525	2.674	3.541	98.31%	1.05	2.631	
B	7	K	1	0.5829	0.5829	0.5829	0	5.000%			1.24
B	7	R	23	1.148	2.468	2.818	6.458	96.53%	1.184	2.803	
B	22	T	1	0.05411	0.0541	0.05411	0	5.000%			
B	22	A	23	1.148	2.468	2.818	5.972	96.53%	1.184	2.803	
B	47	I	2	0.5829	1.572	2.562	1.979	50.00%	0.5829	2.562	
B	47	V	22	1.123	2.108	2.821	6.458	98.31%	1.148	2.818	
B	76	R	1	1.148	1.148	1.148	0	5.000%			
B	76	Q	23	1.05	2.468	2.818	6.458	96.53%	1.184	2.803	
B	137	K	1	2.562	2.562	2.562	0	5.000%			
B	137	E	23	1.05	1.749	2.818	6.458	96.53%	1.148	2.803	
B	142	G	1	1.195	1.195	1.195	0	5.000%			
B	142	S	23	1.05	2.468	2.818	6.458	96.53%	1.148	2.803	
B	196	I	1	2.833	2.833	2.833	0	5.000%			
B	196	V	23	1.05	1.749	2.803	6.458	96.53%	1.148	2.631	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
B	203	K	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	203	R	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	226	L	1	0.05411	0.0541	0.05411	0	5.000%			
B	226	M	23	1.148	2.468	2.818	5.972	96.53%	1.184	2.803	
B	236	N	1	1.302	1.302	1.302	0	5.000%			
B	236	K	23	1.05	2.468	2.818	6.458	96.53%	1.148	2.803	
B	258	T	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	258	K	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	271	D	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	271	N	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	273	G	1	1.05	1.05	1.05	0	5.000%			
B	273	D	2	2.833	4.672	6.512	3.68	50.00%	2.833	6.512	
B	273	E	21	0.8659	1.749	2.717	3.541	97.34%	1.148	2.631	
B	351	D	1	2.818	2.818	2.818	0	5.000%			
B	351	E	23	1.05	1.749	2.803	6.458	96.53%	1.148	2.631	
B	352	A	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	352	M	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	379	I	2	0.5406	0.5623	0.584	0.0434	50.00%	0.5406	0.584	
B	379	V	22	1.175	2.515	2.821	6.458	98.31%	1.184	2.818	
B	396	R	1	2.562	2.562	2.562	0	5.000%			
B	396	K	23	1.05	1.749	2.818	6.458	96.53%	1.148	2.803	
B	417	K	1	1.749	1.749	1.749	0	5.000%			
B	417	R	23	1.05	2.468	2.818	6.458	96.53%	1.148	2.803	
B	428	M	1	1.749	1.749	1.749	0	5.000%			
B	428	I	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	428	V	15	2.468	2.631	2.833	5.463	96.48%	2.468	2.833	
B	485	V	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	485	I	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	541	V	1	1.749	1.749	1.749	0	5.000%			
B	541	I	23	1.05	2.468	2.818	6.458	96.53%	1.148	2.803	
B	547	S	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	547	G	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	594	V	1	1.148	1.148	1.148	0	5.000%			
B	594	I	23	1.05	2.468	2.818	6.458	96.53%	1.184	2.803	
B	609	I	3	1.749	2.468	2.833	1.084	75.00%	1.749	2.833	

Virus Type/ Subtype	PA Amino Acid Position	Amino Acid	No. of Values	25% Percentile	Median	75% Percentile	Range	Confidence Level	Lower Confidence Limit	Upper Confidence Limit	EC_{50} Value FC of Molecular Clone Containing Individual Substitution
B	609	V	21	0.8168	1.302	2.81	6.458	97.34%	1.05	2.803	
B	617	L	1	2.818	2.818	2.818	0	5.000%			
B	617	I	23	1.05	1.749	2.803	6.458	96.53%	1.148	2.631	
B	625	I	1	2.803	2.803	2.803	0	5.000%			
B	625	V	23	1.05	1.749	2.818	6.458	96.53%	1.148	2.631	
B	673	S	4	1.105	1.938	3.347	2.546	87.50%	1.05	3.595	
B	673	G	20	0.7249	2.108	2.814	6.458	95.86%	1.148	2.803	
B	700	V	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	700	A	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	
B	709	L	1	0.5829	0.5829	0.5829	0	5.000%			
B	709	F	23	1.148	2.468	2.818	6.458	96.53%	1.184	2.803	
B	723	V	8	0.5512	0.5835	1.192	1.248	99.22%	0.05411	1.302	
B	723	I	16	1.929	2.621	2.833	5.463	97.87%	1.749	2.833	

Source: FDA Virology analysis
Source data include all baseline PA sequences with associated EC_{50} values from Trials CP40563, T0822, and T0833.
Bold text indicates substitutions recommended for further evaluation.
Abbreviations: EC_{50}, half maximal effective concentration; FC, fold change; PA, polymerase acidic

The association of baseline genotype with treatment response was evaluated for the following endpoints: Change from baseline in virus shedding titer at Day 2, time to sustained virus negativity, and time to alleviation/improvement of symptoms (Table 101). Notable associations with these endpoints were identified for several genotypes, including A/H3N2 PA I668V, a nonconsensus variant associated with greater reductions in virus shedding at Day 2 and shorter time to alleviation of symptoms; however, this result is confounded by the higher (by approximately 2 $\log_{10}$) baseline virus shedding titer of subjects with I668V variant and earlier treatment (median time since onset of symptoms was ≤12 hours versus 12 to 24 hours for subjects with the consensus variant (data not shown).

There were two type B genotypes represented across the three pediatric trials. The minor variant among pooled sequences was PA variant K258T/N271D/M352A/V(M)428I/I485V/G547S/A700V (subsequently referred to as K258T), which was associated with longer time to alleviation of symptoms; however, the K258T variant was not evenly distributed across trials: K258T represented 100% (of 5), 42% (of 7) of 0% (of 12) type B viruses in Trials CP40563, T0822, and T0833, respectively. These type B variants likely represent Yamagata (258K) and Victoria (258T) lineages, although the lineage is determined by the HA sequence (unknown). There are conflicting data on whether the type B lineages typically differ in their disease characteristics (Xu et al. 2015; Seleka et al. 2017) and any differences likely depends on the status of pre-existing immunity in individuals, among other factors. Taken together, firm conclusions are difficult to draw from these types of genotypic association analyses carried out on pooled data from a limited number of studies, as the associations are often confounded by other factors that covary due to chance (e.g., trial, treatment dose, and study population) and are not necessarily related to virus genotype.

Table 101. Association of Baseline Genotype With Selected Endpoints

Genotype			Change From Baseline at Day 2					TTSVN					TTAS				
Type/Subtype	PA amino acid position	Baseline AA	Number of values	Median	Confidence level	Lower confidence limit	Upper confidence limit	Number of values	Median	Confidence level	Lower confidence limit	Upper confidence limit	Number of values	Median	Actual confidence level	Lower confidence limit	Upper confidence limit
A/H1N1	13	V	3	-4.501	75.00%	-5.251	-2.251	3	120	75.00%	24	240	3	64.8	75.00%	32	269.4
A/H1N1	13	I	26	-4.501	97.10%	-5.501	-3.251	26	24	97.10%	24	120	26	122.8	97.10%	67.2	166.1
A/H1N1	24	H	1	-4.751	5.000%			1	120	96.43%			1	77.3	5.000%		
A/H1N1	24	Y	28	-4.501	96.43%	-5.251	-3.251	28	24	5.000%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	29	R	1	-4.501	5.000%			1	24	5.000%			1	114.9	5.000%		
A/H1N1	29	K	28	-4.501	96.43%	-5.251	-3.251	28	24	96.43%	24	120	28	112.7	96.43%	64.8	166.1
A/H1N1	61	V	1	-3.7	5.000%			1	216	5.000%			1	154.3	5.000%		
A/H1N1	61	I	28	-4.501	96.43%	-5.251	-3.251	28	24	96.43%	24	120	28	104.8	96.43%	64.8	166.1
A/H1N1	100	M	1	-4.751	5.000%			1	120	5.000%			1	77.3	5.000%		
A/H1N1	100	I	28	-4.501	96.43%	-5.251	-3.251	28	24	96.43%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	196	G	1	-5.251	5.000%			1	240	96.43%			1	64.8	5.000%		
A/H1N1	196	R	28	-4.501	96.43%	-5.001	-3.251	28	24	5.000%	24	120	28	122.8	96.43%	67.2	166.1
A/H1N1	225	G	2	-3.876	50.00%	-4.501	-3.251	2	24	98.08%	24	24	2	100.9	50.00%	86.9	114.9
A/H1N1	225	S	27	-4.501	98.08%	-5.501	-3.001	27	24	50.00%	24	120	27	130.8	98.08%	58.93	170.2
A/H1N1	252	G	1	-3.7	5.000%			1	216	5.000%			1	154.3	5.000%		
A/H1N1	252	E	28	-4.501	96.43%	-5.251	-3.251	28	24	96.43%	24	120	28	104.8	96.43%	64.8	166.1
A/H1N1	254	K	1	-3.251	5.000%			1	24	96.43%			1	86.9	5.000%		
A/H1N1	254	N	28	-4.501	96.43%	-5.251	-3.7	28	24	5.000%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	269	I	2	-5.5	50.00%	-6.7	-4.3	2	48	98.08%	24	72	2	16.19	50.00%	14.88	17.5
A/H1N1	269	R	27	-4.501	98.08%	-5.251	-3.001	27	24	50.00%	24	120	27	130.8	98.08%	67.2	170.2
A/H1N1	275	H	1	-5.501	5.000%			1	24	96.43%			1	211.1	5.000%		
A/H1N1	275	L	28	-4.501	96.43%	-5.001	-3.251	28	24	5.000%	24	120	28	104.8	96.43%	64.8	164
A/H1N1	284	M	1	-2.751	5.000%			1	24	5.000%			1	93.7	5.000%		
A/H1N1	284	L	28	-4.501	96.43%	-5.251	-3.7	28	24	96.43%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	285	T	1	-1.251	5.000%			1	24	5.000%			1	67.2	5.000%		
A/H1N1	285	M	28	-4.501	96.43%	-5.251	-3.7	28	24	96.43%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	291	G	1	-2.8	5.000%			1	48	96.43%			1	45.7	5.000%		
A/H1N1	291	S	28	-4.501	96.43%	-5.251	-3.7	28	24	5.000%	24	120	28	122.8	96.43%	67.2	166.1
A/H1N1	330	I	2	-5.5	50.00%	-6.7	-4.3	2	48	98.08%	24	72	2	16.19	50.00%	14.88	17.5
A/H1N1	330	V	27	-4.501	98.08%	-5.251	-3.001	27	24	50.00%	24	120	27	130.8	98.08%	67.2	170.2
A/H1N1	335	F	1	-5.501	5.000%			1	120	96.43%			1	36.4	5.000%		
A/H1N1	335	L	28	-4.501	96.43%	-5.001	-3.251	28	24	5.000%	24	120	28	122.8	96.43%	67.2	166.1
A/H1N1	343	T	4	-4.4	87.50%	-7.3	-2	4	36	87.50%	24	264	4	94.84	87.50%	45.27	170.2
A/H1N1	343	A	25	-4.501	95.67%	-5.251	-3.251	25	24	95.67%	24	120	25	114.9	95.67%	67.2	166.1
A/H1N1	354	V	1	-3.001	5.000%			1	120	5.000%			1	138	5.000%		
A/H1N1	354	I	28	-4.501	96.43%	-5.251	-3.7	28	24	96.43%	24	120	28	104.8	96.43%	64.8	166.1
A/H1N1	363	A	1	-3.001	5.000%			1	120	96.43%			1	138	5.000%		
A/H1N1	363	T	28	-4.501	96.43%	-5.251	-3.7	28	24	5.000%	24	120	28	104.8	96.43%	64.8	166.1
A/H1N1	394	N	2	-3.126	50.00%	-5.001	-1.251	2	24	50.00%	24	24	2	80.95	50.00%	67.2	94.7
A/H1N1	394	D	27	-4.501	98.08%	-5.501	-3.251	27	24	98.08%	24	120	27	130.8	98.08%	58.93	170.2
A/H1N1	400	S	1	-5.001	5.000%			1	24	5.000%			1	94.7	5.000%		
A/H1N1	400	L	3	-4.501	75.00%	-5.251	-2.251	3	120	95.67%	24	240	3	64.8	75.00%	32	269.4
A/H1N1	400	P	25	-4.501	95.67%	-5.501	-3.251	25	24	75.00%	24	120	25	130.8	95.67%	67.2	166.1
A/H1N1	406	G/W	1	-4	5.000%			1	24	96.43%			1	130.8	5.000%		
A/H1N1	406	W	28	-4.501	96.43%	-5.251	-3.251	28	24	5.000%	24	120	28	104.8	96.43%	64.8	166.1

Genotype			Change From Baseline at Day 2					TTSVN					TTAS				
Type/Subtype	PA amino acid position	Baseline AA	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Actual confidence evel	Lower confidence imit	Upper confidence imit
A/H1N1	424	E/G	1	-1.251	5.000%			1	24	5.000%			1	67.2	5.000%		
A/H1N1	424	E	28	-4.501	96.43%	-5.251	-3.7	28	24	96.43%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	448	V	1	-2.251	5.000%			1	24	5.000%			1	269.4	5.000%		
A/H1N1	448	A	28	-4.501	96.43%	-5.251	-3.7	28	24	96.43%	24	120	28	104.8	96.43%	64.8	164
A/H1N1	636	A	1	-5.001	5.000%			1	24	96.43%			1	94.7	5.000%		
A/H1N1	636	V	28	-4.501	96.43%	-5.251	-3.251	28	24	5.000%	24	120	28	122.8	96.43%	64.8	166.1
A/H1N1	650	H	1	-4.751	5.000%			1	120	96.43%			1	77.3	5.000%		
A/H1N1	650	Y	28	-4.501	96.43%	-5.251	-3.251	28	24	5.000%	24	120	28	122.8	96.43%	64.8	166.1
A/H3N2	20	T	3	-3.6	75.00%	-5.5	-1.8	3	96	75.00%	24	144	2	122.5	50.00%	117.4	127.6
A/H3N2	20	A	138	-4	95.02%	-4.5	-3.8	139	24	95.86%	24	48	139	69.62	95.86%	52.42	87.6
A/H3N2	28	P	2	-3.9	50.00%	-7.5	-0.3	2	72	50.00%	24	120	2	61.18	50.00%	19.42	103
A/H3N2	28	L	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	70.5	95.86%	53.6	89.62
A/H3N2	62	I	5	-4	93.75%	-6.8	-3.7	5	120	93.75%	24	240	5	49.5	93.75%	21.67	87.13
A/H3N2	62	V	136	-4	95.18%	-4.5	-3.751	137	24	96.01%	24	48	136	74.38	95.18%	53.7	94.4
A/H3N2	63	I	1	-7.5	5.000%			1	120	5.000%			1	19.42	5.000%		
A/H3N2	63	V	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	65	F	1	-3.8	5.00%			1	24	5.000%			1	24.13	5.000%		
A/H3N2	65	L	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	86	I	5	-2.8	93.75%	-4	-0.8	5	72	93.75%	24	264	5	26.85	93.75%	20.3	138.2
A/H3N2	86	M	136	-4.001	95.18%	-4.501	-3.8	137	24	96.01%	24	48	136	72.35	95.18%	53.7	89.62
A/H3N2	98	A	1	-0.6	5.000%			1	24	5.000%			1	62.52	5.000%		
A/H3N2	98	T	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	52.42	92.3
A/H3N2	101	E	2	-4.9	50.00%	-5.3	-4.5	2	108	50.00%	24	192	2	21.08	50.00%	12.25	29.92
A/H3N2	101	G	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	74.2	95.86%	53.7	92.3
A/H3N2	105	Y	1	-3.7	5.000%			1	216	5.000%			1	26.75	5.000%		
A/H3N2	105	F	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	115	S	1	-7.5	5.000%			1	24	5.000%			1	75.52	5.000%		
A/H3N2	115	N	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	92.3
A/H3N2	126	D	2	-3.25	50.00%	-3.5	-3	2	96	50.00%	24	168	2	117.7	50.00%	98.7	136.7
A/H3N2	126	E	139	-4	95.86%	-4.501	-3.8	140	24	96.58%	24	48	139	69.62	95.86%	52.42	87.6
A/H3N2	127	I	1	-4	5.000%			1	24	5.000%			1	19.75	5.000%		
A/H3N2	127	V	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	155	I	1	-7.3	5.000%			1	120	5.000%			1	46.58	5.000%		
A/H3N2	155	M	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	158	R	6	-3.35	96.88%	-6.5	-2.3	6	24	96.88%	24	216	6	56.12	96.88%	9.133	178.5
A/H3N2	158	K	135	-4	96.15%	-4.501	-3.8	136	24	95.18%	24	48	135	74.2	96.15%	53.6	92.3
A/H3N2	216	N	1	-3.3	5.000%			1	24	5.000%			1	15.5	5.000%		
A/H3N2	216	D	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	221	L	1	-3.001	5.000%			1	24	5.000%			1	67.4	5.000%		
A/H3N2	221	P	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	52.42	92.3
A/H3N2	268	V	3	-4.251	75.00%	-4.75	-3.001	3	216	75.00%	24	240	3	112.3	75.00%	81	149.2
A/H3N2	268	I	138	-4	95.02%	-4.5	-3.751	139	24	95.86%	24	48	138	69.4	95.02%	52.42	87.6
A/H3N2	269	R	2	-3.375	50.00%	-3.75	-3	2	252	50.00%	240	264	2	174.6	50.00%	116.7	232.5
A/H3N2	269	K	139	-4	95.86%	-4.501	-3.8	140	24	96.58%	24	48	139	69.62	95.86%	52.42	87.6
A/H3N2	272	N	6	-3.5	96.88%	-5.8	-1.3	6	60	96.88%	24	168	6	39.08	96.88%	9.883	250
A/H3N2	272	S	134	-4	95.35%	-4.501	-3.8	135	24	96.15%	24	48	134	74.38	95.35%	53.88	92.3

Genotype			Change From Baseline at Day 2					TTSVN					TTAS				
Type/Subtype	PA amino acid position	Baseline AA	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Actual confidence evel	Lower confidence imit	Upper confidence imit
A/H3N2	277	H	1	-4	5.000%			1	144	5.000%			1	182.4	5.000%		
A/H3N2	277	Y	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	317	R/W	1	-0.6	5.000%			1	24	5.000%			1	62.52	5.000%		
A/H3N2	317	W	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	52.42	92.3
A/H3N2	346	R	2	-3.251	50.00%	-4.751	-1.751	2	24	50.00%	24	24	2	145.3	50.00%	99.4	191.1
A/H3N2	346	Q	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	69.62	95.86%	52.42	87.6
A/H3N2	350	I	1	-1.251	5.000%			1	24	5.000%			1	310.2	5.000%		
A/H3N2	350	N	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	354	T	1	-5	5.000%			1	264	5.000%			1	321.1	5.000%		
A/H3N2	354	I	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	356	K	2	-3.9	50.00%	-7.5	-0.3	2	72	50.00%	24	120	2	61.18	50.00%	19.42	103
A/H3N2	356	R	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	70.5	95.86%	53.6	89.62
A/H3N2	385	K	1	-4.8	5.000%			1	168	5.000%			1	69.62	5.000%		
A/H3N2	385	R	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	52.42	92.3
A/H3N2	387	T	2	-3.376	50.00%	-4.751	-2.001	2	24	50.00%	24	24	2	90.8	50.00%	65.7	115.9
A/H3N2	387	I	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	70.5	95.86%	52.42	89.62
A/H3N2	388	G	1	-7	5.000%			1	24	5.000%			1	224.2	5.000%		
A/H3N2	388	S	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	407	M	11	-3.751	98.83%	-4.501	-0.251	11	24	98.83%	24	24	11[1]	163[1]	98.83%[1]	92.3[1]	345.6[1]
A/H3N2	407	I	130	-4	95.67%	-4.501	-3.8	131	24	96.44%	24	72	130[1]	67.9[1]	95.67%[1]	46.58[1]	79.6[1]
A/H3N2	409	N	1	-7	5.000%			1	168	5.000%			1	106.1	5.000%		
A/H3N2	409	S	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	421	I	10	-4.15	97.85%	-5.8	-1.3	10	24	97.85%	24	48	10	47.08	97.85%	15.5	291.4
A/H3N2	421	V	131	-4	96.44%	-4.501	-3.751	132	24	95.51%	24	48	131	74.2	96.44%	53.6	92.3
A/H3N2	492	R	12	-3.85	96.14%	-5.5	-2.8	12	108	96.14%	24	168	11	78.12	98.83%	60.95	127.6
A/H3N2	492	K	129	-4	96.58%	-4.501	-3.751	130	24	95.67%	24	48	130	69.84	95.67%	46.37	94.4
A/H3N2	535	Y	3	-3.8	75.00%	-4.5	-3.3	3	24	75.00%	24	24	3	55.2	75.00%	15.5	291.4
A/H3N2	535	H	138	-4	95.02%	-4.501	-3.751	139	24	95.86%	24	48	138	72.35	95.02%	53.6	89.62
A/H3N2	539	R	2	-4.626	50.00%	-4.751	-4.501	2	96	50.00%	24	168	2	63.95	50.00%	53.7	74.2
A/H3N2	539	K	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	70.5	95.86%	52.42	92.3
A/H3N2	543	I	1	-5.5	5.000%			1	24	5.000%			1	102.5	5.000%		
A/H3N2	543	L	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	548	I	1	-4.7	5.000%			1	240	5.000%			1	25	5.000%		
A/H3N2	548	M	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	53.6	92.3
A/H3N2	554	V	2	-5.15	50.00%	-6.3	-4	2	108	50.00%	24	192	2	30.29	50.00%	21.67	38.92
A/H3N2	554	I	139	-4	95.86%	-4.5	-3.751	140	24	96.58%	24	48	139	74.2	95.86%	53.7	92.3
A/H3N2	594	N	1	-3.001	5.000%			1	24	5.000%			1	67.4	5.000%		
A/H3N2	594	S	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	72.35	96.58%	52.42	92.3
A/H3N2	608	A	1	-1.8	5.000%			1	96	5.000%			1	127.6	5.000%		
A/H3N2	608	T	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	614	D	1	-4.001	5.000%			1	24	5.000%			1	92.3	5.000%		
A/H3N2	614	N	140	-4	96.58%	-4.501	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	632	P/S	1	-7	5.000%			1	24	5.000%			1	224.2	5.000%		
A/H3N2	632	S	140	-4	96.58%	-4.5	-3.751	141	24	95.71%	24	48	140	70.06	96.58%	52.42	89.62
A/H3N2	668	V	18[2]	-6.1[2]	96.91%[2]	-6.8[2]	-4.5[2]	18	48	96.91%	24	120	18[1]	38.58[1]	96.91%[1]	21.07[1]	53.88[1]
A/H3N2	668	I	123[2]	-4[2]	95.31%[2]	-4.251[2]	-3.7[2]	124	24	96.16%	24	48	123[1]	79.6[1]	95.31%[1]	65.7[1]	103[1]

Genotype			Change From Baseline at Day 2					TTSVN					TTAS				
Type/Subtype	PA amino acid position	Baseline AA	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Actual confidence evel	Lower confidence imit	Upper confidence imit
B	6	A	2	-5.85	50.00%	-7.5	-4.2	2	192	50.00%	144	240	2	27.59	50.00%	26.42	28.77
B	6	T	19	-4	98.08%	-4.8	-2.5	20	168	95.86%	144	192	20	60.55	95.86%	37.83	115.9
B	7	K						1	144	5.000%			1	122.2	5.000%		
B	7	R						21	168	97.34%	144	192	21	45.6	97.34%	28.45	92.4
B	47	I	2	-3.901	50.00%	-4.001	-3.8	2	156	50.00%	144	168	2	80.38	50.00%	13.77	147
B	47	V	19	-4.2	98.08%	-5	-2.5	20	168	95.86%	144	192	20	49.16	95.86%	28.77	92.4
B	76	R	1	-5.7	5.000%			1	168	5.000%			1	86.87	5.000%		
B	76	Q	20	-4.001	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	115.9
B	137	K	1	-3.8	5.000%			1	168	5.000%			1	13.77	5.000%		
B	137	E	20	-4.101	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	52.72	97.34%	28.77	115.9
B	142	G	1	-2.5	5.000%			1	168	5.000%			1	133.8	5.000%		
B	142	S	20	-4.101	95.86%	-4.8	-3	21	168	97.34%	144	192	21	45.6	97.34%	28.45	92.4
B	196	I	1	-7.5	5.000%			1	144	5.000%			1	26.42	5.000%		
B	196	V	20	-4.001	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	52.72	97.34%	28.77	115.9
B	203	K	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6	136.6	96.88%	81.7	173.3
B	203	R	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16	38.01	97.87%	19.58	68.38
B	226	M	21	-4.001	97.34%	-4.8	-2.7	22	168	98.31%	144	192	22	49.16	98.31%	28.45	115.9
B	236	N	1	-1	5.000%			1	168	5.000%			1	139.4	5.000%		
B	236	K	20	-4.101	95.86%	-4.8	-3	21	168	97.34%	144	192	21	45.6	97.34%	28.45	92.4
B	258	T	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	258	K	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	271	D	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	271	N	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	273	G	1	-5.5	5.000%			1	24	5.000%			1	45.6	5.000%		
B	273	D	2	-5.85	50.00%	-7.5	-4.2	2	192	50.00%	144	240	2	27.59	50.00%	26.42	28.77
B	273	E	18	-3.9	96.91%	-4.8	-2.5	19	168	98.08%	144	192	19	68.38	98.08%	28.45	122.2
B	351	D	1	-3.6	5.000%			1	192	5.000%			1	52.72	5.000%		
B	351	E	20	-4.101	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	115.9
B	352	A	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	352	M	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	379	I	1	-4.251	5.000%			1	24	5.000%			1	173.3	5.000%		
B	379	V	20	-4.001	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	92.4
B	396	R	1	-3.8	5.000%			1	168	5.000%			1	13.77	5.000%		
B	396	K	20	-4.101	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	52.72	97.34%	28.77	115.9
B	417	K	1	-2.3	5.000%			1	120	5.000%			1	45.5	5.000%		
B	417	R	20	-4.101	95.86%	-4.8	-3	21	168	97.34%	144	192	21	52.72	97.34%	28.45	115.9
B	428	M	1	-2.3	5.000%			1	120	5.000%			1	45.5	5.000%		
B	428	I	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	428	V	15	-4.3	96.48%	-5	-3.6	15	168	96.48%	144	192	15[1]	37.83[1]	96.48%[1]	19.58[1]	68.38[1]
B	485	V	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	485	I	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	541	V	1	-2.3	5.000%			1	120	5.000%			1	45.5	5.000%		
B	541	I	20	-4.101	95.86%	-4.8	-3	21	168	97.34%	144	192	21	52.72	97.34%	28.45	115.9
B	547	S	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	547	G	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	594	V	1	-5.7	5.000%			1	168	5.000%			1	86.87	5.000%		

Genotype			Change From Baseline at Day 2					TTSVN					TTAS				
Type/Subtype	PA amino acid position	Baseline AA	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Confidence evel	Lower confidence imit	Upper confidence imit	Number of values	Median	Actual confidence evel	Lower confidence imit	Upper confidence imit
B	594	I	20	-4.001	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	115.9
B	609	I	3	-2.7	75.00%	-3	-2.3	3	192	75.00%	120	192	3	37.83	75.00%	19.25	45.5
B	609	V	18	-4.226	96.91%	-5	-3.6	19	168	98.08%	144	192	19	68.38	98.08%	28.45	122.2
B	617	L	1	-3.6	5.000%			1	192	5.000%			1	52.72	5.000%		
B	617	I	20	-4.101	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	115.9
B	625	I	1	-4	5.000%			1	192	5.000%			1	68.38	5.000%		
B	625	V	20	-4.101	95.86%	-4.8	-2.7	21	168	97.34%	144	192	21	45.6	97.34%	28.45	115.9
B	673	S	4	-4.55	87.50%	-5.5	-2.2	4	84	87.50%	24	168	4	28.88	87.50%	18.3	45.6
B	673	G	17	-4	95.10%	-4.8	-2.7	18	168	96.91%	144	192	18	75.04	96.91%	28.77	122.2
B	700	V	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	700	A	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]
B	709	L						1	144	5.000%			1	122.2	5.000%		
B	709	F						21	168	97.34%	144	192	21	45.6	97.34%	28.45	92.4
B	723	V	5	-2.5	93.75%	-4.251	-1	6	156	96.88%	24	168	6[1]	136.6[1]	96.88%[1]	81.7[1]	173.3[1]
B	723	I	16	-4.25	97.87%	-5	-3	16	168	97.87%	120	192	16[1]	38.01[1]	97.87%[1]	19.58[1]	68.38[1]

Source: FDA Virology analysis
Source data include all baseline PA sequences with associated parameter values from Trials CP40563, T0822, and T0833.
[1] P<0.01 difference between variants
[2] P<0.0001 difference between variants
Abbreviations: AA, amino acid; PA, polymerase acidic; TTAS, time to alleviation of influenza signs and symptoms; TTSVN, time to sustained virus negativity

19.1.6.1. Conclusion: Baseline Genotypic Analysis of Pediatric Studies

Together, firm conclusions are difficult to draw from baseline genotypic association analyses carried out on pooled data from a limited number of studies, as the associations are often confounded by other factors that covary due to chance (e.g., trial, treatment dose, and study population) and are not necessarily related to virus genotype. Polymorphisms associated with reduced response to treatment should be evaluated for their impact on baloxavir susceptibility.

19.1.7. Supplemental Clinical Virology Data

Table 102. Rates of Virus Rebound in Adult/Adolescent Trials Evaluated to Date

	Trials T0821/T0831/T0832		
Virus Rebound (n)	**Baloxavir**	**Oseltamivir**	**Placebo**
All	190/1065 (18)	206/709 (29)	276/654 (42)
Type A	116/808 (14)	138/538 (26)	196/458 (43)
Type B	74/257 (29)	68/171 (40)	80/196 (41)

Source: FDA Virology analysis of data descr bed in Clinical Virology Reviews of the Original NDA (N210854.000); and Supplement 1 (N210854.SE-001.077).

Table 103. Cumulative Data for Evaluations of Baloxavir Susceptibility of Molecular Clones in Cell Culture

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
A/H1N1	rgA/WSN/33-PA/A20S	PA	20	A20S	0.5	0.27	1.19	S-033188-EB-235-N
A/H1N1	rgA/WSN/33- PA/A20S+I38T	PA	20	A20S+I38T	11.43	2.6	27.38[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33- PA/A20S+I38F	PA	20	A20S+I38F	3.38	1.16	8.1[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/E23K	PA	23	E23K	1.98	0.48	4.74[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33 PA/E23K	PA	23	E23K	1.232	0.69	3.1391[1]	S-033188-EB-329-N
A/H1N1	rgA/WSN/33 PA/E23G	PA	23	E23G	0.691	0.15	1.7593	S-033188-EB-329-N
A/H1N1	rgA/WSN/33 PA/E23R	PA	23	E23R	1.502	0.61	3.8230[1]	S-033188-EB-329-N
A/H1N1	rgA/WSN/33-PA/Y24H	PA	24	Y24H	0.545	0.08	1.3880	S-033188-EB-329-N
A/H1N1	rgA/WSN/33 PA/Y24H+V122A	PA	24	Y24H+V122A	0.454	0.03	1.1551	S-033188-EB-329-N
A/H1N1	rgA/WSN/33-PA/A36V	PA	36	A36V	1.5	0.37	3.59	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	11.37	1.85	27.24[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/I38F	PA	38	I38F	4.43	1.95	10.61[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/I38M	PA	38	I38M	4.07	1.84	13.15[1]	S-033188-EB-276-N
A/H1N1	rgA/WSN/33-PA/I38V	PA	38	I38V	0.97	0.8	2.18	S-033188-EB-290-N
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	20.53	5.13	43.92[1]	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PA/I38T+PB1/K757N	PA	38	PA/I38T+PB1/K757N	20.75	13.15	44.39[1]	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PA/I38T+PB2/Q288L	PA	38	PA/I38T+PB2/Q288L	11.48	3.21	24.55[1]	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PA/I38T+PB1/K757N+PB2/Q288L	PA	38	PA/I38T+PB1/K757N+ PB2/Q288L	21.90	5.23	46.85[1]	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PA/ I38T	PA	38	I38T	6.9	2.94	19.16[1]	S-033188-EB-335-N
A/H1N1	rgA/WSN/33-PA/I38N	PA	38	I38N	8.52	2.87	23.66[1]	S-033188-EB-335-N
A/H1N1	rgA/WSN/33-PA/I38T	PA	38	I38T	16.71	9.30	26.30[1]	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PA/I38S	PA	38	I38S	7.90	3.90	12.43[1]	S-033188-EB-356-N
A/H1N1	rgA/WSN/33-PA/I38L	PA	38	I38L	4.02	3.51	6.33[1]	S-033188-EB-356-N
A/H1N1	rgB/Maryland/1/59-PB2/G76R	PB2	76	G76R	9.90	4.20	0.95	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PB1/M92T	PB1	92	M92T	0.33	0.05	0.79	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/E119D	PA	119	E119D	2.7	1.5	6.46[1]	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/A221T	PB2	221	A221T	0.38	0.06	0.9	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-NA/H274Y	NA	274	H274Y	0.32	0.06	0.77	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/Q288L	PB2	288	Q288L	0.64	0.21	1.36	S-033188-EB-319-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
A/H1N1	rgA/WSN/33-PB2/Q288L+I638V	PB2	288	Q288L+I638V	0.48	0.08	1.03	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PB2/I310M	PB2	310	I310M	0.29	0.08	0.71	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/T333I	PB2	333	T333I	0.24	0.02	0.58	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/R356K	PA	356	R356K	0.38	0.07	1.07	S-033188-EB-335-N
A/H1N1	rgA/WSN/33-PA/E397G	PA	397	E397G	0.33	0.08	0.92	S-033188-EB-335-N
A/H1N1	rgA/WSN/33 PA/W406G	PA	406	W406G	0.275	0.09	0.7000	S-033188-EB-329-N
A/H1N1	rgA/WSN/33-PB1/V418I	PB1	418	V418I	0.3	0.1	0.71	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PA/I465M	PA	465	I465M	0.29	0.05	0.93	S-033188-EB-276-N
A/H1N1	rgA/WSN/33-PA/V545T	PA	545	V545T	0.31	0.11	0.73	S-033188-EB-235-N
A/H1N1	rgA/WSN/33-PB2/I638V	PB2	638	I638V	0.46	0.16	0.99	S-033188-EB-319-N
A/H1N1	rgA/WSN/33-PB1/K757N	PB1	757	K757N	0.47	0.1	1	S-033188-EB-319-N
A/H1N1	rgA/WSN/33				0.31	0.11		S-033188-EB-276-N
A/H1N1	rgA/WSN/33				0.45	0.22		S-033188-EB-290-N
A/H1N1	rgA/WSN/33				0.47	0.05		S-033188-EB-319-N
A/H1N1	rgA/WSN/33				0.36	0.03		S-033188-EB-335-N
A/H1N1	rgA/WSN/33				0.393	0.12		S-033188-EB-329-N
A/H1N1	rgA/WSN/33				0.64	0.35		S-033188-EB-356-N
A/H1N1	rgA/WSN/33				0.42	0.12		S-033188-EB-235-N
A/H1N1	rgB/Maryland/1/59				10.40	1.95		S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75- PB2/S12L	PB2	12	S12L	0.91	0.3	0.86	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/E23K	PA	23	E23K	6.2	2.86	5.5[1]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75-PA/E23G	PA	23	E23G	2.75	1.48	2.39[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E23G+C_{24}1F	PA	23	E23G+C_{24}1F	2.04	1.35	1.77	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/L28P	PA	28	L28P	2.15	0.13	2.58[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/L28P+V63I	PA	28	L28P+V63I	2.4	0.32	2.88[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/L28V	PA	28	L28V	1.47	0.78	2.02[1]	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/K34E	PA	34	K34E	1.43	1.6	1.96	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/A36V	PA	36	A36V	6.87	2.76	6.09[1]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75-PA/A37T	PA	37	A37T	6.78	4.04	8.13[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	63.8	3.4	56.59[1]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75-PA/I38F	PA	38	I38F	22.69	10.82	20.13[1]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75-PA/I38T*	PA	38	I38T*	40.76	11.94	48.9[1]	S-033188-EB-276-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
A/H3N2	rgA/Victoria/3/75-PA/I38T+E623K	PA	38	I38T+E623K	35.34	16.12	42.41[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I38M	PA	38	I38M	11.48	1.43	13.77[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	57.33	6.81	49.76[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+S60P	PA	38	I38T+S60P	55.55	4.64	48.21[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/D60G	PA	38	I38T+PB2/D60G	49.37	19.05	42.85[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/K197R	PA	38	I38T+PB2/K197R	23.12	20.73	20.07[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38V	PA	38	I38V	2.11	0.81	1.83	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+I201T	PA	38	I38T+I201T	39.09	5.29	33.92[1]	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	26.18	7.76	24.85[1]	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	14.8	5.86	20.33[1]	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	45.74	8.66	25.489[1]	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I38M	PA	38	I38M	6.561	1.71	3.6561[1]	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I38M+I201T	PA	38	I38M+I201T	16.40	7.92	9.1406[1]	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	PA	38	I38T	55.97	7.99	33.97[1]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38N	PA	38	I38N	17.01	9.37	10.32[1]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38S	PA	38	I38S	9.63	5.93	5.85[1]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/I38L	PA	38	I38L	3.57	2.51	2.17[1]	S-033188-EB-356-N
A/H3N2	rgA/Victoria/3/75-PA/S60P	PA	60	S60P	0.46	0.22	0.4	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PB2/D60G	PB2	60	D60G	1.06	0.15	0.92	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V63I	PA	63	V63I	1.44	0.33	1.73	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/P68L	PA	68	P68L	0.89	0.4	1.23	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/L71M	PA	71	L71M	0.46	0.08	0.64	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/V90A	PA	90	V90A	0.83	0.45	1.14	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/T98N	PA	98	T98N	0.38	0.08	0.52	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/G99E	PA	99	G99E	0.71	0.28	0.61	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PB2/R101G	PB2	101	R101G	0.85	0.14	0.8	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PB2/V105M	PB2	105	V105M	0.67	0.18	0.58	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/E119D	PA	119	E119D	5.09	2.48	4.51[1]	S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75- PA/D160G	PA	160	D160G	0.59	0.16	0.81	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/T162A	PA	162	T162A	1.96	0.3	1.7	S-033188-EB-290-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
A/H3N2	rgA/Victoria/3/75-PA/A183V	PA	183	A183V	0.59	0.4	0.51	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/G186D	PA	186	G186D	0.21	0.13	0.18	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/R192H	PA	192	R192H	0.62	0.1	0.85	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PB2/K197R	PB2	197	K197R	1.56	0.69	1.36	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E199G	PA	199	E199G	3.72	1.37	4.46[1]	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75- PA/E199G	PA	199	E199G	2.95	0.3	2.8[1]	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/E199G+PB2/S12L	PA	199	E199G+PB2/S12L	2.87	0.41	2.73[1]	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/I201T	PA	201	I201T	1.26	0.61	1.1	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/I201T	PA	201	I201T	1.438	0.48	0.8013	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75- PB2/M202L	PB2	202	M202L	1.8	0.36	1.7	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PB1/I205M	PB1	205	I205M	0.73	0.17	0.63	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PB2/R209K	PB2	209	R209K	0.55	0.15	0.53	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/R212C	PA	212	R212C	0.79	0.33	0.68	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/S224F	PA	224	S224F	0.9	0.84	0.78	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/A231V	PA	231	A231V	0.67	0.3	0.58	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/C_{24}1F	PA	241	C_{24}1F	0.65	0.17	0.56	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/P271S	PA	271	P271S	0.6	0.22	0.52	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PB1/M290T	PB1	290	M290T	0.39	0.24	0.34	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/G299R	PA	299	G299R	1.54	0.77	1.34	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/G316R	PA	316	G316R	0.3	0.07	0.26	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/G316R+E630K	PA	316	G316R+E630K	0.41	0.18	0.36	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PB2/K353R	PB2	353	K353R	0.84	0.22	0.73	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/R356K	PA	356	R356K	0.8	0.49	0.96	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/T357A	PA	357	T357A	1.07	0.86	0.93	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/K362R	PA	362	K362R	1.05	0.66	1.25	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PB2/I385V	PB2	385	I385V	0.74	0.13	0.64	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/R385K	PA	385	R385K	1.22	0.46	1.06	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/S395N	PA	395	S395N	0.7	0.44	0.6	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PA/E397K	PA	397	E397K	0.56	0.39	0.77	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/S405C	PA	405	S405C	0.8	0.62	0.69	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/N412D	PA	412	N412D	0.45	0.02	0.54	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/I421T	PA	421	I421T	1.26	1.14	1.1	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75- PB2/M475I	PB2	475	M475I	1.38	0.37	1.31	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/L482I	PA	482	L482I	0.6	0.06	0.52	S-033188-EB-290-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
A/H3N2	rgA/Victoria/3/75-PA/E493G	PA	493	E493G	0.51	0.39	0.44	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V517A	PA	517	V517A	0.43	0.22	0.52	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75- PB1/I517M	PB1	517	I517M	1.02	0.18	0.97	S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75-PA/I545M	PA	545	I545M	0.49	0.17	0.43	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/M561I	PA	561	M561I	1.05	0.23	0.91	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V602I	PA	602	V602I	1.31	0.76	1.14	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E623K	PA	623	E623K	1	0.29	1.2	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/E623G	PA	623	E623G	1.2	0.72	1.04	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/E630K	PA	630	E630K	0.46	0.19	0.4	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/S632P	PA	632	S632P	0.61	0.28	0.74	S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75-PA/L649M	PA	649	L649M	0.47	0.1	0.41	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75-PA/V668I	PA	668	V668I	0.93	0.48	0.81	S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75				1.13	0.51		S-033188-EB-235-N
A/H3N2	rgA/Victoria/3/75				0.83	0.28		S-033188-EB-276-N
A/H3N2	rgA/Victoria/3/75				1.15	0.59		S-033188-EB-290-N
A/H3N2	rgA/Victoria/3/75				1.05	0.35		S-033188-EB-319-N
A/H3N2	rgA/Victoria/3/75				0.73	0.41		S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75				1.795	0.66		S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75				1.65	0.69		S-033188-EB-356-N
B	rgB/Maryland/1/59- PA/R7K	PA	7	R7K	9.45	3.43	1.24	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/E23K	PA	23	E23K	8.73	0.56	0.81	S-033188-EB-235-N
B	rgB/Maryland/1/59- PA/S25G	PA	25	S25G	7.2	1.8	0.95	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/F36A	PA	36	F36A	8.46	0.88	0.79	S-033188-EB-235-N
B	rgB/Maryland/1/59-PA/F36V	PA	36	F36V	8.6	3.17	0.8	S-033188-EB-235-N
B	rgB/Maryland/1/59-PA/I38T	PA	38	I38T	61.79	9.17	5.76[1]	S-033188-EB-235-N
B	rgB/Maryland/1/59-PA/I38F	PA	38	I38F	25.59	0.54	2.39[1]	S-033188-EB-235-N
B	rgB/Maryland/1/59- PA/I38M	PA	38	I38M	41.71	14.71	8.04[1]	S-033188-EB-276-N
B	rgB/Maryland/1/59-PA/I38T	PA	38	I38T	86.80	58.48	8.72[1]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38N	PA	38	I38N	>240.23	N/C	>24.14[1]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38S	PA	38	I38S	>169.02	N/C	>16.99[1]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38V	PA	38	I38V	23.29	14.32	2.34[1]	S-033188-EB-356-N
B	rgB/Maryland/1/59-PA/I38L	PA	38	I38L	26.33	18.68	2.65[1]	S-033188-EB-356-N
B	rgB/Maryland/1/59- PA/T60V	PA	60	T60V	8.63	3.28	0.86	S-033188-EB-290-N
B	rgB/Maryland/1/59- PA/T62K	PA	62	T62K	3.67	1.25	0.48	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/D112N	PA	112	D112N	6.17	3.22	0.61	S-033188-EB-290-N
B	rgB/Maryland/1/59-PA/E120D	PA	120	E120D	21.1	11.06	1.97	S-033188-EB-235-N

Type/ Subtype	Strain	Primary Gene	Primary Amino Acid Position	Substitution(s)	Mean EC_{50} Value (nM)	SD	Fold-Change	Study Report
B	rgB/Maryland/1/59- PA/D201E	PA	201	D201E	7.58	1.89	1	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/D201G	PA	201	D201G	10.32	1.08	1.36	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/E333K	PA	333	E333K	7.08	1.88	0.7	S-033188-EB-290-N
B	rgB/Maryland/1/59- PA/E333G	PA	333	E333G	9.58	2.7	1.26	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/N354K	PA	354	N354K	10.58	2.31	1.39	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/Y361H	PA	361	Y361H	10.42	3.7	1.03	S-033188-EB-290-N
B	rgB/Maryland/1/59- PA/S415G	PA	415	S415G	9.3	2.45	1.22	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/S415N	PA	415	S415N	11.91	0.72	1.57	S-033188-EB-335-N
B	rgB/Maryland/1/59-PA/G548R	PA	548	G548R	12.17	1.88	1.13	S-033188-EB-235-N
B	rgB/Maryland/1/59-PA/E680K	PA	680	E680K	8.786	1.05	0.7789	S-033188-EB-329-N
B	rgB/Maryland/1/59				10.73	5.52		S-033188-EB-235-N
B	rgB/Maryland/1/59				5.19	1.29		S-033188-EB-276-N
B	rgB/Maryland/1/59				10.07	5.45		S-033188-EB-290-N
B	rgB/Maryland/1/59				7.6	5.22		S-033188-EB-335-N
B	rgB/Maryland/1/59				11.29	3.82		S-033188-EB-329-N
B	rgB/Maryland/1/59				9.95	2.92		S-033188-EB-356-N

Source: FDA Virology analyses of indicated study report.
[1] Fold change >2-fold
Abbreviations: EC_{50}, half maximal effective concentration; PA, polymerase acidic; SD, standard deviation

Table 104. Cumulative Data for Baloxavir Treatment-Emergent Substitutions

Type/ Subtype	Gene	Amino	BL Amino Acid[1]	Postbaseline Amino Acid	STUDYID	USUBJID
A/H1N1	PA	23	E	K	T0821	(b) (6)
A/H1N1	PA	23	E	K/R/E/G	T0833	
A/H1N1	PA	24	Y	H	T0833	
A/H1N1	PA	38	I	T	CP40563	
A/H1N1	PA	38	I	S/I	CP40563	
A/H1N1	PA	38	I	N	T0832	
A/H1N1	PA	38	I	F	T0821	
A/H1N1	PA	38	I	T	T0821	
A/H1N1	PA	38	I	T	T0821	
A/H1N1	PA	38	I	F	T0821	
A/H1N1	PA	38	I	T/I	T0833	
A/H1N1	PA	122	V	A	T0833	
A/H1N1	PA	259	(P)	L	CP40563	
A/H1N1	PA	259	(P)	L	1719T0834	
A/H1N1	PA	266	(R)	H/R	CP40563	
A/H1N1	PA	274	P	H	T0832	
A/H1N1	PA	283	L	M	1719T0834	
A/H1N1	PA	296	(S)	S/G	CP40563	
A/H1N1	PA	328	K	K/E	CP40563	
A/H1N1	PA	328	K	E	T0832	
A/H1N1	PA	344	G	E	T0832	
A/H1N1	PA	356	R	K	T0833	
A/H1N1	PA	363	T	I	CP40563	
A/H1N1	PA	365	Q	R	T0832	
A/H1N1	PA	376	P/L	P	T0832	
A/H1N1	PA	397	E	G	T0832	
A/H1N1	PA	401	R	K	T0832	
A/H1N1	PA	406	G/W	W	T0833	
A/H1N1	PA	419	(D)	D/G	CP40563	
A/H1N1	PA	445	Y	N	T0832	
A/H1N1	PA	521	(V)	A	CP40563	
A/H1N1	PA	595	I	I	1719T0834	
A/H1N1	PA	653	P	T/P	CP40563	
A/H1N1	PA	677	E	D	1719T0834	
A/H3N2	PA	23	E	K/E	CP40563	
A/H3N2	PA	23	E	K/E	CP40563	
A/H3N2	PA	23	E	K	T0832	
A/H3N2	PA	23	E	E/G	T0831	
A/H3N2	PA	23	E	K	T0831	
A/H3N2	PA	28	L	V	T0832	
A/H3N2	PA	34	K	E	T0832	
A/H3N2	PA	37	A	T	T0822	
A/H3N2	PA	37	A	T	T0831	
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	T/I	CP40563	
A/H3N2	PA	38	I	T/I	CP40563	
A/H3N2	PA	38	I	T/I	CP40563	
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	T/I	CP40563	
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	M	CP40563	

Type/ Subtype	Gene	Amino	BL Amino Acid[1]	Postbaseline Amino Acid	STUDYID	USUBJID
A/H3N2	PA	38	(I)	T	CP40563	(b) (6)
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	T	CP40563	
A/H3N2	PA	38	I	T/I	CP40563	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	M	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0832	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	I/M	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T/I	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	M	T0822	
A/H3N2	PA	38	I	T	T0822	
A/H3N2	PA	38	I	M	T0822	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T/I	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T/I	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	I/M	T0831	
A/H3N2	PA	38	I	T/I	T0831	
A/H3N2	PA	38	I	T	T0831	

Type/ Subtype	Gene	Amino	BL Amino Acid[1]	Postbaseline Amino Acid	STUDYID	USUBJID
A/H3N2	PA	38	I	T	T0831	(b) (6)
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T/T/I/M	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T/T/I/M	T0831	
A/H3N2	PA	38	I	T	T0831	
A/H3N2	PA	38	I	T/I	T0833	
A/H3N2	PA	38	I	M	T0833	
A/H3N2	PA	38	I	T/I	T0833	
A/H3N2	PA	38	I	M	T0833	
A/H3N2	PA	60	S	P	T0822	
A/H3N2	PA	68	P	L	T0832	
A/H3N2	PA	80	E	K/E	CP40563	
A/H3N2	PA	90	V	A	T0832	
A/H3N2	PA	98	N	T	T0832	
A/H3N2	PA	99	G	E/G	T0831	
A/H3N2	PA	160	D	G	T0832	
A/H3N2	PA	162	T	T/A	T0822	
A/H3N2	PA	183	A/V	A	T0831	
A/H3N2	PA	183	A	A/V	T0831	
A/H3N2	PA	186	G	D/G	T0831	
A/H3N2	PA	191	F	L	T0832	
A/H3N2	PA	192	H/R	H	T0832	
A/H3N2	PA	199	E	G	T0822	
A/H3N2	PA	201	I	T	T0831	
A/H3N2	PA	201	I	T	T0833	
A/H3N2	PA	203	E	K	T0832	
A/H3N2	PA	208	T	T/I	CP40563	
A/H3N2	PA	212	R	R/C	T0831	
A/H3N2	PA	221	P	L	T0832	
A/H3N2	PA	224	S	S/F	T0831	
A/H3N2	PA	231	A	A/V	T0831	
A/H3N2	PA	241	C	C/F	T0831	
A/H3N2	PA	253	V	M	1719T0834	
A/H3N2	PA	271	P	P/S	T0831	
A/H3N2	PA	294	D	N	T0832	
A/H3N2	PA	295	P	L	T0832	
A/H3N2	PA	299	G/R	G	T0831	
A/H3N2	PA	309	K/R	R	T0832	
A/H3N2	PA	315	F	I	T0832	
A/H3N2	PA	316	G	R/G	T0831	
A/H3N2	PA	357	T	T/A	T0831	
A/H3N2	PA	379	M	M	1719T0834	

Type/ Subtype	Gene	Amino	BL Amino Acid[1]	Postbaseline Amino Acid	STUDYID	USUBJID
A/H3N2	PA	385	R	K/R	T0831	(b) (6)
A/H3N2	PA	395	S	N	T0832	
A/H3N2	PA	395	S	N/S	T0831	
A/H3N2	PA	397	E	K	T0832	
A/H3N2	PA	399	E	K/E	CP40563	
A/H3N2	PA	405	S	S/C	T0831	
A/H3N2	PA	412	N	D	T0822	
A/H3N2	PA	417	L	P	T0832	
A/H3N2	PA	421	V	T	T0831	
A/H3N2	PA	482	I	L	T0831	
A/H3N2	PA	493	E	E/G	T0831	
A/H3N2	PA	517	V	A/V	T0822	
A/H3N2	PA	526	S	S/F	T0822	
A/H3N2	PA	545	I	I/M	T0831	
A/H3N2	PA	561	M	I	T0831	
A/H3N2	PA	602	I	V	T0831	
A/H3N2	PA	610	K/E	E	T0832	
A/H3N2	PA	623	E	K/E	T0822	
A/H3N2	PA	623	E	E/G	T0831	
A/H3N2	PA	628	I/V	V	T0832	
A/H3N2	PA	630	E	K/E	T0831	
A/H3N2	PA	632	P	S	T0822	
A/H3N2	PA	649	L	M/L	T0831	
A/H3N2	PA	668	V	I/V	T0831	
A/H3N2	PA	690	I	V	CP40563	
B	PA	7	R	K	T0832	
B	PA	25	S	G	T0832	
B	PA	38	I	T	T0832	
B	PA	38	I	T/I	T0831	
B	PA	60	A	V	T0831	
B	PA	62	T	K	T0832	
B	PA	112	D/N	D	T0831	
B	PA	201	D	G	T0832	
B	PA	201	D	E	T0832	
B	PA	289	L	V	T0832	
B	PA	326	V	A	T0832	
B	PA	328	S	G	T0832	
B	PA	329	E	K	T0832	
B	PA	332	N	K	T0832	
B	PA	333	E	G	T0832	
B	PA	333	E	K/E	T0831	
B	PA	354	N	N/K	T0833	
B	PA	361	Y	H/Y	T0831	
B	PA	365	A	S	T0832	
B	PA	412	T/I	T	T0832	
B	PA	415	S	N	T0832	
B	PA	415	S	G	T0832	
B	PA	445	E	G	T0832	
B	PA	454	V	I	T0832	
B	PA	548	G	J	T0821	
B	PA	578	L	I/L	T0833	
B	PA	619	T	I	T0832	
B	PA	680	E	K/E	T0833	
B	PA	715	K	Q	T0832	

Type/ Subtype	Gene	Amino	BL Amino Acid[1]	Postbaseline Amino Acid	STUDYID	USUBJID
A/H1N1	PB1	92	M	T/M	T0821	(b) (6)
A/H1N1	PB1	418	V	I/V	T0821	
A/H3N2	PB1	205	I	I/M	T0822	
A/H3N2	PB1	231	A	A/V	T0831	
A/H3N2	PB1	250	G	E/G	T0822	
A/H3N2	PB1	290	M	T/M	T0822	
A/H3N2	PB1	517	I	I/M	T0831	
B	PB1	34	T/A	T	T0833	
A/H1N1	PB2	221	A	A/T	T0821	
A/H1N1	PB2	310	I	M/I	T0821	
A/H1N1	PB2	333	T	T/I	T0821	
A/H3N2	PB2	60	D/G	D/G	T0822	
A/H3N2	PB2	101	R	G	T0831	
A/H3N2	PB2	105	V	M	T0822	
A/H3N2	PB2	171	E	K/E	T0822	
A/H3N2	PB2	197	K	R	T0822	
A/H3N2	PB2	202	L	M	T0831	
A/H3N2	PB2	209	R	K/R	T0831	
A/H3N2	PB2	353	R	K/R	T0822	
A/H3N2	PB2	385	I	I/V	T0822	
A/H3N2	PB2	475	M	I	T0831	
A/H3N2	PB2	585	P	L	T0831	

Source: FDA Virology analysis
[1] Consensus, if BL not available
Abbreviations: BL, baseline; EC_{50}, half maximal effective concentration; PA, polymerase acidic

Table 105. Change From Baseline at Day 2 (24 Hours Post-Treatment Initiation) in Viral RNA Shedding in Pediatric Trials

Virus Type/Subtype	CP40563		T0822	T0833
Day 2 Viral RNA Shedding Change From Baseline (Subjects positive at baseline)	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
All				
N	70	39	104	33
Median (log_{10} copies/mL)	-1.802	-1.084	-1.98	-1.6
95% CI lower limit	-2.209	-1.499	-2.23	-2.1
95% CI upper limit	-1.526	-0.7689	-1.6	-1.15
P-value baloxavir vs. oseltamivir	0.0008			
A/H1N1				
N	17	9	2	11
Median (log_{10} copies /mL)	-1.903	-0.8534	-2.865	-1.83
95% CI lower limit	-2.447	-1.472	-3.23	-2.74
95% CI upper limit	-1.625	0.729	-2.5	-0.71
P-value baloxavir vs. oseltamivir	0.0029			
A/H3N2				
N	45	28	87	9
Median (log_{10} copies /mL)	-2.018	-1.121	-2.03	-2.17
95% CI lower limit	-2.312	-1.582	-2.3	-3.06
95% CI upper limit	-1.445	-0.9074	-1.73	-1.15
P-value baloxavir vs. oseltamivir	0.0113			

Virus Type/Subtype	CP40563		T0822	T0833
Day 2 Viral RNA Shedding Change From Baseline (Subjects positive at baseline)	Baloxavir	Oseltamivir	Baloxavir	Baloxavir
B				
N	4	2	8	12
Median (log_{10} copies /mL)	-0.8164	0.008528	-0.64	-1.2
95% CI lower limit	-2.28	-0.3219	-2.12	-2
95% CI upper limit	3.388	0.3389	0.71	-0.29
P-value baloxavir vs. oseltamivir	0.5333			
P-value vs. type A	0.0562	0.081	0.006	0.0172

Source: FDA Virology analysis
Analyses includes all subjects in the ITTI set who were viral RNA-positive at baseline.
All p-values are based on a Mann-Whitney test implemented in Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA).
Abbreviations: CI, confidence interval; ITTI, intent-to-treat-infected

Table 106. Time to Alleviation of Symptoms (Hours) by Weight and RAS (Treatment-Emergent Resistance-Associated Substitution) Status: Pooled Data From Baloxavir Marboxil-Treated Subjects in Pediatric Trials T0822, T0833, and CP40563

	<20 kg		≥20 kg	
Parameter	No RAS	RAS	No RAS	RAS
Number of subjects	47	21	76	17
Time to alleviation of symptoms (hours)				
Minimum	12.25	7.85	4.667	29.62
25% Percentile	28.45	37.8	32.85	56.78
Median	58.93	116.9	77.71	91
75% Percentile	130.8	198.7	138.7	155.2
Maximum	345.6	321.1	361.6	232.5
Range	333.4	313.3	356.9	202.9
95% CI of median				
Actual confidence level	96.00%	97.34%	97.14%	95.10%
Lower confidence limit	37.83	38.23	53.6	69.62
Upper confidence limit	86.87	198.1	102.5	144.4
Mean	79.89	128.3	98.06	105.8
Std. deviation	67.74	95.42	80.81	62.06
Std. error of Mean	9.881	20.82	9.27	15.05

Source: FDA Virology analysis
Descriptive statistics generated using Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA)
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution

Table 107. Time to Sustained Virus Negativity (Hours) by Weight and RAS (Treatment-Emergent Resistance-Associated Substitution) Status: Pooled Data From Baloxavir Marboxil-Treated Subjects in Pediatric Trials T0822, T0833, and CP40563

	<20 kg		≥20 kg	
Parameter	**No RAS**	**RAS**	**No RAS**	**RAS**
Number of subjects	47	21	76	18
Time to sustained virus negativity (hours)				
Minimum	24	24	24	24
25% Percentile	24	168	24	42
Median	120	240	24	144
75% Percentile	192	264	90	198
Maximum	264	264	264	264
Range	240	240	240	240
95% CI of median				
Actual confidence level	96.00%	97.34%	97.14%	96.91%
Lower confidence limit	72	168	24	48
Upper confidence limit	168	264	24	192
Mean	121.5	206.9	58.42	132
Std. deviation	77.27	71.79	58.04	79.07
Std. error of mean	11.27	15.67	6.658	18.64

Source: FDA Virology analysis
Descriptive statistics generated using Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA)
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution

Table 108. Time to Alleviation of Symptoms (Hours) by Age and RAS (Treatment-Emergent Resistance-Associated Substitution) Status: Pooled Data From Baloxavir Marboxil-Treated Subjects in Pediatric Trials T0822, T0833, and CP40563

	<5 years		≥5 years	
Parameter	**No RAS**	**RAS**	**No RAS**	**RAS**
Number of subjects	33	19	90	19
Time to alleviaton of symptoms (hours)				
Minimum	12.25	7.85	4.667	29.62
25% Percentile	28.61	37.37	29.32	43.95
Median	68.38	116.9	68.68	87.13
75% Percentile	133.7	199.3	138.3	144.4
Maximum	345.6	321.1	361.6	232.5
Range	333.4	313.3	356.9	202.9
95% CI of median				
Actual confidence level	96.49%	98.08%	95.54%	98.08%
Lower confidence limit	37.83	37.37	49.23	43.95
Upper confidence limit	115.9	199.3	92.3	144.4
Mean	88.21	133.5	92.18	103
Std. deviation	73.7	98.21	77.62	60.55
Std. error of mean	12.83	22.53	8.182	13.89

Source: FDA Virology analysis
Descriptive statistics generated using Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA)
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution

Table 109. Time to Sustained Virus Negativity (Hours) by Age and RAS (Treatment-Emergent Resistance-Associated Substitution) Status: Pooled Data From Baloxavir Marboxil-Treated Subjects in Pediatric Trials T0822, T0833, and CP40563

	<5 years		≥5years	
Parameter	**No RAS**	**RAS**	**No RAS**	**RAS**
Number of values	33	19	90	20
Time to sustained virus negativity (hours)				
Minimum	24	24	24	24
25% Percentile	48	168	24	84
Median	168	240	24	168
75% Percentile	192	264	96	216
Maximum	264	264	264	264
Range	240	240	240	240
95% CI of median				
Actual confidence level	96.49%	98.08%	95.54%	95.86%
Lower confidence limit	120	168	24	120
Upper confidence limit	192	264	48	216
Mean	138.9	197.1	61.87	148.8
Std. deviation	78.86	85.63	58.12	75.73
Std. error of mean	13.73	19.65	6.126	16.93

Source: FDA Virology analysis
Descriptive statistics generated using Prism (GraphPad Prism version 8.00 for Windows, GraphPad Software, La Jolla California USA)
Abbreviations: CI, confidence interval; RAS, resistance-associated substitution

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The clinical investigators Drs. Baker, Yudovich, Matsuda, and Ono were inspected in support of this application. Based on the results of these inspections, the studies (Protocols CP40563 and 1719T0834) appear to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indications.

For Study 1719T0834, which was solely conducted in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) shared with OSI brief inspection report (b) (4) Based on PMDA's inspection reports, no issues of significant concern were found.

Office of Science Investigations Inspection Reports

(1) Site #315110 for CP40563, Jeffrey Baker, MD, Idaho Falls, ID
Inspection dates: May 26–June 3, 2020

At this site for Protocol CP40563, 19 subjects were screened and 16 were enrolled, all of whom completed the study. The inspection reviewed the subject-specific records for the 16 enrolled subjects. These records included, but were not limited to, study eligibility, dosing, primary efficacy endpoint data (TTAS), subject disposition, adverse events, concomitant medications, and protocol deviations. Regulatory records reviewed included FDA Form 1572, financial disclosures, Independent Review Board (IRB) approvals, delegation logs, training records, drug accountability records, and monitoring reports. The primary efficacy endpoint data in the

subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted. It was observed that an adverse event of "kidney infection" and the concomitant medication sulfatrim (as reported by the subject's mother) were not recorded in the case report form or reported to the sponsor. Specifically, according to the medical chart, Subject # (b) (6) (in baloxavir marboxil treatment group) had a "kidney infection" and took sulfatrim from (b) (6).

The OSI reviewers recommends that the review division consider this under reported adverse event when evaluating the safety profile of the study drug. Dr. Baker acknowledged that the reviewers missed reporting this adverse event and stated that they have already implemented quality assurance training as a preventive action.

(2) Site #317919 for CP40563, Martin Yudovich, M.D., Houston, Tx
Bioavailability (BA)/bioequivalence (BE) inspection dates: June 8–18, 2020
OP13 assessment dates: July 1–3, 2020

At this site for Protocol CP40563, a total of 35 subjects were screened and 30 were enrolled—all of whom completed the study. Following the selection of this site for GCP inspections, a BA/BE inspection was conducted for this protocol that reviewed the study records for all 35 screened subjects. These records included, but were not limited to, informed consent, e-Diaries, eligibility, adverse events, the control and receipt of the investigational study drugs, and documentation of the dosing of the active control drug (oseltamivir) and the study drug. Therefore, the decision was made to conduct an investigation (in lieu of a full CI GCP site inspection) for this protocol at this site with the focus on the efficacy and safety data. The assessment reviewed 15 enrolled subjects for the primary efficacy endpoint data and safety data. The primary efficacy endpoint data were verified against the data line listings provided by the sponsor and no discrepancies were noted. There was no evidence of underreporting of adverse events.

(3) Site #PMA for T0834, Tadashi Matsuda, M.D., Kuwana City, Japan
Remote regulatory assessment dates: July 13–21, 2020

A remote investigation (in lieu of a full CI GCP site inspection) was conducted for this site in Japan due to travel restrictions during the COVID-19 pandemic. Video conferencing via Webex, document sharing via an online platform (box.com), and read-only access to the online trial master file were utilized for the assessment. At this site for Protocol 1719T0834, 19 subjects were screened, all of whom were enrolled and completed the study.

This investigation reviewed the records for all 19 screened subjects. These subject-specific records included, but were not limited to, screening and study eligibility, subject diaries, primary efficacy data, laboratory reports, adverse events, concomitant medications, protocol deviations, and individual drug dispensing logs. Regulatory documents reviewed included FDA Form 1572, financial disclosures, site visit log, screening and enrollment log, delegation log, correspondences between sponsor and Dr. Matsuda, and monitoring visit reports. The primary efficacy endpoint data were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

(4) Site #PGB for T0834, Ryuta Ono, M.D., Kawasaki City, Japan
Remote regulatory assessment dates: July 21–31, 2020 and August 3–4, 2020

A remote investigation (in lieu of a full CI GCP site inspection) was conducted for this site in Japan due to travel restrictions during the COVID-19 pandemic. Video conferencing via Webex, document sharing via an online platform (box.com), and read-only access to the online trial master file were utilized for the assessment. At this site for Protocol 1719T0834, 37 subjects were screened and 36 were enrolled, all of whom completed the study.

This investigation reviewed the records for all 36 enrolled subjects. These subject-specific records included, but were not limited to, screening and study eligibility, subject diary, primary efficacy data, adverse events, concomitant medications, protocol deviations, and individual drug dispensing logs. Regulatory documents reviewed included FDA 1572, financial disclosures, IRB approvals, delegation log, randomization/dosing, IP accountability/reconciliation, training records/ certifications, and laboratory accreditation.

The primary efficacy endpoint data in the subjects' source documents (raw data) were verified against the data line listings provided by the sponsor, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

Review of Inspection Reports by Pharmaceuticals and Medical Devices Agency in Japan

(b) (4)

(b) (4)

21. Labeling Summary of Considerations and Key Additional Information

Overview of Major Labeling Changes:

- Information highlighted below are significant changes made to the prescribing information from the Applicant's proposed label submitted on January 23, 2020 for and last approved labeling dated October 16, 2019 with the to-be-approved USPI.
- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the full Prescribing Information.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

(b) (4)

1.2 Post-Exposure Prophylaxis of Influenza

The following indication was added, "XOFLUZA is indicated for post-exposure prophylaxis of influenza in persons 12 years of age and older following contact with an individual who has influenza *[see Clinical Studies (14.3)]*." (b) (4)

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

Two available dosage forms for XOFLUZA was outlined with instructions to take XOFLUZA as soon as possible after influenza symptom onset or exposure to influenza.

2.2 Recommended Dosage

Dosage recommendation was split for patients 12 years of age or older based on the dosage formulation. Table 1 outlines dosing using tablet formulation and Table 2 outlines dosing using oral suspension formulation. (b) (4)

2.3 Preparation of XOFLUZA for Oral Suspension by Healthcare Provider

Additional detail on how to prepare and administer XOFLUZA for oral suspension was added with important dosing information for healthcare provider to mitigate any potential medication error. Refer to Section 7.7.3 for additional details.

3 DOSAGE FORMS AND STRENGTHS

Description of XOFLUZA for Oral Suspension was added.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Summary statement of overall safety profile of XOFLUZA "based on data from 1,943 subjects 12 years of age and older in 4 controlled clinical trials" was added along with brief summary of Trials 1-4. Safety summary of post-exposure prophylaxis of influenza in adult and adolescents subjects 12 years of age and older was added. Refer to Section 7.6 for additional details.

Post-Exposure Prophylaxis of Influenza

The safety of XOFLUZA in adult and adolescent subjects is based on data from one placebo-controlled clinical trial in which 374 subjects, of which 303 were adult and adolescent subjects ≥ 12 years received XOFLUZA: Eight (3%) subjects were adults 65 years of age or older, and 12 (4%) subjects were adolescents 12 to 17 years of age. The most frequently reported AE in the total study population was nasopharyngitis which occurred in 6% of subjects who received XOFLUZA and 7% on placebo *[see Clinical Studies (14.3)]*.

6.2 Postmarketing Experience

The following edits were made to the postmarketing experience section. Refer to Section 7.3 for additional details.

Immune System Disorders: Anaphylactic reactions, anaphylactic shock, anaphylactoid reactions, hypersensitivity reactions, angioedema (swelling of face, eyelids, tongue and lips).

Skin and Subcutaneous Tissue Disorders: Rash, urticaria, erythema multiforme

Gastrointestinal Disorders: Vomiting, hematochezia, melena, colitis

Psychiatric Disorders: Delirium, abnormal behavior, hallucinations

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Treatment of Acute Uncomplicated Influenza in Pediatric Subjects

Additional details of Trials 2 and 3 for the treatment of acute uncomplicated influenza in pediatric subjects 12 years of age and older were added with reference to subsection 12.4 Microbiology for information on baloxavir resistance in subjects less than 12 years of age.

Post-Exposure Prophylaxis of Influenza in Pediatric Subjects

Description of Trial 4, which studied safety and effectiveness of XOFLUZA for pos-exposure prophylaxis in adolescents (12 years to <18 years) was added which showed, (b) (4)

(b) (4). The adverse events reported in adolescent subjects were similar to those reported in adults in the same trial." Refer to Section 8.3 for additional details.

11 DESCRPTION

Description of new XOFLUZA for oral suspension was added.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Baloxavir pharmacokinetic parameters for healthy adults and adolescents were converted from text to tabular form and editorial changes were made elsewhere in this section.

Polyvalent cation percent decrease based on animal studies in monkeys was added.

12.4 Microbiology

The following edits were made under Resistance in Clinical Studies. Refer to Section 5, 7.7.2, 19.1.4, and 19.1.6 for additional details.

In adult and adolescent subjects who had a confirmed influenza virus infection, the overall frequencies of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir were 4.5% (6/134), 10.9% (53/485), and 0.9% (2/224) in influenza A/H1N1, A/H3N2, and B virus infections, respectively, in pooled data from Trials 1, 2, and 3 *[see Clinical Studies (14)]*. In Trial 4, of 374 subjects, including 71 subjects <12 years of age, who received XOFLUZA post-exposure prophylaxis, 49 were viral RNA-positive post-baseline, including 31 subjects who were evaluated for resistance. Of these 31 subjects, influenza virus with substitutions associated with reduced susceptibility to baloxavir was identified in 7/7 subjects who developed clinical influenza (as described for the primary endpoint) and 8/24 other subjects evaluated who did not meet the primary endpoint definition for clinical influenza *[see Clinical Studies (14)]*. Selection of influenza viruses with reduced susceptibility to baloxavir has occurred at higher frequencies in pediatric subjects, and such viruses were detected with overall frequencies of 20% (4/20), 27.9% (34/122), and 0% (0/21) in influenza A/H1N1, A/H3N2, and B virus infections, respectively, in pooled data from 3 pediatric treatment trials in subjects <12 years of age.

14 CLINICAL STUDIES

14.3 Post-Exposure Prophylaxis of Influenza

Description of Trial 4 and efficacy results were added. Refer to Section 6.2.2 for additional details.

14.3 Post-Exposure Prophylaxis of Influenza

Trial 4 was a phase 3, randomized, double-blind, multicenter, placebo-controlled study designed to evaluate the efficacy of a single oral dose of XOFLUZA compared with placebo in the prevention of influenza in subjects who were household contacts of influenza-infected patients in Japan. Influenza-infected index patients were required to have onset of symptoms for ≤ 48 hours, and subjects (household contacts) were required to have lived with the influenza-infected index patient for ≥ 48 hours.

A total of 607 subjects (XOFLUZA N=303, placebo N=304) ≥ 12 years of age were randomized and received a single oral dose of XOFLUZA according to body weight and age, or placebo, on day 1. Subjects received 40 mg or 80 mg of XOFLUZA according to body weight (40 to < 80 kg or ≥ 80 kg, respectively). The primary efficacy endpoint was the proportion of household subjects who were infected with influenza virus and presented with fever and at least one respiratory symptom from day 1 to day 10. Influenza was confirmed by reverse transcription polymerase chain reaction (RT-PCR), fever was defined as a body temperature (axillary) ≥ 37.5°C, and respiratory symptoms were defined as having a symptom of "cough" or "nasal discharge/nasal congestion" with a severity of moderate or severe as assessed by the subject.

The mean age of subjects that were ≥ 12 years of age in Trial 4 was 40 years; 33 (5%) were ≥ 12 to < 18 years of age, 551 (91%) were ≥ 18 to < 65 years of age, and 23 (4%) were ≥ 65 years of age. All subjects were Asian, 84% were female, and 16% were male. The predominant influenza virus strains in the index patients of this study were the A/H3N2 subtype (49%) and the A/H1N1 subtype (46%), followed by the B subtype (1%).

In subjects that were ≥12 years of age, there was a statistically significant reduction in the proportion of household contacts (subjects) with laboratory-confirmed clinical influenza from 13% in the placebo group to 1% in the XOFLUZA group (see Table 11).

Table 11. Proportion of Household Contacts (Subjects 12 Years of Age and Older) Infected With Influenza Virus With Fever and at Least One Respiratory Symptom (Trial 4)

XOFLUZA % (95% CI[a]) N=303	Placebo % (95% CI[a]) N=304
1% (0, 3)	13% (10, 17)

[a] CI: Confidence interval
[b] XOFLUZA treatment resulted in a significant reduction in the risk ratio of patients who were infected with influenza virus and presented with fever compared to placebo using modified Poisson regression for a binary response (p-value: < 0.0001).

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied, handling and storage conditions for XOFLUZA for oral suspension was added.

17 PATIENT COUNSELING INFORMATION

Important dosing information for tablet and for oral suspension was added with cross reference to subsections 2.2 and 2.3 for additional detail.

22. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) are being issued as PREA commitments and to further characterize baloxavir resistance-associated substitutions observed in pediatric trials for their independent contribution to reduced baloxavir susceptibility.

The following PMRs were agreed upon with the Applicant:

- PMR 3961-1: Submit the clinical study reports including the pharmacokinetic/ pharmacodynamic modeling data and the supporting PK, safety, and efficacy data from all

the relevant studies in adult and pediatric patients to extrapolate efficacy of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age for the prevention of influenza as postexposure prophylaxis in household contacts of an index case. Include characterization of baloxavir-resistant substitutions including supporting datasets.

- Final Protocol Submission: Submitted
- Study Completion: 09/2021
- Final Report Submission: 12/2021

- 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.
  - Final Protocol Submission: Submitted
  - Study Completion: Completed
  - Final Report Submission: 12/2021

- PMR (b) (4): Evaluate the impact of the following substitutions on the susceptibility of influenza virus to baloxavir in cell culture: PA substitutions R269I, V330I, K328E, and T363I in A/H1N1 virus and I554V in A/H3N2 virus.
  - Final Protocol Submission: 12/2020
  - Study Completion: 10/2021
  - Final Report Submission: 12/2021

- 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
  - Study Completion: Completed
  - Final Report Submission: 12/2021

23. Financial Disclosure

Table 110. Covered Clinical Studies: CP40563 and T0834

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 633		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 633		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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Guidances for Industry

Guidance for Industry *Influenza: Developing Drugs for Treatment and/or Prophylaxis* (April 2011)

Guidance for Clinical Investigators, Industry, and FDA Staff *Financial Disclosure by Clinical Investigators* (February 2013)

Guidance for Industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* (January 2006)

Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

Guidance for Industry *Bioanalytical Method Validation* (May 2018)

25. Review Team

Table 111. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Christine Kim, PharmD, RAC-US
Nonclinical Reviewer (DPT-ID)	Deacqunita Diggs, PhD
Nonclinical Team Leader (DPT-ID)	Hanan Ghantous, PhD, DABT
Clinical Virology Reviewer	William Ince, PhD
Clinical Virology Team Leader	Julian O'Rear, PhD
Office of Clinical Pharmacology Reviewer	Hazem Hassan, PhD
Office of Clinical Pharmacology Team Leader	Mario Sampson, PharmD
Clinical Reviewer	Melisse Baylor, MD
Clinical Team Leader	Mary Singer, MD, PhD
Statistical Reviewer	Fraser Smith, PhD
Statistical Team Leader	Thamban Valappil, PhD
Cross-Disciplinary Team Leader	Mary Singer, MD, PhD
Division Director (DPT-ID)	Hanan Ghantous, PhD, DABT
Division Director (OCP/DIDP)	Kellie Reynolds, PharmD
Division Director (OB/DVIV)	Dionne Price, PharmD
Division Director (DAV)	Debra Birnkrant, MD
Office Director (or designated signatory authority)	Debra Birnkrant, MD

Abbreviations: DAV, Division of Antivirals; DPT-ID, Division of Pharm/Tox for Infectious Diseases; OCP, Office of Clinical Pharmacology; DIDP, Division of Infectious Disease Pharmacology; OB, Office of Biostatistics; DBIV, Division of Biometrics IV; OID, Office of Infectious Diseases

Table 112. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Thomas Oliver, PhD Wailin (Sheena) Wang, PhD Erika Englund, PhD Karina Zuck, PhD Ali Al Hakim, PhD Abdollah Koolivand, PhD Bo Jiang, PhD Daniel Schu, PhD Erika Pfeiler, PhD Mathew John, PhD Elsbeth Chikhale, PhD Shamika Brooks, PharmD Anh-Thy Ly, PharmD
OPDP	Nima Ossareh, PharmD, RAC Sam Skariah, PharmD, RAC
OSI	Jenn Sellers, MD, PhD Philip Kronstein, MD
OSE/DMEPA	Valerie Vaughan, PharmD Sevan Kolejian, PharmD, MBA, BCPPS
DMPP	Ruth Mayrosh, PharmD Barbara Fuller, RN, MSN, CWOCN LaShawn Griffiths, MSHS-PH, BSN, RN
Clinical Data Scientists	Anne Bunner, PhD Jinzhong Liu, PhD (OND TL)
Medical Editors	Katharine Bradley Elizabeth Hayes

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis;; DMPP, Division of Medical Policy Programs; OND, Office of New Drugs; TL, team leader

Table 113. Signatures of Reviewers

See next page.

Table 113. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Melisse Baylor, MD	OID/DAV	☒ Authored Section(s): 1, 2, 3, 4, 6.3, 7.1-7.6, 7.7.3, 8.1-8.3, 10, 11, 17, 20, 23 ☒ Approved
Primary Reviewer	**Signature:** Melisse S. Baylor -S Digitally signed by Melisse S. Baylor -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300143768, cn=Melisse S. Baylor -S Date: 2020.11.18 15:50:44 -05'00'		
Clinical	Mary Singer, MD, PhD	OID/DAV	☒ Authored Section(s): (contributed to) 1, 2, 3, 4, 6, 7, 10, 11 ☒ Approved 1, 2, 3, 4, 6, 7, 10, 11, 12, 15, 16, 16, 17, 19, 20, 21, 23
Cross-Disciplinary Team Lead	**Signature:** Mary E. Singer -S Digitally signed by Mary E. Singer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mary E. Singer -S, 0.9.2342.19200300.100.1.1=1300225942 Date: 2020.11.18 12:04:06 -05'00'		
Pharmacology/Toxicology	Deacqunita Diggs, PhD	OID/DPT-ID	☒ Authored Section(s): 7.1, 8.4, 13.1, 13.2 ☒ Approved
Primary Reviewer	**Signature:** Deacqunita L. Diggs -S Digitally signed by Deacqunita L. Diggs -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002226049, cn=Deacqunita L. Diggs -S Date: 2020.11.18 12:12:59 -05'00'		
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OID/DPT-ID	☐ Authored Section(s): ☒ Approved
Division Director	**Signature:** Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300169484, cn=Hanan N. Ghantous -S Date: 2020.11.18 15:02:13 -05'00'		
Clinical Virology	William Ince, PhD	OID/DAV	☒ Authored Section(s): 6.3, 7.7.1, 7.7.2, 18, 19 ☒ Approved
Primary Reviewer	**Signature:** William L. Ince -S Digitally signed by William L. Ince -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000523497, cn=William L. Ince -S Date: 2020.11.18 12:55:26 -05'00'		
Clinical Virology	Jules O'Rear, PhD	OID/DAV	☐ Authored Section(s): ☒ Approved
Team Leader	**Signature:** Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2020.11.18 13:28:10 -05'00'		
Clinical Pharmacology	Justin Earp, PhD	OCP/DPM	☒ Authored Section(s): 14.2 ☒ Approved
Primary Reviewer	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2020.11.18 16:05:24 -05'00'		

Clinical Pharmacology	Mario Sampson, PharmD	OCP/DIDP	☒ Authored Section(s): 5, 6.1, 6.3.1, 8.1, 8.2, 14.1 ☒ Approved
Primary Reviewer/Team Leader	**Signature:** Mario Sampson -S Digitally signed by Mario Sampson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mario Sampson -S, 0.9.2342.19200300.100.1.1=2001365806 Date: 2020.11.18 11:23:08 -05'00'		
Statistical Primary Reviewer	Fraser Smith, PhD	OB/DBIV	☒ Authored Section(s): 6.2.1.3, 6.2.1.4, 6.2.2.3, 6.2.2.4, 6.3.2.1, 6.3.2.2, 6.3.2.3, 6.3.2.4, 6.3.3, 15.1, 15.2, 16.1, 16.2 ☒ Approved
Primary Reviewer	**Signature:** Fraser B. Smith -S Digitally signed by Fraser B. Smith -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300174109, cn=Fraser B. Smith -S Date: 2020.11.18 16:31:29 -05'00'		
Statistical	Thamban Valappil, PhD	OB/DBIV	☐ Authored Section(s): ☒ Approved
Team Leader	**Signature:** Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151694, cn=Thamban I. Valappil -S Date: 2020.11.20 07:35:58 -05'00'		
Statistical	Dionne Price, PhD	OB/DBIV	☐ Authored Section(s): ☒ Approved
Division Director	**Signature:**		
Cross-Disciplinary	Erika Englund, PhD	OPQ/ONDP	☒ Authored Section(s): 9 ☒ Approved
Team Leader	**Signature:** Erika E. Englund -S Digitally signed by Erika E. Englund -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000532787, cn=Erika E. Englund -S Date: 2020.11.19 14:49:05 -05'00'		
Regulatory	Christine Kim, PharmD	ORO/DRO-ID	☒ Authored Section(s): 12 ☒ Approved
Project Manager	**Signature:** Christine Kim -S Digitally signed by Christine Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Christine Kim -S, 0.9.2342.19200300.100.1.1=2001518469 Date: 2020.11.20 12:04:20 -05'00'		
Cross-Disciplinary	Stacey Min, PharmD	OID/DAV	☒ Authored Section(s): 21 ☒ Approved
Associate Director of Labeling	**Signature:** Stacey Min -S Digitally signed by Stacey Min -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacey Min -S, 0.9.2342.19200300.100.1.1=2000365089 Date: 2020.11.18 11:11:04 -05'00'		
Cross-Disciplinary	Jeffrey Murray, MD, MPH	OID/DAV	☐ Authored Section(s): ☒ Approved
Deputy Director	**Signature:** Jeffrey S. Murray -S Digitally signed by Jeffrey S. Murray -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300079703, cn=Jeffrey S. Murray -S Date: 2020.11.20 08:13:38 -05'00'		
Cross-Disciplinary	Debra Birnkrant, MD	OID/DAV	☐ Authored Section(s): ☒ Approved
Division Director	**Signature:** Debra B. Birnkrant -S Digitally signed by Debra B. Birnkrant -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300049410, cn=Debra B. Birnkrant -S Date: 2020.11.20 08:10:52 -05'00'		

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