CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	210854
Priority or Standard	Priority
Submit Date(s)	April 24, 2018
Received Date(s)	April 24, 2018
PDUFA Goal Date	October 24, 2018
Division/Office	Division of Antiviral Products / Office of Antimicrobial Products
Reviewer Name(s)	Melisse Baylor, M.D.
Review Completion Date	September 30, 2018
Established/Proper Name	Baloxavir marboxil
(Proposed) Trade Name	Xofluza™
Applicant	Shionogi, Incorporated
Dosage Form(s)	20 mg and 40 mg tablets
Applicant Proposed Dosing Regimen(s)	Single oral dose based on body weight Patient body weight of 40 kg to < 80 kg: 40 mg Patient body weight ≥ 80 kg: 80 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAVP	Division of Antiviral Products
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HCP	health care provider
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITTI	intent to treat infected
MedDRA	Medical Dictionary for Regulatory Activities
MDCK	Madin-Darby Canine Kidney
NAIs	neuraminidase inhibitors

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory drug
NP	nasopharyngeal
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RAT	rapid antigen testing
REMS	risk evaluation and mitigation strategy
RIDT	rapid influenza diagnostic test
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Baloxavir marboxil is a new molecular entity (NME) with a novel mechanism of action for the treatment of influenza. Baloxavir marboxil is a prodrug that is converted through hydrolysis to its active form, baloxavir. Baloxavir inhibits influenza virus polymerase acidic (PA) protein endonuclease resulting in inhibition of viral RNA synthesis.

The proposed indication for baloxavir marboxil is treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Baloxavir marboxil is administered as a single oral dose and is available as 20 mg and 40 mg tablets. The recommended dosage is 40 mg in patients who weigh less than 80 kilograms and 80 mg in patients who weigh 80 kilograms or more.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This Application contains substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of baloxavir marboxil for the treatment of acute uncomplicated influenza in patients 12 years of age or older who have been symptomatic for no more than 48 hours. This evidence comes from a Phase 3 trial, 1601T0831, and a Phase 2, dose-finding trial, 1518T0821. Trial 1601T0831 was a large, randomized, double-blind, placebo- and active (oseltamivir)-controlled trial in which baloxavir marboxil was robustly shown to reduce the time to alleviation of influenza symptoms compared to placebo. The median time to alleviation of symptoms was 54 hours in subjects who received baloxavir marboxil compared to 80 hours in those who received placebo. Trial 1518T0821 was a Phase 2, randomized, double-blind, placebo-controlled dose-finding trial. The median time to alleviation of influenza symptoms was statistically significantly shorter in all three baloxavir arms, regardless of dose, than in the placebo arm. At the to-be-marketed dose, the median time to alleviation of symptoms was 50 hours compared to 78 hours in the placebo arm. Substantial improvements in time to alleviation of the individual symptoms components comprising the primary endpoint were observed in both studies. Further support to the efficacy claim was provided by the observation of a consistent baloxavir marboxil effect across multiple secondary endpoints and among various subgroups defined by age, race, sex, and region.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Baloxavir marboxil inhibits influenza virus polymerase acidic protein endonuclease resulting in inhibition of viral RNA synthesis. This is a novel mechanism of action. Cross-resistance with other anti-influenza drugs is not anticipated, and baloxavir marboxil will retain activity against influenza strains with amino acid substitutions conferring resistance to the neuraminidase inhibitor class of anti-influenza agents. The proposed indication for baloxavir marboxil is the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

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 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. In an analysis of each influenza seasons from 2010 and 2016, the CDC estimated that there were between 140,000 and 170,000 hospitalizations each year for influenza. The 2017/ 2018 influenza season in the U.S. was a very severe influenza season, and the CDC estimated that there were approximately 900,000 influenza-related hospitalizations across the U.S. during the influenza season. The CDC monitors deaths due to influenza in children through the Influenza-Associated Pediatric Mortality System. During the 2017/ 2018 influenza season, 183 pediatric deaths due to laboratory-confirmed influenza were 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. Health care 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 between 2010 and 2016. The estimated number of deaths was considerably higher in the 2017/ 2018 influenza season (approximately 80,000 deaths).

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. When administered within 48 hours of illness onset, neuraminidase inhibitors (NAIs) can shorten the duration of acute uncomplicated influenza illness in previously healthy adults. 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. 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. In contrast, the level of resistance to neuraminidase inhibitors is uncommon, but isolated instances of increased rates of resistance among

influenza A virus isolates were reported in 2007.

Two pivotal trials were conducted to support the safety and efficacy of baloxavir marboxil. In the Phase 3 trial, 1601T0831, a robust treatment effect was observed in the baloxavir marboxil arm compared to placebo. The median time to alleviation of influenza symptoms was 54 hours in subjects who received a single oral dose of baloxavir marboxil compared to 80 hours in subjects who received placebo. The median time to alleviation of symptoms was identical in the baloxavir marboxil and oseltamivir arms. A treatment effect was also observed for the individual influenza symptoms comprising the primary endpoint and across the subgroups of age, race, sex, and geographic region. However, in the subset analysis, while efficacy was demonstrated against influenza A viruses, it was not demonstrated against influenza B virus. In the Phase 2, dose-finding trial, a statistically significant treatment effect was observed for all three baloxavir marboxil doses compared to placebo when the DAVP-recommended method of statistical analysis was used. The median time to alleviation of influenza symptoms in subjects who received the to-be-marketed dose of baloxavir marboxil was 50 hours compared to 78 hours in subjects who received placebo. In this study, a treatment effect against influenza B was observed. The median time to alleviation of symptoms for subjects with influenza B was 63 hours in the baloxavir marboxil arm and 83 hours in the placebo arm. Thus, efficacy results for treatment of influenza B-infected subjects with baloxavir marboxil were discordant across the two trials, and some questions remain regarding use of baloxavir marboxil for treatment of influenza type B. The study of, and the use of, anti-influenza agents is complicated because of the differences in circulating influenza strains from year-to-year. More than one single strain circulates each influenza season, but a single subtype of influenza A (H1N1 or H3N2) or a single lineage of influenza type B (Yamagata or Victoria) may be the predominant influenza strain circulating. It is difficult to predict the exact strains that will circulate each season, and anti-influenza drug efficacy may vary by strain. A person's response to influenza may also be affected by pre-existing immunity to the same strain or a similar strain. Therefore, some variation in efficacy is expected by season. The discordant influenza B response observed in the two clinical studies may be related to differences in the circulating influenza B strains in the two seasons. However, neither study was powered to analyze efficacy by influenza strain, so the influenza B results also may have been affected by the smaller number of subjects with influenza B. The concern regarding the discordant results for influenza B was discussed with the Applicant, and the Applicant submitted preliminary efficacy results for a second Phase 3 trial in subjects at high risk of influenza complications to the NDA. In this Phase 3 trial, the median time to alleviation of influenza B symptoms was shorter in the baloxavir marboxil arm (75 hours) compared to the placebo arm (102 hours). The review team discussed including a Limitation of Use in the Indications section of the package insert to address the discordant influenza B results. However, a more general revision was made to the Limitation of Usage, for the following reasons, 1) the discordant results may be explained by different circulating influenza B strains, 2) efficacy in subjects with influenza B was observed in a second Phase 3 study, and 3) limiting baloxavir marboxil use against influenza B may limit its use against any influenza strain since influenza typing/subtyping is not always performed in the clinical setting, where influenza is frequently diagnosed based on clinical signs and symptoms when influenza is

circulating in the community.

Adverse events were reported infrequently in subjects who received baloxavir marboxil. In the pivotal trials, only diarrhea (3%) and bronchitis (2%) were reported in ≥ 2% of subjects who received baloxavir marboxil. The only adverse drug reaction reported in more than 2% of subjects in the baloxavir marboxil arm was diarrhea (3%). Treatment-related diarrhea was reported in 5% of subjects in the placebo arm. In the 11 Phase 1 studies, one pediatric study in Japanese subjects, and two pivotal trials, there were only two serious adverse events in subjects who received baloxavir marboxil. One SAE was a case of viral meningitis in a subject who had not responded to treatment with baloxavir marboxil. The investigators did not rule out influenza as a cause of meningitis, and it is possible that baloxavir marboxil is related to the SAE due to lack of treatment effect. The other SAE was an inguinal hernia, which was clearly not related to baloxavir marboxil.

In conclusion, approval of baloxavir marboxil 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 is fully supported by the available evidence of efficacy and safety. Based on the robust treatment effect, the convenience of a single oral dose, and the low incidence of adverse events, this reviewer recommends baloxavir marboxil for traditional approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza is a respiratory virus that causes illness in 5% to 20% of the U.S. population each year. The CDC estimates that there are between 9.2 million and 35.6 million illnesses annually • Illness due to influenza virus is typically a self-limited respiratory viral infection that typically lasts for 3 to 7 days. • Influenza illness may be severe. CDC estimates that there are between 140,000 and 170,000 hospitalizations each year in the U.S. due to influenza. There are 12,000 to 56, 000 deaths due to influenza each year in the U.S.	Influenza infection is a common cause of respiratory disease and is a significant source of morbidity and mortality in the United States each year.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Two classes of anti-influenza antiviral drugs are marketed in US • Neuraminidase inhibitors: o Oseltamivir is the only orally available neuraminidase inhibitor, peramivir is available as a single intravenous dose, and zanamivir is only available as a powder for inhalation. o Use of zanamivir has been associated with bronchospasm. Zanamivir is not recommended for patients with underlying reactive airway disease. o Resistance to neuraminidase inhibitors has been observed, resistance to one neuraminidase inhibitor confers resistance to others (cross-resistance). • Adamantanes o Two are FDA approved: amantadine and rimantadine. o Both only active against influenza A. o Majority of circulating seasonal influenza A strains are resistant to adamantanes, so use is not recommended.	There is a need for additional antiviral drugs for treatment of influenza that are effective and available in an oral formulation. Amino acid substitutions conferring resistance have been reported with the available anti-influenza drugs. There remains an unmet need for antiviral drugs with a novel mechanism of action, which are active against influenza virus strains resistant to neuraminidase inhibitors and adamantanes.
Benefit	• The efficacy of baloxavir marboxil was demonstrated in two pivotal trials. The primary endpoint in both trials was the median time to alleviation of influenza symptoms. • In the Phase 3 trial, with 1,064 subjects in the ITTI population, the median time to alleviation of symptoms was 54 hours in the baloxavir marboxil arm compared to 80 hours in the placebo arm. • In the Phase 2, dose-finding trial, the median time to alleviation of influenza symptoms in subjects who received the to-be-marketed dose of baloxavir marboxil was 50 hours compared to 78 hours in subjects who received placebo.	A large Phase 3 trial and a smaller Phase 2 trial demonstrated that baloxavir marboxil in highly effective in the treatment of acute uncomplicated influenza in subjects 12 years of age and older who have been symptomatic for ≤ 48 hours. In a recently completed clinical trial in acute, uncomplicated influenza, subjects who were at high risk for influenza complications were

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In a subset analysis, discordant results for efficacy were observed across the phase 2 and 3 trials in subgroups of subjects with influenza type B, so there remains some uncertainty about use of baloxavir marboxil for influenza type B.	enrolled. Summary data from that trial, were submitted with this NDA. Efficacy of baloxavir marboxil against influenza B appears to have been demonstrated in this trial. The median time to alleviation of symptoms in subjects with influenza B who received baloxavir marboxil was 75 hours compared to 102 hours in subjects who received placebo.
Risk and Risk Management	• The safety database included 1,318 subjects exposed to baloxavir marboxil including 901 who received the to-be-marketed dose. • Diarrhea (3%) and bronchitis (2%) were the only adverse events reported in ≥ 2% of subjects who received baloxavir marboxil in pivotal trials. These adverse events were not reported more commonly than in the placebo arms. • There were two serious adverse events, viral meningitis and an inguinal hernia. Neither was judged by the investigator as related to baloxavir marboxil. • Only a very small number of Blacks and Latinos were exposed to baloxavir marboxil in the pivotal trials. We are therefore asking the Applicant to ensure that the postmarketing trials include a sufficient number of Blacks and Latinos to assess efficacy and safety. • Influenza viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were observed in the pivotal clinical trials. The incidence of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir was 11% in the Phase 3 trial and 2.7% in the Phase 2 trial.	The overall size of the safety database was adequate. There were no safety signals identified, and adverse drug reactions were uncommon. Additional safety data regarding baloxavir marboxil in Blacks and Latinos was requested. Routine pharmacovigilance is planned for postmarketing. The Applicant has agreed to provide an annual update on the emergence of resistance as a postmarketing commitment. This update will include information from clinical trials, national and international databases, and published literature.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
X	□	Clinical outcome assessment (COA) data, such as		
	X	□	Patient reported outcome (PRO) Influenza symptom score Measurement of body temperature Quality of life questionnaires	For 1601T0831: 2.7.3.3.1 2.7.3.3.2 CSR sections: 11.4.1.2.17, 11.4.1.3.3.1, 11.4.1.3.3.2 For 1518T032 2.7.3.3.3.1 2.7.3.3.3.6 CSR sections: 11.4.1.2.4 11.4.1.2.6 For Datasets: QS dataset ADQS dataset
		□	Observer reported outcome (ObsRO)	
	X	□	Clinician reported outcome (ClinRO) Influenza related complications	For 1601T0831: CSR 11.4.1.2.18 For Datasets: ADSL dataset
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were			

	considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Influenza viruses are RNA viruses from the family, Orthomyxoviridae. Influenza viruses are divided into types A and B on the basis of antigenic differences in two major external glycoproteins, hemagglutinin and neuraminidase. Influenza viruses typically circulate in the United States annually, most commonly from late fall through early spring. Since 1977, influenza A virus subtypes H1N1 and H3N2 and influenza B viruses have been in global circulation. All three influenza types circulate during each influenza season, but one type typically predominates in a single influenza season.

Influenza virus is spread person-to-person either by inhalation of droplets from a sneeze or cough of an infected individual, or by direct contact with a contaminated object or infected person, and subsequent transfer to mucous membranes. Influenza then replicates in the epithelial cells of the upper respiratory tract and spreads to adjacent cells. Although infected persons may already be shedding influenza virus, symptoms do not typically start until 48 hours after infection.

According to the Centers for Disease Control, 5 to 20% of the U.S. population is infected with influenza each year. Disease due to seasonal influenza can range from a self-limited febrile illness with respiratory symptoms (referred to as acute uncomplicated influenza) to serious disease with complications that can include hospitalization and death. The severity of influenza disease depends on the influenza virus strain; the host and the presence of extremes in age or of conditions that predispose to complications; and co-infection with other bacteria or viruses. Influenza onset is usually abrupt. The typical symptoms of influenza are fever, nasal congestion, sore throat, nonproductive cough, myalgia, headache, malaise, and/or chills. Gastrointestinal symptoms, such as abdominal pain, vomiting and diarrhea, may be observed in

children, but are generally uncommon in adults with influenza. Uncomplicated influenza usually resolves within 3 to 7 days. In some individuals, the cough from influenza may last up to two weeks. Complications of influenza infection include influenza virus pneumonia, myocarditis, or and rarely, central nervous system disease. More commonly, serious disease is due to pneumonia with bacterial superinfection or decompensation of underlying diseases, such as asthma, chronic lung disease, or heart disease. Clearly, influenza disease results in considerable morbidity and mortality in the U.S. each year.

2.2. Analysis of Current Treatment Options

Five licensed prescription influenza antiviral agents are available in the United States: oseltamivir, peramivir, zanamivir, amantadine, and rimantadine. Oseltamivir, zanamivir, and peramivir are related antiviral medications classified as neuraminidase inhibitors (NAIs). When administered within 48 hours of illness onset, the three approved NAIs can reduce the severity and shorten the duration of acute uncomplicated influenza illness in previously healthy adults. Oseltamivir and zanamivir are active against both influenza A and B viruses. Peramivir is active against influenza A viruses, but there were an insufficient number of subjects with influenza B in the pivotal trials of peramivir to determine efficacy against influenza B. The three NAIs differ in pharmacokinetics, recommended dosages, approved age group, route of administration, and safety profile. Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Peramivir is provided as a solution in a single dose vial and is administered intravenously.

The adamantanes are the other class of approved influenza antiviral agents and include amantadine and rimantadine. Adamantanes are thought to interact with the viral M2 ion channel protein. When administered within 48 hours of illness onset, amantadine and rimantadine can reduce the severity and shorten the duration of acute uncomplicated influenza A illness among healthy adults; however, they have no activity against influenza B virus. In recent years, widespread adamantine resistance among influenza A virus strains (H3N2, H1N1pdm09) has made this class of medications less useful clinically. Therefore, amantadine and rimantadine are not recommended by the Centers for Disease Control (CDC) for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

Table 1: Available Treatments for Influenza

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						
Neuraminidase Inhibitors						
Oseltamivir	Treatment of acute uncomplicated influenza Approved for use in patients ≥ 2 weeks of age	1999	Oral, twice daily for 5 days	In pivotal trials in adults, the time to alleviation of symptoms was 1.3 days shorter in the oseltamivir arm than in the placebo arm.	Rare cases of anaphylaxis and serious skin reactions reported. Nausea was observed in 10% of adults in trials. Vomiting was observed in 16% of pediatric subjects in trials. Dose adjustment recommended for patients with decreased creatinine clearance and end stage renal disease. Frequency of circulating resistant influenza strains varies by influenza season.	Efficacy has not been demonstrated in hospitalized, seriously ill patients with influenza.
Peramivir	Treatment of acute uncomplicated influenza Approved for use in patients ≥ 2 years of age	2014	Intravenous, single dose	In pivotal trials in adults, the time to alleviation of symptoms was 21 hours shorter in peramivir arm compared to placebo.	Rare cases of serious skin reactions and hypersensitivity (erythema multiforme, Stevens Johnson) reported.	Efficacy not demonstrated in study of hospitalized patients. Efficacy against influenza B has not been demonstrated, because of small numbers of subjects with influenza B in trials.
Zanamivir	Treatment of acute uncomplicated influenza	1999	Powder for disc inhalation, 10 mg (2	In pivotal trials in adults, the time to alleviation of symptoms	Serious cases of bronchospasm reported after use of zanamivir have	Patients with underlying lung disease are at increased risk of complications with influenza

	Approved for treatment in patients ≥ 7 years of age		inhalations) twice daily for 5 days	was 1 to 1.5 days shorter in subjects who received zanamivir compare to placebo.	been observed in patients with and without underlying lung disease. Not recommended for use in patients with reactive airway disease. Allergic reactions including oropharyngeal edema and anaphylaxis have been reported.	disease. However, zanamivir cannot be used in this population. Zanamivir is not indicated for patients younger than 7 years of age because of difficulties with drug inhalation. Large burden of influenza is in pediatric patients younger than 5 years of age.
Adamantines						
Amantadine	Treatment of signs and symptoms of infection caused by influenza A	1966	Oral, once or twice daily for 5 days	Reduction in febrile illness of 1 day	Overdose can be fatal due to anticholinergic effects. Has been associated with blurred vision, dizziness, and change in mental status (such as lightheadedness, hallucinations, confusion). Dose reduction recommended in patients with renal dysfunction.	Not recommended for use because of widespread resistance. Not active against influenza B.
Rimantadine	Treatment of illness caused by various strains of influenza A virus in adults	1994	Oral, twice daily for 7 days	Reduction in febrile illness of 1 day	Increased risk of seizures in patients with history of seizures. CNS side effects may be seen, particularly in elderly patients. GI side effects are common.	Not recommended for use because of widespread resistance. Not active against influenza B. Not indicated for treatment of pediatric patients.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Baloxavir marboxil is an NME that is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant submitted a pre-IND for baloxavir marboxil in the third quarter of 2015. The FDA provided written responses to the pre-IND meeting request on September 15, 2015. The Applicant opened the U.S. IND on January 12, 2016.

The Applicant met with DAVP on August 17, 2016 to discuss the results of the Phase 2, proof-of-concept study which was conducted in Japan and was not conducted under U.S. IND. The design of the Phase 3 trials in otherwise healthy subjects and in subjects at risk of influenza complications were discussed at that time. Both Phase 3 trials were initiated in the 2016/2017 Northern Hemisphere influenza season. The main topic of discussion was the proposed dose in Phase 3 trials. DAVP Clinical Pharmacology reviewers noted that there was a significant decrease in exposure in U.S. subjects compared to Japanese subjects, and that there were significant food effects on baloxavir plasma exposures. In addition, DAVP Virology reviewers stated that because of the decreased EC_{50} observed in nonclinical studies of influenza B, higher doses might be needed for the treatment of influenza B infections. The Applicant stated that they were considering weight-based dosing in Phase 3. Aside from concerns regarding the dose used, DAVP agreed to the study design for the Phase 3 trial in otherwise healthy subjects. There was also considerable discussion regarding the use of a rapid influenza diagnostic test (RIDT) for study entry. RIDTs are commonly used in Japan, but in the United States, the diagnosis of influenza is typically based on clinical symptoms. DAVP Virology reviewers stated their concern that use of the RIDT would result in under-enrollment of subjects with influenza B and that a population defined by RIDT results may not reflect a U.S. population. The Applicant agreed to use both RIDT and symptoms for diagnosis of influenza in Japanese subjects; all subjects regardless of region enrolled would have influenza confirmed by RT-PCR.

A Type C meeting was held on June 29, 2017 and a pre-NDA meeting was held on October 31, 2017 to discuss the Phase 3 development of baloxavir marboxil and the contents of the NDA. At this meeting, DAVP recommended that the Applicant submit the New Drug Application for baloxavir marboxil based on the results of the Phase 3 trial, 1601T8031, and the Phase 2 trial, 1518T0821. The preliminary results of the Phase 3 Trial, 1601T0831, were discussed. The

(b) (4)

DAVP stated that the specific indication would be a review issue. The size of the safety database was discussed. DAVP expressed concerns that the safety database would have fewer

than the 1,500 subjects receiving baloxavir marboxil at the to-be-marketed dose, as recommended. The Applicant stated that the because of exposure differences in U.S. and Japanese subjects and with the submission of high level safety data from the Phase 3 trial in subjects at risk of influenza complications in the safety update report (SUR), the safety database would include more than 1,400 subjects. DAVP agreed to the size of the safety database.

3.3. Foreign Regulatory Actions and Marketing History

Baloxavir marboxil was approved for use in Japan on February 23, 2018. Baloxavir marboxil is not approved in any other countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspection sites were chosen from the two pivotal trials, 1601T0831 and 1510T0821. Four sites were selected, 2 U.S. sites and 2 Japanese sites. These sites were chosen based on enrollment, number of pediatric subjects, efficacy outcome, number of premature study discontinuations, number of adverse events, and previous inspection history.

On inspection of the four study sites, no deficiencies were noted at two of the sites. At the other two sites, OSI inspectors observed minor deficiencies, but none that may have affected the study results. OSI reviewers determined that the studies were conducted adequately, and that the data from these sites were acceptable in support of the Application.

4.2. Product Quality

Baloxavir marboxil is supplied as a film coated, immediate release tablet for oral administration. The baloxavir marboxil tablet comes in two strengths, 20 mg and 40mmg. The tablets are supplied in blister packs containing either two 20 mg tablets or two 40 mg tablets. The Applicant originally requested approval for both Dosepak (b) (4) container closure systems for drug packaging, but during the review cycle, the Applicant clarified that the Dosepak had not yet been confirmed (b) (4) Appropriate testing was performed, and the Applicant confirmed that the Dosepak container closure system (b) (4) decided to use the Dosepak for the marketing launch of baloxavir marboxil in the US.

Clinical trials were conducted using the 20 mg tablet. The Applicant requested a biowaiver for conducting a clinical bioequivalence study comparing the 40 mg tablet with the 20 mg tablet. The biowaiver request was based on 1) the drug substance has linear pharmacokinetics over

the therapeutic dose range; 2) the 20 mg and 40 mg tablets are dose proportiona (b) (4) the same dosage form, same release mechanism, and same manufacturing process; and 3) the two tablet strengths demonstrated similar dissolution profiles at pH 1.0, 4.5, and 6.8. The biowaver was granted.

The baloxavir marboxil drug substance is a white to yellow powder; it is not hygroscopic and is practically insoluble in water. The drug substance is combined with lactose monohydrate and other commonly used compendial excipients. The tablet is then coated (b) (4) The final tablet is oblong, white to yellow in color. The 20 mg tablet is debossed with the Applicant trademark and "772" on one side and 20 on the other side. The 40 mg tablet is debossed with BXM40 on one side. (b) (4)

4.3. Clinical Microbiology

This section provides a brief summary of key baloxavir marboxil nonclinical virology characteristics. Limited discussions regarding clinical virology assessments pertaining to the pivotal clinical trials are found in Section 6. Please see the Clinical Virology review of Dr. William Ince and Dr. Michael Thomson for additional details.

Preclinical virology

Influenza is a negative-sense, single-stranded, segmented RNA virus from the Orthomyxoviridae family of viruses. Baloxavir selectively inhibits the endonuclease activity of the influenza virus polymerase acidic subunit of the viral polymerase complex and as a result prevents viral mRNA transcription needed for viral replication.

Baloxavir was tested against multiple influenza strains in a plaque reduction assay using MDCK cells. The median EC_{50} value of baloxavir against different influenza virus subtype A/H1N1 strains was 0.75 nM, against subtype influenza A/H3N3 strains was 0.67 nM, and against type influenza B strains was 5.97 nM. The higher EC_{50} against influenza B strains was concerning, and Virology reviewers raised the possibility that a higher baloxavir marboxil dose might be needed for influenza B at the End-of-Phase 2 meeting. As a result, the Applicant agreed to use weight-based dosing in Phase 3 trials.

The antiviral activity of baloxavir marboxil was demonstrated in mouse models of influenza virus infection and in a non-lethal ferret model. Therapeutic treatment with baloxavir marboxil was associated with a significant reduction in lung virus titers and improved survival compared with vehicle control. Interestingly, in a combination study with oseltamivir, some dose combinations resulted in a statistically significant improvement in survival time suggesting that use of both drugs in combination may be beneficial in seriously ill subjects with influenza.

Resistance in clinical trials

Resistance mutations were observed in a single subject pre-treatment. This amino acid substitution, PA A36V (A/H1N1) conferred a 3.6-fold increase in baloxavir EC_{50} but did not result in a decreased treatment response in this subject.

Influenza isolates from subjects in the pivotal trials and in the Japanese pediatric trial were evaluated for treatment-emergent resistance conferred by substitutions in the PA gene. The rates of emergence of substitutions that were identified in more than one subject or that reduced susceptibility to baloxavir marboxil in cell culture in Trials 1518T0821, Trial 1601T0831, and the pediatric trial 1618T0822, were 2.7%, 11.1%, and 25.6%, respectively. The increased rate observed in pediatric subjects is consistent with what has been observed for neuraminidase inhibitors. PA substitutions that were treatment-emergent in more than one subject were defined as potentially resistance-associated substitutions (RAS) and were, in subtype A/H1N1, E23K (n=1) and I38F (n=2); in subtype A/H3N2, E23G (n=1), E23K (n=1), A37T (n=2), I38M (n=6), I38T (n=50), S60P (n=1), and E623G/K (n=2); and in type B, I38T (n=1) and A60V (n=1). Substitutions E23G/K, A37T, I38F/M/T, and E199G conferred a >2-fold reduction in susceptibility to baloxavir relative to reference (EC_{50} value fold change range: 2.4-57). In addition, E23G/K, A37T, I38F/M/T, and E199G were associated with virus rebound in ≥ 50% of the subjects in whom they were observed. Substitutions E23G/K, A37T, I38F/M/T, and E199G were proposed for inclusion in the USPI as resistance-associated substitutions.

In an analysis of subjects in the pivotal trials with type A virus infections, treatment-emergent RAS were associated with an increase in the time to alleviation of symptoms in baloxavir marboxil arms. The median times to alleviation of symptoms for subjects with and without a treatment-emergent RAS were 63 hours (n=44) and 50 (n=413) hours, respectively (p=0.0198). In spite of the presence of treatment-emergent RAS, the median time to alleviation of symptoms was shorter for subjects with influenza A and treatment-emergent RAS than for subjects with influenza A who received placebo (80 hours). This analysis could not be performed for subjects with influenza B because of the discordant clinical response observed in the two clinical trials.

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4.4. Nonclinical Pharmacology/Toxicology

This section provides a brief overview of the key findings from nonclinical toxicology studies conducted in support of this application. Please refer to the Pharmacology/Toxicology Review by Dr. Deacqunita Diggs for additional details.

Safety Pharmacology and Repeat-Dose Toxicity

Repeat-dose studies were conducted in rats (20, 200, or 2000 mg/kg/day) and monkeys (1, 10, 100 mg/kg/day) for one month with a one month recovery period. Target organs of toxicity were the liver and thyroid. Liver findings in SD rats included increased weights; accentuated lobular pattern and liver enlargement at the high dose; and histopathology findings of minimal centrilobular hypertrophy, minimal to mild macrovesicular fatty change in periportal hepatocytes, and a mild increase in Kupffer cell phagocytosis. These effects resolved during recovery. In monkeys, there was an increase in hepatic enzymes (AST, ALT, ALP, GGT, and GLDH). At the end of recovery the increases in hepatic enzymes had resolved.

Minimal diffuse follicular epithelial hyperplasia of the thyroid with minimal to mild decrease in colloid was observed in the thyroid at the mid and high doses in repeat-dose study in rats. These effects resolved during recovery. In the repeat-dose study in monkeys, increased thyroid weight in males at the high dose was observed at the end of dosing and remained through recovery. Abnormal thyroid histopathology findings in monkeys were observed at all doses in both the treatment cohort and in controls; the findings resolved during recovery. Exposure multiples at the NOAELs in rats and monkeys are 0.6 and 2.5 times the exposure at the recommended clinical dose, respectively.

Fertility and Early Embryonic Development

Baloxavir marboxil-related effects observed in the embryo-fetal studies in rats and rabbits were a decrease in maternal body weights and food intake. Additional effects observed in rabbits included abortions and fetal skeletal variations (cervical rib and supernumerary ribs). Exposure at the maternal and fetal NOAELs in rats and rabbits were 5 and 7 times the exposure at the recommended clinical dose, respectively.

Photoxicity /Local Tolerance

Baloxavir marboxil is not phototoxic to the skin or cause skin reactions in in vivo studies but showed phototoxic potential in in vitro assays.

Genetic Toxicology

All genotoxicity studies were negative.

4.5. Clinical Pharmacology

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK) and pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Drs. Hazem Hassan, Simbarashe Zvada, and Su-Young Choi for full details.

The following summarizes baloxavir marboxil pharmacokinetics in humans following oral

administration:

Absorption:

- Tmax is 4 hours.
- Food decreased C_{max} and $AUC_{0\text{-}inf}$ by approximately 48% and 36%, respectively
- Solubility/permeability are decreased in the presence of polyvalent cations.
- Absolute bioavailability was not established.

Distribution:

- The apparent volume of distribution is 1180 liters
- Protein binding ranges between 93% and 94%.
- Blood-to-plasma ratio ranges between 49% and 54%.

Elimination:

- The apparent oral clearance is 10.3 Liter/hour.
- The elimination half-life is 79 hours.
- Baloxavir marboxil is rapidly hydrolyzed to its active metabolite by esterases in the GI lumen, liver, and blood.
- Baloxavir is metabolized by UGT1A3 with minor contribution from CYP3A4.
- About 80% of the administered dose is excreted in the feces, and urine excretion accounts for <15% of the dose.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable to this application

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The following table contains a summary of select clinical trials in the Applicant's safety database for baloxavir marboxil. The table includes a summary of the two pivotal clinical trials and of an open-label, single-arm study in Japanese pediatric subjects. The results of these three studies as well as of 11 Phase 1 studies were included in this NDA.

Baloxavir marboxil was administered as a single oral dose in all three studies described in the table below.

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Table 2. Clinical Trials of Baloxavir Marboxil

Trial Identity	NCT no.	Trial Design	Regimen/ schedule	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		Controlled Studies to Support Efficacy and Safety					
1601 T0831	02954354	Phase 3, randomized, controlled, double-blind study of baloxavir compared to placebo and oseltamivir in the treatment of uncomplicated influenza in otherwise healthy subjects from 12 to < 65 years of age	Weight based dosing of baloxavir with single oral 40 mg for subjects < 80 kg and 80 mg for subjects ≥ 80 kg, Oseltamivir 75 mg twice daily for 5 days, or Placebo	Time to alleviation of influenza symptoms	21 days	1432 (610 baloxavir, 309 placebo, 513 oseltamivir	Otherwise healthy patients with acute uncomplicated influenza in Japan, US and Canada
1518 T0821	---	Phase 2, dose finding, double-blind, randomized, placebo-controlled trial of safety, PK and efficacy in subjects from 20 to < 65 years of age	Single oral dose of 10 mg, 20 mg, or 40 mg of baloxavir or placebo	Time to alleviation of influenza symptoms	21 days	400 (100 per arm)	Otherwise healthy patients with acute uncomplicated influenza in Japan
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
1618 T0822	---	Open-label, single arm, safety, PK, and efficacy study of baloxavir marboxil in pediatric subjects with acute uncomplicated influenza	Enrolled subjects from 6 months to < 12 years of age and dosed by weight using tablet formulation: 5-< 10 kg – 5 mg 10 - < 20 kg – 10 mg 20 - < 40 kg – 20 mg ≥ 40 kg – 40 mg	Time to alleviation of influenza symptoms	21 days	107	Otherwise healthy Japanese pediatric patients with acute uncomplicated influenza from 6 months to <12 years of age

5.2. Review Strategy

This clinical review reflects extensive collaboration with the statistical reviewer, Dr. Fraser Smith, and the clinical virology reviewer, Dr. William Ince. In addition, there were significant interactions with the clinical pharmacology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. The assessments of the other reviewers are summarized in this document in the relevant sections. Complete descriptions of their findings are available in their respective discipline reviews.

The clinical review for baloxavir marboxil is based primarily on the Phase 2 trial, 1518T0821, and the Phase 3 trial, 1601T0831. The Clinical Study Reports and datasets were reviewed, and the results are summarized in this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of baloxavir marboxil in patients with acute uncomplicated influenza was supported by the results of two studies, Trial 1601T0831 and Trial 1518T0821. Trial 1601T0831 was a Phase 3, randomized, controlled, safety and efficacy trial of baloxavir marboxil in subjects 12 to 64 years of age conducted in Japan and North America (US and Canada). Trial 1518T0821 was a Phase 2, randomized, placebo-controlled, dose-finding study in subjects from 20 to 64 years of age conducted only in Japan.

6.1. Trial 1601T031

6.1.1. Study Design

Overview and Objective

Trial 1601T0831 was a Phase 3, randomized, controlled, pharmacokinetic, safety, and efficacy trial of baloxavir marboxil in subjects from 12 to ≤ 64 years of age who had acute uncomplicated influenza.

The primary objective of the study was to evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo by measuring the time to alleviation of symptoms in subjects with uncomplicated influenza virus infection.

Secondary efficacy objectives were to evaluate the efficacy of baloxavir marboxil compared with:

- Oseltamivir by measuring the time to alleviation of symptoms,
- Placebo by measuring the secondary endpoints in subjects with uncomplicated influenza

infection, and
- Oseltamivir by measuring the secondary endpoints in subjects with uncomplicated influenza infection.

The virologic endpoint was to evaluate the polymorphic and treatment-emergent amino acid substitutions in the polymerase acidic (PA) gene and drug susceptibility in patients with evaluable virus.

The safety objectives of the study were to compare:
- The safety and tolerability of baloxavir marboxil with placebo,
- The safety and tolerability of baloxavir marboxil with oseltamivir, and
- The frequency of adverse events in subjects with influenza of baloxavir marboxil with oseltamivir and with placebo.

The pharmacokinetic objective of the study was to determine the PK of the active form of baloxavir marboxil (i.e., baloxavir) in subjects with acute uncomplicated influenza infection.

Trial Design

Study 1601T0831 was a randomized, double-blind, active (oseltamivir) and placebo-controlled, safety and efficacy trail of baloxavir marboxil in otherwise healthy adults and adolescents who had influenza and who were from 12 to 64 years of age. Eligible patients were those with a clinical diagnosis of influenza, defined as having 1) fever (temperature ≥ 38° C), and 2) at least one general systemic symptom of moderate or greater severity (headache, feverishness/chills, muscle or joint pain, or fatigue), and 3) at least one respiratory symptom of moderate or severe severity (cough, sore throat, or nasal congestion). Patients had to be symptomatic for no more than 48 hours in order to participate in the study. Patients with a diagnosis of clinical influenza had a nasopharyngeal swab for influenza A and/or B virus using a commercial rapid influenza diagnosis test (RIDT). If the RIDT result was negative, the patients were informed of the RIDT results and about the sensitivity of the RIDT and then asked if he/she wished to continue in the study. A specimen for RT-PCR was obtained at the same time; RT-PCR for diagnosis of influenza was performed at a central laboratory.

Study treatment and randomization differed by age group (12 to < 20 years of age) and ≥ 20 to ≤ 64 years of age); the Applicant planned that approximately 15% of the study population would be subjects from 12 to < 20 year age group. Subjects from 12 to < 20 years of age were randomized to receive either a single oral dose of baloxavir marboxil or a single oral dose of matching placebo. Baloxavir marboxil dosage was determined by subject weight: subjects weighing < 80 kg received 40 mg of baloxavir marboxil and subjects weighing ≥ 80 kg received 80 mg. Oseltamivir was not used in subjects < 20 years of age because of concerns by Japanese Pharmaceuticals and Medical Devices Agency of neuropsychiatric adverse events in this age

group.

Study subjects from 20 to 64 years of age were randomized in a 2:2:1 ratio to receive baloxavir marboxil, oseltamivir, or placebo. Subjects in the baloxavir marboxil arm received a single oral dose of baloxavir marboxil; subjects weighing < 80 kg received 40 mg of baloxavir marboxil and subjects weighing ≥ 80 kg received 80 mg. Subjects 20 to 64 years of age in the oseltamivir arm received oseltamivir 75 mg twice daily for 5 days as recommended in the oseltamivir package insert. Subjects in the placebo arm received placebo for baloxavir marboxil on Day 1 and placebo for oseltamivir administered twice daily for 5 days. Subjects in the baloxavir marboxil arm received baloxavir marboxil and placebo for oseltamivir, while subjects in the oseltamivir arm received both oseltamivir and placebo for baloxavir marboxil.

Baloxavir marboxil or the placebo for baloxavir marboxil was administered at the clinical study site. Baloxavir marboxil was administered as a 20 mg tablet (i.e. two 20 mg tablets for the 40 mg dose and four 20 mg tablets for the 80 mg dose). Subjects were instructed to take the study drug without regard to food.

Each subject recorded his/her signs and symptoms of influenza on a paper questionnaire on Day 1 prior to treatment. Subjects then received an electronic Diary (eDiary) to record signs and symptoms of influenza. Subjects were to self-assess 7 influenza symptoms daily: cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue and rated the severity of each symptom on a 4-point scale [0 (none), 1 (mild), 2 (moderate), and 3 (severe)]. Symptoms were assessed and recorded in the eDiary twice daily until Day 9 and once daily from Day 10 to Day 14. Subjects were provided with a thermometer on Day 1 and were to measure and record their temperature four times a day (morning, noon, evening, and bedtime) until Day 3 and twice daily from Day 4 to Day 14.

If influenza symptoms were so severe that the subjects needed rescue therapy between Day 1 and Day 22, subjects were permitted to take acetaminophen at a dose of up to 3000 mg/day for the relief of fever or pain. Subjects were to record the date and time of each acetaminophen dose in the subject eDiary. Subjects were instructed to measure and record body temperature and to assess and record influenza symptoms either immediately before the use of acetaminophen or more than 4 hours after an acetaminophen dose.

Additional information to be collected on the eDiary included the self-assessment of health, the results of the EQ-5D-5L (EuroQol-5 Dimensions-5 Levels), a questionnaire regarding quality of life; and a work productivity questionnaire. Subjects self-assessed his or her health on a scale of 0 (worst possible health) to 10 (normal health for someone your age and condition) predose and then once daily in the evening until Day 14. No other description of this self-assessment was provided. The EQ-5D-5L is a two-part assessment tool, which was used to measure health economic outcomes. Subjects were to complete the questionnaire predose on Day 1, twice

daily until Day 9, and once daily in the evening from Day 10 to Day 14. The Work Productivity questionnaire was completed at the Day 22 visit and contained questions about number of hours worked and number of hours missed from work. The Applicant did not provide information for the validation of any of the three questionnaires. For this reason, the information obtained from these questionnaires were not reviewed for this NDA.

A nested investigation of intrahousehold infection rate was conducted at Japanese sites only. Information on the household size, number of household members with influenza, and the date of influenza diagnosis of infected household members were collected on Day 1. Subjects were re-interviewed from Day 1 to Day 15 about the number of household members diagnosed with influenza. No other information about this nested study was provided. While this information is of interest, this nested study cannot be considered a true transmission study without a more detailed study design to include detailed entry criteria, use of RT-PCR and/or viral culture to identify exposed and infected household members, statistical power to identify increased transmission, and other information.

The presence of influenza-related complications (sinusitis, bronchitis, otitis media, and pneumonia) was documented at each study visit. The criteria for diagnoses of each of these complications were not provided. The Applicant was informed it would not be appropriate to describe any differences in the incidence of influenza-related complications unless detailed criteria for the diagnosis of individual influenza-related complications were pre-defined and included in the study protocol.

Blood samples were collected for pharmacokinetic assessment on Days 2 and 4. If "circumstances permitted," samples were also collected within the period of 0.5 hours to 4 hours after dosing on Day 1, Day 3, and Day 15.

Nasopharyngeal swabs for influenza were collected at study visits until Day 9; nasopharyngeal swabs were collected on Days 15 and 22 from subjects who had symptoms of influenza. Serum for anti-influenza antibody titers were collected on Days 1 and 22.

Each subject had a minimum of 7 study visits. Subjects were to be followed for 14 days for efficacy and for 22 days for safety. The study duration for individual subjects was 22 days.

Study Population:
Inclusion criteria:
The trial enrolled males and females ≥ 12 to ≤ 64 years of age with a clinical diagnosis of influenza. Influenza diagnosis confirmed by all three of the following:

- Fever ≥ 38° C (axillary) in the predose examination or more than 4 hours after dosing of antipyretics, if they were taken;
- At least one of the following general systemic symptoms with a severity of moderate or

greater:
  - Headache,
  - Feverishness or chills,
  - Muscle or joint pain, or
  - Fatigue
- At least one of the following respiratory symptoms with a severity of moderate or greater:
  - Cough,
  - Sore throat, or
  - Nasal congestion.

The time interval between the onset of symptoms and the predose examination must have been ≤ 48 hours. The onset of symptoms was defined as the time either of the first increase in body temperature (increase of at least 1° C from normal body temperature) or time when the patient experiences at least one general systemic or respiratory symptom.

Exclusion criteria:

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

- Severe influenza virus infection requiring inpatient treatment;
- Concurrent infection(s) requiring systemic antimicrobial and/or antiviral therapy at the predose examination;
- Receipt of peramivir, laninamivir (not FDA-approved), oseltamivir, zanamivir, rimantidine, umifenovir (not FDA-approved), or amantadine within 30 days prior to the predose examination;
- Creatinine clearance ≤ 60 mL/min (≤ 30 mL/min in Japan); and
- Presence of risk factors for severe influenza disease based on the definition of high risk by the Centers of Disease Control and Prevention.

Study Endpoints

The primary efficacy endpoint was the time to alleviation of symptoms. Time to alleviation of symptoms was defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of influenza symptoms was defined as the time when all of the 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the subject as 0 (none) or 1 (mild) in the eDiary for a duration of at least 21.5 hours (24 hours +/- 10%).

The secondary efficacy endpoints included:

- Time to alleviation of individual 7 symptoms at each study visit;
- Time to resolution of fever (self-measured axillary temperature < 37° C for at least 12

hours);
- Proportion of subjects reporting a normal temperature (< 37° C) at each study visit;
- Time to return to pre-influenza health status based on information from three questionnaires; and
- Incidence of influenza-related complications (hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia) after the initiation of study treatment.

The virologic endpoints were secondary endpoints and included:
- Proportion of subjects positive for influenza by viral culture and proportion of subjects positive by RT-PCR at each time point and
- Time from initiation of study treatment to cessation of viral shedding by influenza virus culture and by RT-PCR.

See Dr. Ince's Virology review for a complete discuss of virologic outcomes.

Statistical Analysis Plan

Subjects 12 to < 20 years of age were randomized in a 2:1 ratio to baloxavir marboxil or placebo. Subjects ≥ 20 to ≤ 64 years of age were randomized in a 2:2:1 ratio to receive baloxavir marboxil, oseltamivir, or placebo. Randomization was stratified by region (Japan/Asia /rest of world), weight (< 80 kg / ≥ 80 kg), and baseline composite symptom score (≤ 11 / ≥ 12). Information was obtained on current smoking status and whether the subject had an influenza vaccine in the previous 6 months. This information was used for subgroup analyses; but subjects were not stratified by either smoking status or previous vaccination, and the study was not powered for either analysis.

The trial was conducted in a double-blind, double-dummy fashion by using two different placebos, one matching baloxavir marboxil and one matching oseltamivir. All study subjects, investigators, study personnel, and data analysts were blinded to treatment assignment until database lock. Plasma drug concentrations were not reported to the sponsor until after the database lock.

The calculated sample size for the comparison of baloxavir marboxil vs. placebo for the primary efficacy endpoint, time to alleviation of symptoms was 1496 subjects (144 subjects in the 12 to < 20 year stratum and 1350 subjects in the 20 to 64 years stratum). This assumed a RT-PCR positive rate of 65% resulting in an intent-to-treat infected (ITTI) population of 968 subjects (93 subjects in the 12 to < 20 year stratum and 875 subjects in the 20 to 64 years stratum). This sample size was also based on an assumed median time to alleviation of symptoms in the placebo group of 100 hours. The median times to alleviation of symptoms in the placebo arms of three oseltamivir trials of acute uncomplicated influenza were 116.5, 103.3, and 93.3 hours, but the median time to alleviation of symptoms in the Phase 2 study of baloxavir marboxil was

77.7 hours. The sponsor assumed that the difference in time to alleviation of symptoms between the baloxavir marboxil and placebo would be 28 hours. This was based on the difference of 28.2 hours between the baloxavir marboxil 40 mg arm (49.5 hours) and the placebo arm (77.7 hours) in the Phase 2 trial. This sample size and these assumptions together with a two-sided significance level of 0.05 would result in at least a 90% power to detect a difference between the two arms.

The proposed sample size allowed for an ITTI population of 700 subjects for the comparison of baloxavir marboxil (N=350) and oseltamivir (N=350) in subjects from 20 to ≤ 64 years of age. The statistical power using different sets of differences in time to alleviation of symptoms is shown in the table below.

Table 3: Statistical Power to Compare Baloxavir Marboxil and Oseltamivir

Median Time to Alleviation of Symptoms		Statistical Power for Comparison*
baloxavir marboxil Arm	Oseltamivir Arm	
72 hours	84 hours	42.1%
70 hours	84 hours	54.8%
68 hours	84 hours	67.4%
66 hours	84 hours	78.5%
64 hours	84 hours	87.2%

*Statistical power using stratified generalized Wilcoxon test

The primary efficacy endpoint was the comparison of time to alleviation of symptoms between the baloxavir marboxil and placebo arms. The time to alleviation of symptoms was compared using the stratified generalized Wilcoxon test with composite symptoms score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or rest of the world) as stratification factors. The stratified generalized Wilcoxon test was also used to compare the time to alleviation of symptoms between the baloxavir marboxil and oseltamivir arms in subjects 20 to ≤ 64 years of age. Together with the primary efficacy analysis, this comparison was conducted in a hierarchical manner to control for Type 1 error.

The analysis populations for this trial were as follows.

- The intent-to-treat-infected population (ITTI) included all subjects who received the study drug and had a confirmed diagnosis of influenza virus infection based on RT-PCR results. This population was analyzed according to treatment to which the subjects were randomized. The ITTI population was the primary population for all efficacy analyses.
- The safety population included all randomized subjects who received at least one dose of study drug. This population was analyzed according to treatment received. The safety population was used for all safety analyses.
- The per-protocol set (PPS) includes all randomized subjects in the ITTI population who

did not have any protocol violations and who had adequate follow-up. The PPS was used for a sensitivity analysis for the primary endpoint.

Protocol Amendments

The protocol was amended once after submission to FDA. In response to a comment from FDA, the body weight for the 80 mg dose was changed from ≥ 100 kg to ≥ 80 kg. Other revisions were minor.

6.1.2. Study Results

Compliance with Good Clinical Practices

According to the Applicant, the trial was conducted in compliance with International Council for Harmonization Guidelines and Good Clinical Practice.

During an audit for a different Phase 3 study of baloxavir marboxil, major issues in study conduct were observed by the Applicant, and the Applicant closed the site for cause. This site (Center 811) enrolled 10 subjects in Trial 1601T0831. Sensitivity analyses of the efficacy analyses were conducted with and without these 10 subjects. See the discussion of efficacy in this review.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in FDA guidance for industry, "Financial Disclosure by Clinical Investigators." See Section 13.1 of this review for the NDA financial disclosure form. No clinical investigators or sub-investigators were employees of Shionogi, Incorporated. No investigators or sub-investigators had any disclosable financial interests or arrangements. The trial design also minimizes potential bias, because it was a randomized, double-blind, double-dummy trial. Therefore, in the opinion of this reviewer, there was no bias due to the financial interests of investigators.

Patient Disposition

Trial 1601T031 was conducted at 141 sites in Japan, 149 sites in the United States, and 7 sites in Canada. The first subject was enrolled on December 8, 2016, and the last subject completed the study on April 24, 2017.

A total of 612 subjects were randomized to receive baloxavir marboxil, 310 to receive placebo, and 514 to receive oseltamivir. The majority of study subjects (1366/1436 or 95%) completed the trial. The number of subjects prematurely discontinuing the trial and the reason for premature discontinuation are shown in the following table.

Table 4. Trial 1601T0831 – Patient Disposition and Reason for Premature Discontinuation

	Placebo	Baloxavir	Oseltamivir
Randomized	310	612	514
Completed trial	290 (94%)	578 (94%)	498 (97%)
Prematurely discontinued trial	20 (6%)	34 (6%)	16 (3%)
Reason for premature discontinuation			
Consent withdrawn	9	17	11
Lost to follow-up	5	12	0
Adverse event	2	2	4
Failure to meet entry criteria	0	1	0
Lack of efficacy	2	0	0
Other*	2	2	1

Source: Clinical Study Report 1601T0831, Table 10-1, page 100.
*Other reasons for premature discontinuation are discussed in text below.

As shown in Table 4, the majority of subjects finished the trial, and the percentage of subjects who finished the trial was similar in the three study arms. The most common reasons for premature discontinuation were withdrawn consent and loss to follow-up. Given the 2:1 randomization of subjects to baloxavir marboxil, the proportions of subjects who discontinued due to withdrawn consent and loss to follow-up were similar between these two trial arms. The proportion of subjects who discontinued due to withdrawn consent and loss to follow-up was lower in the oseltamivir arm. However, the numbers of subjects who discontinued prematurely in all three trial arms were small.

Failure to meet entry criteria in a single subject in the baloxavir arm was due to hyperuricemia on Day 1. One subject in the placebo arm discontinued for "other" reasons, but this discontinuation was also due to abnormal laboratory values on Day 1. Additional reasons for premature discontinuation for "other" reasons were problems with eDiary (one subject in baloxavir marboxil arm and one in placebo arm), inability to comply with the trial schedule due to family emergency (one subject in oseltamivir arm), and development of complications that needed treatment in one subject in baloxavir marboxil arm. The subject who needed additional treatment was classified as other and not as an adverse event, because he was withdrawn due to investigator discretion. This subject was a 58 year old male who was diagnosed with acute bronchitis on Day 3; he was discontinued on Day 22 to receive treatment for the AE which had persisted. Lack of efficacy as a reason for premature study discontinuation was only observed in the placebo arm and was reported in two subjects. Discontinuations due to AEs will be discussed in the discussion of Trial 1601T031 safety.

The disposition results for adolescent subjects are similar to those for the overall population The adolescent subgroup included 118 subjects; 42 received placebo and 76 received baloxavir marboxil. Five subjects (7%) in the baloxavir marboxil arm prematurely discontinued the study;

two were lost to follow-up, two withdrew consent, and one failed to meet entry criteria. Two adolescent subjects in the placebo arm (5%) prematurely discontinued the study, both due to withdrawn consent.

Overall, the proportion of subjects prematurely discontinuing was low and similar in the three study arms. The reasons for premature discontinuation were also similar between the arms.

Subjects screened but not randomized

Patients who met the clinical criteria for diagnosis of influenza were tested at the study site for influenza with rapid influenza diagnostic tests (RIDT). Patients with a negative RIDT were informed of the result and then asked if they wanted to participate in the trial. Nasal swabs for RT-PCR for influenza were sent to a central laboratory for testing on all subjects who participated in the trial. Since RIDTs can result in false negatives for influenza B, it was possible that patients with influenza B and a negative RIDT might decline participation in the trial. This might have affected the results by affecting the strains included in the trial for analysis of efficacy.

Nineteen subjects were not randomized because of patient request and 30 were not randomized for other reasons.

Protocol Violations/Deviations

A total of 1436 subjects were randomized to one of the three study arms. The number of subjects in the safety population, intent-to-treat infected population, and per protocol population are shown in the following table.

Table 5. Trial 1601T0831 – Study Populations and Reasons for Exclusion

	Placebo	Baloxavir marboxil	Oseltamivir
All Randomized	310	612	514
Did not receive study drug	1	2	1
Safety population	309 (99.7%)	610 (99.7%)	513 (99.8%)
RT-PCR negative for influenza	78	154	136
Intent-to-treat infected population	231 (75%)	456 (75%)	377 (73%)
Received prohibited medications*	15	21	18
Ineligible	2	8	8
Noncompliant	3	5	4
Inadequate diary completion	1	1	0
Per protocol population	210 (68%)	421 (69%)	347 (68%)

*Six subjects (5 in baloxavir marboxil arm and 1 in oseltamivir arm) were excluded from the per protocol population for two reasons. All six were excluded for receiving prohibited medications plus a second reason, and all six were included in the row for the second reason and not in the row for prohibited medication.
Source: Created by reviewer from information in Table 11-1 and Line Listing 16.2.3.

Almost all study subjects were included in the safety population except for four subjects who were randomized but not treated with study drug. Most subjects (75% in the placebo and baloxavir marboxil arms and 73% in the oseltamivir arm) were included the intent-to-treat infected population. Only subjects who were RT-PCR negative for influenza were included in the safety population but excluded from the ITTI population. The Per Protocol population included slightly more than two-thirds of subjects in each treatment arm (68% of subjects in the placebo arm, 69% of subjects in the baloxavir marboxil arm, and 68% of oseltamivir arm). The most common reason for exclusion from the PP population in each treatment arm was receipt of prohibited medications. All other reasons were reported in fewer than 2% of subjects. Of note, non-compliance with the study procedures or with the study diary was very uncommon.

The study appears to have been well conducted. Almost all subjects with influenza were included in the ITTI population, which was the primary population for analysis of efficacy. An additional 5% to 7% of subjects were excluded from the Per Protocol population, which was a secondary population for analysis of efficacy. In the overall population, the percentages of subjects excluded from the ITTI and from the PP populations and the reasons for exclusion from the populations were similar between the three treatment arms.

Demographic Characteristics

Table of Demographic Characteristics

Table 6. Trial 1601T0831 - Demographic Characteristics of the Intent-to-Treat Population Infected

Demographic Parameters	Placebo (N=231) n (%)	Baloxavir (N=456) n (%)	Oseltamivir (N=377) n (%)
Sex			
Male	120 (52%)	232 (51%)	218 (58%)
Female	111 (48%)	224 (49%)	159 (42%)
Age			
Mean years (SD)	33.9 (13.7)	33.5 (13.5)	36.0 (11.8)
Median (years)	33	32	35
Min, max (years)	12, 64	12, 64	20, 64
Age Group			
≥ 12 - ≤ 19 years	38 (17%)	80 (18%)	0
≥ 20 - ≤ 29 years	61 (26%)	121 (27%)	134 (36%)
≥ 30 - ≤ 39 years	47 (20%)	92 (20%)	104 (28%)
≥ 40 - ≤ 49 years	48 (21%)	97 (21%)	77 (20%)
≥ 50 - ≤ 59 years	30 (13%)	52 (11%)	51 (14%)
≥ 60 - ≤ 64 years	7 (3%)	14 (3%)	11 (3%)
Race			
White	40 (17%)	85 (19%)	60 (16%)
Black or African American	11 (5%)	18 (4%)	9 (2%)
Asian	178 (77%)	349 (77%)	305 (81%)
Native Hawaiian or Other Pacific Islander	0	0	1 (<1%)
Other	2 (1%)	4 (1%)	2 (<1%)
Ethnicity			
Hispanic or Latino	11 (5%)	32 (7%)	25 (7%)
Not Hispanic or Latino	220 (95%)	424 (93%)	352 (93%)
Region			
Japan/Asia	175 (76%)	343 (75%)	303 (80%)
Rest of the World	56 (24%)	113 (25%)	74 (20%)
Weight			
< 80 kg	190 (82%)	377 (83%)	306 (81%)
≥ 80 kg	41 (18%)	79 (17%)	71 (19%)

Source: Clinical Study Report 1601T0831, Table 11-2, page 105.

Approximately one-half of the population was male and one-half female. The mean age ranged from 33.5 to 36 years; 11% of subjects or 118 were younger than 20 years of age. The majority

of subjects were enrolled in Japan or Asia (77%), and the majority of subjects (78%) were Asian. Twenty-three percent of subjects were enrolled in other parts of the world, but primarily in the US. In addition to Asian, 17% of subjects were White, 4% were Black or African American and <2% were Other or Native Hawaiian / Pacific Islander. Six percent of subjects were Hispanic or Latino. The racial and ethnic makeup of the study population differs from that of the U.S. population. According to the US Census Bureau (https://www.census.gov/quickfacts/fact/table/US/PST045217), in 2017 the US population was 77% White, 13% Black or African American, and 6% Asian and 18% of the US population was Hispanic or Latino. Only 18 Black or African Americans received baloxavir and only 32 subjects in the baloxavir marboxil arm were of Hispanic or Latino origin. As a result, there are few safety and efficacy data for this population in this study. Most subjects (82%) weighed less than 80 kg, while 18% weighed 80 kg or more. The average weight for a male 20 years of age and older in the US is 88.8 kg and the average weight for a female is 76.4 kg. (https://www.cdc.gov/nchs/fastats/body-measurements.htm). Therefore, a larger proportion of the US population than the study population will weigh at least 80 kg and require the 80 mg dose of baloxavir marboxil. Therefore, it is important to analyze the safety and efficacy results for the 80 kg dose of baloxavir marboxil, and discussions of safety and efficacy by dose are included in this review.

The demographic characteristics for sex, race, ethnicity, region, and weight were similar between the three treatment arms. There was a higher percentage of subjects in the oseltamivir arm who were in the age cohorts ≥ 20 - ≤ 29 years of age and ≥ 30 - ≤ 39 years of age compared to the baloxavir marboxil and placebo arms. This is likely because no adolescents (12 to < 18 years of age) were enrolled in the oseltamivir arm and proportions in each age group were shifted accordingly.

Overall, the baseline characteristics of the overall population for this study, except for age as described previously, were similar between the three treatment arms. The majority of the study population was enrolled in Asia, and the study population is not consistent with the demographic makeup of the U.S. population. In particular, Blacks/African Americans and Hispanics/Latinos were underrepresented in this study. However, there is no biologically plausible reason to support a difference in the safety or efficacy of baloxavir marboxil by race or ethnicity. The Applicant has agreed to enroll a sufficient number of Black/African Americans and Latinos in future studies of baloxavir marboxil in order to better assess safety and efficacy of baloxavir marboxil in these demographic groups. In addition, the percentage of subjects in this study who weighed at least 80 kg and received the 80 mg dose of baloxavir marboxil was low (N=79 or 17%). A substantial percentage of US population weighs 80 kg or more and the 80 mg dose of baloxavir marboxil is likely to be used often in the U.S.; therefore, the analysis of safety and efficacy by weight and dose is important and will be addressed later in this review.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Additional baseline characteristics
Influenza is more common in persons who smoke and often more severe; 24% of the study population were smokers (ranging from 21% to 27% in the three treatment arms).

One-fourth of subjects (the percentage ranged from 24% to 26% in the three treatment groups) had received the influenza vaccine prior to study participation. There are no data on the possible interaction between baloxavir marboxil and inactivated or live attenuated influenza vaccine. However, inactivated vaccine and baloxavir marboxil are unlikely to interact and the live attenuated influenza vaccine was not recommended for use during the influenza season (2016-2017) in which this study was conducted. Therefore, it is unlikely that previous vaccination affected the results of this trial.

Disease characteristics
All subjects were enrolled within 48 hours of onset of influenza symptoms. The duration of influenza symptoms prior to treatment was captured by time period (e.g., 0 to ≤ 12 hours, 12 to ≤ 24 hours, 24 to ≤ 36 hours, and 36 to ≤ 48 hours). The time from influenza symptom onset to treatment are shown in the table below.

Table 7. Trial 1601T0831 – Time from Influenza Symptom Onset to Treatment

Hours	Placebo (N=231) n (%)	Baloxavir (N=456) n (%)	Oseltamivir (N=377) n (%)
0 to ≤ 12 hours	34 (15%)	60 (13%)	41 (11%)
> 12 to ≤ 24 hours	87 (38%)	178 (39%)	163 (43%)
> 24 to ≤ 36 hours	67 (29%)	139 (31%)	94 (25%)
> 36 to ≤48 hours	43 (19%)	79 (17%)	79 (21%)

Source: Clinical Study Report 1601T0831, Table 11-2, page 106.

Most subjects (68%) were enrolled from 12 to 36 hours from onset of symptoms; fewer subjects were enrolled either within 12 hours of symptom onset or 36 hours or longer after symptom onset. The time from symptom onset to treatment was similar across treatment arms.

The influenza virus subtypes identified by viral subtyping are shown in the following table. The population of subjects in this table is subjects who had influenza virus type identified.

Table 8. Trial 1601T0831 – Influenza Virus Types and Subtypes

Median hours	Placebo (N=222) n (%)	Baloxavir (N=437) n (%)
A/H1N1	7 (3%)	7 (2%)
A/H3N2	195 (88%)	392 (90%)
B	20 (9%)	38 (9%)

Source: Clinical Study Report 1601T0831, Table 11-6, page 114.

The most common influenza subtype identified in the ITTI population was A/H3N2, which was identified in 89% of subjects. Influenza A/H1N2 was identified in 2% of subjects and influenza B in 9% of subjects. The percentages of each subtype were similar across the treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

Baloxavir marboxil was administered as a single oral dose. In this trial, the dose of baloxavir marboxil was administered by study personnel at the study site on the Day 1 visit, so compliance with baloxavir marboxil was 100%.

Non-compliance with oseltamivir was defined as taking less than 80% of the prescribed doses. Only two subjects (0.4%) took less than 80% of their oseltamivir. One subject took only 30% of their prescribed dose; this subject was included in the ITTI population but not the PP population. The other subject took approximately 60% of their oseltamivir and was included in both the ITTI and PP population. Another nine subjects were excluded from the PP population for noncompliance with oseltamivir. This included five subjects who took their oseltamivir once daily instead of twice daily as indicated and four subjects who took one extra dosage of oseltamivir during the study.

Overall, compliance with study drugs was excellent indicating that the study was well conducted.

Concomitant medications

The percentage of subjects who received any concomitant medication was 41% in the placebo arm 39% in the baloxavir marboxil arm, and 39% in the oseltamivir arm. However, this included subjects who continued medications that they were using chronically prior to study entry and included medications started during safety follow-up. An analysis was conducted of concomitant medications taken during the influenza treatment period; in the concomitant medication dataset "during" influenza treatment was the time from Day 1 to Day 6. A total of 172 subjects starting concomitant medications during the influenza treatment period: 35 subjects (15%) in the placebo arm, 79 subjects (17%) in the baloxavir marboxil arm, and 58 subjects (15%) in the oseltamivir arm. The most frequently used concomitant medications

were analgesics and antipyretics or anti-inflammatory medicines such as non-steroidal anti-inflammatory agents and medicines to treat influenza symptoms such as cough and nasal congestion. Thirteen subjects (4%) in the placebo arm used cold medicines and 23 (7%) used an antipyretic or anti-inflammatory medicine, such as NSAIDs or acetaminophen. A total of 26 subjects (4%) in the baloxavir marboxil arm used cold medications and 55 subjects (9%) used an antipyretic or anti-inflammatory agent. In the oseltamivir arm, 16 subjects (3%) used a cold medication and 23 (7%) used an antipyretic or anti-inflammatory medication.

Subjects were rarely started on other antiviral drugs (NAIs) for treatment of influenza (two subjects in the placebo arm and one in the baloxavir marboxil arm). Antibiotic use was uncommon, but the frequency of antibiotic use was similar in the three treatment arms. Eleven subjects (4%) in the placebo arm received antibiotics; nine antibiotics were used to treat adverse events (bronchitis and/or sinusitis). Fourteen subjects (2%) in the baloxavir marboxil arm received antibiotics: nine antibiotics were used to treat adverse events (bronchitis and otitis media). Twelve subjects (2%) in the oseltamivir arm received antibiotics; four antibiotics were used to treat adverse events (bronchitis or otitis media). All other subjects received antibiotics to "treat influenza" except for two subjects for "other" reasons.

The percentage of subjects who used antipyretics and medications for the symptomatic relief of influenza signs and symptoms of influenza was similar in the three treatment arms. Baloxavir marboxil did not appear to reduce the need for concomitant medications for influenza-related symptoms. The incidence of antibiotic use was similar in the baloxavir marboxil and oseltamivir arm but higher in the placebo arm. However, the number of subjects starting on antibiotics during their influenza illness was too small to discern any differences between the three treatment arms.

Rescue medication use

The use of acetaminophen was allowed, as defined in the trial protocol, as a rescue medication. If influenza symptoms were so severe that the subjects needed rescue therapy between Day 1 and Day 22, subjects were permitted to take acetaminophen at a dose of 3000 mg/day or less for the relief of fever or pain. Use of other antipyretics, cold medications, antivirals, and antibiotics, as discussed above, were prohibited medications and resulted in exclusion from the per protocol population. The proportion of subjects who used acetaminophen as a rescue medication was similar in the three treatment arms (12% in the placebo arm, 13% in the baloxavir marboxil arm, and 12% in the oseltamivir arm). The majority of subjects took a total of one to two doses of acetaminophen (ranging from 9% to 11% of subjects in the treatment arms). Only six subjects (< 1%) took five or more doses; three of these subjects were in the placebo arm and three in the baloxavir marboxil arm. Overall, there was no difference in the use of rescue medication between the three arms.

Efficacy Results – Primary Endpoint

Please see Dr. Fraser Smith's Biostatistics review for an additional discussion of efficacy.

The primary efficacy endpoint was the comparison of time to alleviation of symptoms between the baloxavir marboxil and placebo arms; the results are shown in the following table.

Table 9. Trial 1601T0831 – Results for Primary Efficacy Endpoint: Time to Alleviation of Symptoms (Intent-to-Treat-Infected Population)

	Baloxavir marboxil N=456	Placebo N=231
Median in hours (95% CI*)	53.7 (49.5, 58.5)	80.2 (72.6, 87.1)
Difference vs. placebo in hours (95% CI*)	-26.5 (-35.8, -17.8)	---
P value#	<0.0001	---

*CI = confidence interval
#P value was calculated using both the stratified Peto-Prentice's generalized Wilcoxon test.
Source: Clinical Study Report 1601T0831, Table 11-4, page 111.

The median time to alleviation of symptoms in the baloxavir marboxil arm was 54 hours compared to 80 hours in the placebo arm. The difference between the two medians was 26.5 hours. This difference is calculated by subtracting one median from the other median. Simple subtraction of two medians may not accurately reflect the difference between the two arms. The median values represent the value separating the lower half of the data sample from the upper half; therefore, the median may not reflect the tails or extremes of the data. In other words, the data from the primary analysis are continuous and not necessarily symmetrical around the median; therefore, simply subtracting median values may not be an accurate way to characterize the treatment effect. Dr. Smith analyzed the results using Hodges-Lehmann estimates to correct for any bias and determined that the median difference in time to alleviation of symptoms was 21 hours. Regardless of method used to determine the difference in time to alleviation of symptoms between the baloxavir marboxil and placebo arm was statistically significant. The primary endpoint was met, and the efficacy of baloxavir marboxil in the treatment of influenza in otherwise healthy subjects was demonstrated.

A sensitivity analysis of the primary endpoint was performed using the per protocol population. In this analysis, the median time to alleviation of symptoms in the baloxavir marboxil arm was 51 hours (95% CI of 46.4, 55.1). The median time to alleviation of symptoms in the placebo arm was 80 hours (95% CI of 71.9, 86.8). The time to alleviation of symptoms in the baloxavir marboxil arm was 29 hours shorter than in the placebo arm ($p < 0.0001$). Efficacy was also demonstrated in this analysis of the primary endpoint.

Subgroup analyses of the primary endpoint

Analyses of the primary endpoint for different subpopulations are shown in this section of the review. Subgroup analyses for gender and race were not provided for this study but were provided for both pivotal trials in the Clinical Summary of Efficacy. These results will be discussed in the Integrated Summary of Efficacy section of this review.

Time to alleviation of symptoms by age

The time to alleviation of symptoms in adolescents (12 to < 18 years of age) was compared to time to alleviation of symptoms in adults (≥ 18 to <65 years of age). A total of 90 adolescent subjects were included in the ITTI populations. The median time to alleviation of symptoms for adolescents who received baloxavir marboxil was 54 hours (95% CI of 43.5, 80.7), and the median time to alleviation of symptoms for adolescents who received placebo was 93 hours (95% CI of 64.1, 118.0). Time to alleviation of symptoms was 39 hours shorter in adolescents who received baloxavir marboxil compared to in those who received placebo (p = 0.0055). The median time to alleviation of symptoms in adults from 18 to < 65 years of age and who received baloxavir marboxil was 54 hours (95% CI of 49.1, 57.5); the median time to alleviation of symptoms in adults who received placebo was 79 hours (95% CI of 69.5, 86.8). Time to alleviation of symptoms was 25 hours shorter in adults who received baloxavir marboxil compared to in those who received placebo (p < 0.0001). Efficacy was demonstrated in both adolescents and adults in this Phase 3 trial.

Time to alleviation of symptoms by geographic area

The primary endpoint was analyzed by region. The two regions are called Japan/Asia and the rest of the world; however, there were only study sites in Japan, the United States and Canada. More subjects (75%) were enrolled in Japan compared to US/Canada (25%). The median time to alleviation of symptoms for Japanese subjects who received baloxavir marboxil was 46 hours (95% CI of 43.8, 52.1). The median time to alleviation of symptoms for Japanese subjects who received placebo was 79 hours (95% CI of 68.8, 86.5). The time to alleviation of symptoms was 31 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value < 0.0001). The median time to alleviation of symptoms for subjects in the US and Canada who received baloxavir marboxil was 87 hours (95% CI of 72.9, 96.8). The median time to alleviation of symptoms for subjects from the US and Canada who received placebo was 118 hours (95% CI of 68.8, 86.5). The time to alleviation of symptoms was 31 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value = 0.1373). The differences in the median time to alleviation of symptoms between the baloxavir marboxil and placebo arms were the same in Japan as in the US and Canada (i.e. 31 hours shorter time in baloxavir marboxil arm). The difference in the US and Canada subgroup did not reach statistical significance, but that was likely due to the smaller sample size for US and Canadian subjects (N-169) compared to Japanese subjects (N=516). The trial was not powered to detect statistical differences in subgroup analyses. In addition, the median times to alleviation of symptoms differed by region. In Japan, the median times to alleviation of symptoms were shorter in both the baloxavir

marboxil arm and the placebo arm compared to the median times in the US and Canada. The median time to alleviation of symptoms in the baloxavir marboxil arm in the US and Canada was actually longer than in the placebo arm in Japan. It is unclear why there were differences in the times to alleviation of symptoms for both the baloxavir marboxil and placebo arms between Japan and the US and Canada, but it may be due to differences in influenza strains or to cultural differences in reporting symptoms.

Time to alleviation of symptoms by weight and dose
The primary endpoint was analyzed by baseline weight; because dose was based on weight, the analysis for dose and weight are the same. The majority of subjects (82%) were < 80 kg and received the 40 mg dose of baloxavir marboxil. Eighteen percent of subjects weighed 80 kg or more and received the 80 mg dose of baloxavir marboxil. The median time to alleviation of symptoms for subjects who weighed less than 80 kg and received a single 40 mg dose of baloxavir marboxil was 51 hours (95% CI of 46.4, 55.3). The median time to alleviation of symptoms for subjects weighing less than 80 kg who received placebo was 79 hours (95% CI of 69.5, 87.1). The time to alleviation of symptoms was 28 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value < 0.0001). The median time to alleviation of symptoms for subjects weighing 80 kg or more who received a single 80 mg of baloxavir marboxil was 67 hours (95% CI of 53.5, 82.6). The median time to alleviation of symptoms for subjects who weighed 80 kg or more and received placebo was 85 hours (95% CI of 69.0, 148.5). The time to alleviation of symptoms was 18 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value = 0.0019). Efficacy was demonstrated in both subgroups; these data support the use of both the 40 mg and 80 mg dose, administered according to weight.

Time to alleviation of symptoms by time of last food consumption
In a Phase 1 pharmacokinetic study, the C_{max} for baloxavir was decreased by 48% and the AUC was decreased by 36% when baloxavir was administered with food compared to without food. In Trial 1601T0831, subjects were told to take baloxavir marboxil without regard to food, but food consumption relative to the first dose of baloxavir marboxil was documented. Pharmacokinetic parameters after the first dose of baloxavir were then measured. The primary endpoint was analyzed for three time periods: dosing of baloxavir marboxil more than 4 hours before or after food intake, dosing within 2 to 4 hours before or 2 to 4 hours after food intake, and dosing less than 2 hours before or less than 2 hours after food intake. The results are shown in the following table.

Table 10. Trial 1601T0831 –Time to Alleviation of Symptoms by Food Intake (Intent-to-Treat-Infected Population)

	Baloxavir marboxil	Placebo
Dosing > 4 hours before or > 4 hours after food intake	N=97	N=43
Median in hours (95% CI*)	50 (43.4, 66.3)	79 (62.4, 92.6)
Difference vs. placebo in hours	-29	--
P value#	0.0013	--
Dosing within 2-4 hours before or 2-4 hours after food intake	N=127	N=70
Median in hours (95% CI*)	50 (41.3, 54.9)	77 (62.7, 91.1)
Difference vs. placebo in hours	-27	--
P value#	0.0224	--
Dosing < 2 hours before or < 2 hours after food intake	N=181	N=90
Median in hours (95% CI*)	53 (47.1, 63.2)	80 (69.0, 92.9)
Difference vs. placebo in hours	-27	--
P value#	< 0.0001	--

*CI = confidence interval
#P value was calculated using the stratified Generalized Wilcoxon test.
Source: Clinical Study Report 1601T0831, Table 11-6, page 114.

The median time to alleviation of influenza symptoms was significantly shorter in the baloxavir marboxil arm compared to the placebo arm regardless of the timing of dosing relative to food intake. Therefore, the relationship of food intake to dosing with baloxavir marboxil did not appear to affect the efficacy of baloxavir marboxil and the package insert will state that baloxavir marboxil can be given without regard to food intake.

Time to alleviation of symptoms by time from onset of influenza symptoms to treatment
The primary endpoint was analyzed by time from onset of influenza symptoms to time of treatment. The trial enrolled patients who had symptoms of influenza for 48 hours or less. This analysis compared the median time to alleviation of symptoms for subjects with symptom onset 24 hours or less prior to treatment to that for subjects with symptom onset more than 24 hours but up to 48 hours prior to treatment. The median time to alleviation of symptoms for subjects who had been symptomatic for ≤ 24 hours prior to treatment and who received baloxavir marboxil was 49 hours (95% CI of 44.0, 53.1). The median time to alleviation of symptoms for subjects who had been symptomatic for ≤ 24 hours prior to treatment and who received placebo was 82 hours (95% CI of 69.5, 92.9). The time to alleviation of symptoms was 33 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value < 0.0001). The median time to alleviation of symptoms for subjects who had been symptomatic for > 24 to ≤ 48 hours prior to treatment and who received baloxavir marboxil was 66 hours (95% CI of

54.4, 74.7). The median time to alleviation of symptoms for subjects who had been symptomatic for > 24 to ≤ 48 hours prior to treatment and who received placebo was 79 hours (95% CI of 69.0, 91.1). The time to alleviation of symptoms was 13 hours shorter in the baloxavir marboxil arm compared to the placebo arm (P value = 0.0080). The median time to alleviation of symptoms was significantly lower in the baloxavir marboxil arm compared to placebo regardless whether baloxavir marboxil was administered within 24 hours of symptom onset or from 24 to 48 hours of symptom onset. Efficacy in patients with onset of symptoms longer than 48 hours prior to treatment was not evaluated in this trial.

Time to alleviation of symptoms by influenza subtype
Time to alleviation of symptoms by influenza virus subtype is shown in the following table.

Table 11. Trial 1601T0831 –Time to Alleviation of Symptoms by Influenza Virus Type and Subtype (Intent-to-Treat-Infected Population)

	Baloxavir marboxil	Placebo
Influenza A/H1N1	N=7	N=7
Median in hours (95% CI*)	44 (22.0, 109.1)	141 (82.1, --)
Difference vs. placebo in hours	-97	---
P value#	0.4212	
Influenza A/H3N2	N=392	N=195
Median in hours (95% CI*)	52	80
Difference vs. placebo in hours	-28	---
P value#	<0.0001	---
Influenza B	N=38	N=20
Median in hours (95% CI*)	93	77
Difference vs. placebo in hours	+16	---
P value#	0.8568	---

*CI = confidence interval
#P value was calculated using the stratified Generalized Wilcoxon test.
Source: Clinical Study Report 1601T0831, Table 11-6, page 114.

The majority of influenza identified in Trial 1601T0831 was influenza A/H3N2, and the results for this strain provided the support for the efficacy of baloxavir marboxil. There were two few subjects with A/H1N1 (14 subjects) to reach any definitive conclusions about the efficacy of baloxavir marboxil against A/H1N1 from these data. Influenza B was isolated in 38 subjects (8%) in the baloxavir marboxil arm and in 20 subjects (9%) in the placebo arm. The time to alleviation of symptoms in subjects with influenza B who received baloxavir marboxil was 93 hours compared to 77 hours in subjects with influenza B who received placebo. As a result,

subjects with influenza B in the baloxavir marboxil arm were symptomatic for 16 hours longer than those in the placebo arm. This may have been due to the small sample size for subjects with influenza B; the confidence intervals for the median time to alleviation of symptoms are much wider for influenza B than for H3N2. However, given the higher *in vitro* IC_{50} for influenza B compared to influenza A, differences in efficacy for influenza A and B cannot be ruled out. (See Dr. Ince's Virology review and see the Integrated Review of Efficacy section of this review for a discussion of efficacy of baloxavir marboxil across trials.)

Data Quality and Integrity

Data integrity issues were identified at one study site (Study Center 811) by the Applicant when they audited the site for a different trial. This site enrolled 10 subjects in this trial. One subject was enrolled in the placebo arm, four in the baloxavir marboxil arm, and five in the oseltamivir arm. All 10 subjects were included in the ITTI population. The Applicant conducted a sensitivity analysis of the primary endpoint excluding the data from this site. The exclusion of the subjects from Study Center 811 did not change the median time to alleviation of symptoms in either the baloxavir arm (54 hours) or in the placebo arm (80 hours).

Efficacy Results – Secondary and other relevant endpoints

Results for time to alleviation of symptoms comparing baloxavir marboxil and oseltamivir
Time to alleviation of influenza symptoms was compared between the baloxavir marboxil arm and the oseltamivir arm in subjects 20 years of age and older. Oseltamivir was not used in subjects less than 20 years of age because of concerns of neuropsychiatric adverse events by the Japanese regulatory authorities. The median time to alleviation of symptoms in subjects who received baloxavir marboxil and were at least 20 years of age was 54 hours (95% CI of 48.0, 58.5). The median time to alleviation of symptoms in the oseltamivir arm was also 54 hours (95% CI of 50.2, 56.4). There was no difference between the two treatment arms.

Individual components of the primary endpoint
The primary endpoint, the time to alleviation of symptoms, was composed of temperature, systemic or general symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue), and respiratory symptoms (cough, sore throat, and nasal congestion). The Applicant analyzed the components of the endpoint individually.

Time to resolution of fever
The time to resolution of fever was 25 hours (95% CI of 22.6, 26.6) for subjects who received baloxavir marboxil compared to 42 hours (95% CI of 37.4, 44.6) for subjects who received placebo. The time to resolution of fever was 17 hours earlier in the baloxavir marboxil arm than in the placebo arm ($p < 0.0001$).

Subjects were allowed to take acetaminophen for fever as a rescue medication but were

instructed to take their temperature before taking acetaminophen or at least four hours after acetaminophen dose. Rescue medicine use was similar in the baloxavir arm (13% of subjects) and the placebo arm (12% of subjects). It is unclear whether the use of acetaminophen may have affected this analysis. On analysis of the concomitant medications datasets, 10% of subjects in the baloxavir arm took prohibited medications for fever (NSAIDs or antipyretics) during their influenza illness compared to 9% in the placebo arm. Overall, treatment with baloxavir did not appear to affect the use of medications for fever.

Time to alleviation of systemic symptoms
The median time to alleviation of systemic symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue) for subjects in the baloxavir marboxil was 34 hours (95% CI of 31.0, 38.3) compared to 54 hours in the placebo arm (95% CI of 45.9, 57.3). Systemic symptoms resolved 20 hours earlier in the baloxavir marboxil arm compared to the placebo arm ($p < 0.0001$).

Time to alleviation of respiratory symptoms
The median time to alleviation of respiratory symptoms (cough, sore throat, and nasal congestion) for subjects in the baloxavir marboxil was 46 hours (95% CI of 43.4, 50.6) compared to 69 hours in the placebo arm (95% CI of 63.9, 78.1). Respiratory symptoms resolved 23 hours earlier in the baloxavir marboxil arm compared to the placebo arm ($p < 0.0001$).

The median time to alleviation of each of the three respiratory symptoms was longer than for the individual four systemic symptoms. The median time to alleviation of the individual respiratory symptoms in the baloxavir marboxil arm ranged from 32 to 38 hours and in the placebo arm ranged from 41 to 61 hours. Median time to alleviation of cough was the longest (38 hours in the baloxavir marboxil arm and 61 hours in the placebo arm). In contrast, the median time to alleviation of individual systemic symptoms in the baloxavir marboxil arm ranged from 21 to 26 hours and in the placebo arm ranged from 26 to 41 hours.

<u>Secondary virologic endpoints</u>
Please Dr. Ince's Virology review for full details.

Time to cessation of viral shedding
Nasopharyngeal swabs were sent for viral culture daily from Days 2 to 6 and on Day 9. The median time to cessation of viral shedding by influenza culture was 24 hours in the baloxavir marboxil arm and 96 hours in the placebo arm ($p < 0.0001$). In the subset of subjects 20 years of age and older, the median time to cessation of viral shedding was 24 hours in the baloxavir marboxil arm and 72 hours in the oseltamivir arm ($p < 0.0001$). For reasons stated in this review, the clinical significance of this finding is unclear.

Results on Days 2 to 6 and on Day 9 were compared to examine the proportion of subjects with

viral shedding at each time point. On Day 2, virus was isolated in 48% of subjects in the baloxavir marboxil arm compared to the 96% of subjects in the placebo arm ($p < 0.0001$). There was also a statistically significant decrease in the proportion of subjects with viral shedding in the baloxavir marboxil arm compared to the placebo arm on Day 3 (22% compared to 71%), Day 4 (17% compared to 56%), and Day 5 (14% compared to 30%). On Day 6, there was no longer a statistically significant difference in the proportion of subjects with influenza virus isolated in the baloxavir marboxil arm (8%) compared to the placebo arm (13%).

Although the median time to alleviation of influenza symptoms was identical in the baloxavir marboxil arm and the oseltamivir arm, the proportion of subjects with influenza virus was statistically significantly lower in the baloxavir marboxil arm than in the oseltamivir arm on Days 2, 3 and 5. See Table 12.

Table 12: Trial 1601T0831 –Proportion of Subjects with Positive Influenza Virus Titer by Time Point in Subgroup of Subjects 20 Years of Age and Older (Intent-to-Treat-Infected Population)

	Baloxavir marboxil	Oseltamivir
Day 2	N=161	N=348
Proportion with influenza isolated	47%	91%
P value	< 0.0001	--
Day 3	N=355	N=344
Proportion with influenza isolated	20%	57%
P value	P < 0.0001	--
Day 4	N=87	N=105
Proportion with influenza isolated	16%	28%
P value	P=0.0852	
Day 5	N=333	N=336
Proportion with influenza isolated	13%	21%
P value	P=0.0063	
Day 6	N=71	N=78
Proportion with influenza isolated	6%	9%
P value	P=0.6187	
Day 9	N=336	N=340
Proportion with influenza isolated	3%	3%
P value	P=0.8637	

Source: Clinical Study Report 1601T0831, Table 11-7, page 116.

The number of subjects with samples available on Days 4 and 6 were much smaller than at other visits, because the Day 4 and Day 6 visits were optional.

As shown in the table, the percentage of subjects with influenza virus isolated on Days 2, 3 and 5 were significantly lower in the baloxavir marboxil arm. However, influenza viral shedding has

not been clearly associated with clinical resolution of symptoms; and in this study, there was no difference in the clinical resolution of influenza symptoms between the baloxavir marboxil and oseltamivir arms. It is also important to note that the proportion of subjects with positive viral culture is not a validated surrogate endpoint for transmission, and a formal transmission study of baloxavir marboxil has not been conducted at this time. The Applicant did conduct interviews to query subjects in Japan if other household members were diagnosed with influenza during the study, but there was no statistical difference between treatment arms in this household transmission substudy. Finally, there are issues regarding the methodology of the assays used and about the possibility of false negatives in the baloxavir marboxil arm due to baloxavir marboxil carryover in samples (see Dr. Ince's Virology review). Overall, the clinical significance of these data is not clear at this time.

Incidence of influenza-related complications

Influenza-related complications were reported in 16 subjects (4%) in the baloxavir marboxil arm and in 10 subjects (4%) in the placebo arm. Influenza-related complications diagnosed in subjects in the baloxavir marboxil arm were bronchitis (N=9), sinusitis (N=4), otitis media (N=2), and pneumonia (N=2). The influenza-related complications diagnosed in the placebo arm were bronchitis (N=8), sinusitis (N=2) and pneumonia (N=1). There was no significant difference either in the overall incidence of influenza-related complications or in the incidence of individual types of influenza-related complications.

Results of Quality of Life questionnaires

Although the scores on the three different quality of life scales were better in the baloxavir marboxil arm compared to the placebo arm, none of the differences between the two study arms were statistically significant.

Results for household infection substudy

Although the number of subjects who were diagnosed with influenza within the household was lower in the baloxavir marboxil arm than in the placebo arm on Days 1 through 3, this difference did not reach statistical significance.

Dose/Dose Response

Please see the section in this review entitled, time to alleviation of symptoms by weight and dose.

Durability of Response

Influenza infection leads to a self-limited disease; therefore, the durability of response is not relevant to this review.

Persistence of Effect

Influenza infection leads to a self-limited disease; therefore, the persistence of effect is not relevant to this review.

Additional Analyses Conducted on the Individual Trial

Please see Dr. Smith's Biostatistics review, Dr. Ince's Virology review, and the Clinical Pharmacology reviews for additional analyses of the study efficacy results.

6.2 Trial 1518T0821

6.2.1.1 Study Design

Overview and Objective

Trial 1518T0821 was a Phase 2, randomized, placebo-controlled, dose-finding study in subjects with uncomplicated influenza who were from 20 to 64 years of age. The study design was similar to that of the Phase 3 trial, 1601T0831. Major differences in design of the two trials are shown in the following table.

Table 13. Differences in Trial Design between 1518T0821 and 1601T0831

	Trial 1518T0821 Phase 2 Trial	Trial 1601T0831 Phase 3 Trial
Baloxavir marboxil dose	10, 20, or 40 mg	Weight-based dosing of 40 or 80 mg
Age group studied	12 to ≤ 64 years	12 to ≤ 64 years
Control	Placebo	Placebo or oseltamivir in 20 to ≤ 64 years age group Placebo only in 12 to < 20 years age group
Influenza diagnosis	RAT*	RIDT^ confirmed by RT-PCR
Stratification	Composite symptom score and smoking status	Composite symptom score and geographic region
Tablet used	10 mg and 20 mg	20 mg to-be-marketed tablet
Location	Japan	Japan, US, and Canada

*RAT = rapid antigen test
^RIDT = rapid influenza diagnostic test
Source: Clinical reviewer

This trial (non-IND) was conducted in Japan. The protocol was not submitted to Food and Drug

Administration prior to initiation of the trial.

The primary objective of the study was to evaluate the efficacy of baloxavir marboxil (10 mg, 20 mg, and 40 mg) versus placebo in subjects with influenza virus infection.

The secondary objectives were:

- To assess the efficacy of baloxavir marboxil versus placebo as measured by secondary endpoints,
- To assess the safety of baloxavir marboxil as measured by the frequencies of adverse events and treatment-related AEs, and
- To determine the pharmacokinetics of the active form of baloxavir marboxil, baloxavir, in subjects with influenza virus infection.

Trial Design

Trial 1518T0821 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of baloxavir marboxil in subjects from 20 to 64 years of age with influenza. Eligible subjects were stratified by their composite symptom score at baseline (≤ 11 or ≥ 12) and smoking status and then randomized in a 1:1:1:1 ratio to receive a single 10 mg, 20 mg, or 40 mg oral dose of baloxavir marboxil or to receive a single dose of placebo. The study drug was administered on Day 1 at the study site.

This trial was a dose finding study and the 40 mg dose was identified for Phase 3 trials. After discussions between FDA and the Applicant regarding the PK relationship between weight and exposure, the 80 mg dose was also studied in the Phase 3 trial. The indicated dose for baloxavir marboxil will be weight-based dosing of 40 mg or 80 mg as studied in the Phase 3 trial. Therefore, only the safety and efficacy results for subjects who received the 40 mg dose in Trial 1518T0821 will be included in the package insert.

Subjects were diagnosed with influenza using a commercially available rapid antigen kit; the diagnosis was not confirmed with RT-PCR. In general, rapid antigen kits are less sensitive than RT-PCR, which we typically recommend for identification of the ITTI population (FDA Guidance for Industry, "Influenza: Developing Drugs for Treatment and/or Prophylaxis").

Subjects recorded their symptoms in an electronic Diary (eDiary) to record signs and symptoms of influenza. Subjects were to self-assess 7 influenza symptoms daily: cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue and rated the severity of each symptom on a 4-point scale [0 (none), 1 (mild), 2 (moderate), and 3 (severe)]. Symptoms were assessed and recorded in the eDiary twice daily until Day 9 and once daily from Day 10 to Day 14. Subjects were provided with a thermometer on Day 1 and were to measure and record their temperature four times a day (morning, noon, evening, and bedtime)

until Day 3 and twice daily from Day 4 to Day 14. Noncompliance with the eDiary was defined as failure to record 20% or more of the required assessments.

If influenza symptoms were so severe that the subjects needed rescue therapy between Day 1 and Day 22, subjects were permitted to take acetaminophen at a dose of 3000 mg/day or less for the relief of fever or pain. Subjects were to record the date and time of each acetaminophen dose in the subject eDiary. Subjects were instructed to measure and record body temperature and to assess and record influenza symptoms either immediately before the use of acetaminophen or more than 4 hours after an acetaminophen dose.

Blood samples were collected for pharmacokinetic assessment on Days 2 and 4. If "circumstances permitted," samples were also collected within the period of 0.5 hours to 4 hours after dosing on Day 1, Day 3, and Day 15.

Nasopharyngeal swabs for influenza were collected predose on Day 1 and on Day 2, Day 6; and Day 9. Nasopharyngeal swabs were optional on Day 3. Nasopharyngeal swabs were collected on Days 15 from subjects who still had symptoms of influenza. Nasopharyngeal swabs were used for virus culture, virus subtyping, sensitivity testing and gene sequencing.

Subjects were to rate their ability to perform activities of daily life on a scale of 0 to 10 daily until Day 14. No other description of this self-assessment was provided. Subjects were to complete the two part EQ-5D-5L quality of life questionnaire on Days 1, 2, 6, 9 and 15. The two parts of the EQ-5D-5L were the descriptive part and a visual analog scale. The description part was composed of 5 sections: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each section had 5 responses to rate severity within that level. In the visual analogue section, the subject rated their health on a 20-cm vertical visual analogue with "best health you can imagine" as 100 and "the worst health you can imagine" as 0. These quality of life questionnaires were not assessed by the FDA Clinical Outcome Assessment team and the Applicant did not submit a validation package to support their use. Therefore, these questionnaires are not considered validated and appropriate tools for use to assess quality of life in this trial.

Each subject had a minimum of 7 study visits. Subjects were to be followed for 14 days for efficacy and for 22 days for safety. The study duration for individual subjects was 22 days.

Subjects in the baloxavir marboxil 10 mg arm received one 10 mg tablet, subjects in the 20 mg tablet arm received one 20 mg tablet, and subjects in the 40 mg arm received two 20 mg tablets. The 10 mg tablet was subsequently compared to the 20 mg tablet in a bioequivalence study and was not bioequivalent, i.e., two 10 mg tablets resulted in lower plasma concentrations than one 20 mg tablet of baloxavir marboxil. However, a statistically significance decrease in the median time to alleviation of symptoms was also observed in the

baloxavir marboxil 10 mg dose compared to placebo, as shown in Table 19 in this review.

Study Population:
Inclusion criteria:
The trial enrolled males and females ≥ 20 to ≤ 64 years of age with a clinical diagnosis of influenza. Influenza diagnosis was confirmed by all of the following:

- Positive rapid antigen test (RAT) for influenza from a nasal or throat swab
- Fever ≥ 38° C (axillary);
- At least one of the following general systemic symptoms with a severity of moderate or greater:
    - Headache,
    - Feverishness or chills,
    - Muscle or joint pain, or
    - Fatigue
- At least one of the following respiratory symptoms with a severity of moderate or greater:
    - Cough,
    - Sore throat, or
    - Nasal congestion.
- The time interval between the onset of symptoms and enrollment must have been ≤ 48 hours.

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

- Severe influenza virus infection requiring inpatient treatment;
- Concurrent infection(s) requiring systemic antimicrobial at the predose examination;
- Receipt of peramivir, laninamivir, oseltamivir, zanamivir, rimantidine, umifenovir, or amantadine within 7 days prior to the predose examination (note that neither laninamivir nor umifenovir are FDA-approved for treatment of influenza);
- Presence of risk factors for severe influenza disease based on the definition of high risk by the Centers of Disease Control and Prevention.

Study Endpoints

The primary efficacy endpoint was the time to alleviation of symptoms. Time to alleviation of symptoms was defined as the time between the initiation of the study treatment and the alleviation of influenza symptoms. The alleviation of influenza symptoms was defined as the time when all of the 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the subject as 0 (none) or 1 (mild) in the eDiary for a duration of at least 21.5 hours (24 hours minus 10%).

The secondary efficacy endpoints included:

- Time to alleviation of individual 7 symptoms at each time point;
- Time to resolution of fever (self-measured axillary temperature < 37° C for at least 12 hours);
- Proportion of subjects reporting a normal temperature (< 37° C) at each time point;
- Time to return to pre-influenza health status based on information from questionnaires; and
- Incidence of influenza-related complications (sinusitis, otitis media, bronchitis, and pneumonia) after the initiation of study treatment.

The virologic endpoints were secondary endpoints and included:

- Proportion of subjects positive for influenza by viral culture and proportion of subjects positive by RT-PCR at each time point and
- Time from initiation of study treatment to cessation of viral shedding by virus titer and by RT-PCR.

See Dr. Ince's Virology review for a complete discussion of virologic outcomes.

Statistical Analysis Plan

Subjects were randomized in a 1:1:1:1 ratio using an interactive web response system to a single 10 mg, 20 mg, or 40 mg dose of baloxavir marboxil or placebo. Randomization was stratified by baseline composite symptom score (≤ 11 / ≥ 12) and smoking. The trial was conducted in a double-blind fashion. All study subjects, investigators, study personnel, and data analysts were blinded to treatment assignment until database lock.

The calculated sample size for comparison of baloxavir marboxil and placebo for the primary efficacy endpoint, time to alleviation of symptoms was 400 subjects (100 subjects per arm). The median time to alleviation of symptoms was estimated to be 100 hours. The hazard ratio versus the placebo group was estimated to be 0.65 for the 40 mg arm, 0.7 for the 20 mg arm, and 0.8 for the 10 mg arm. This sample size and these assumptions together with a two-sided significance level of 0.05 would result in at least an 80% power to detect a difference between the baloxavir marboxil arms and the placebo arm. A Cox proportional hazards model was used to identify the p-value.

The primary efficacy endpoint was the comparison of time to alleviation of symptoms between the baloxavir marboxil and placebo arms. The time to alleviation of symptoms was compared using the stratified generalized Wilcoxon test with composite symptoms score at baseline (≤ 11 or ≥ 12) and region (Japan/Asia or rest of the world) as stratification factors. The stratified generalized Wilcoxon test was also used to compare the time to alleviation of symptoms between the baloxavir marboxil and oseltamivir arms in subjects 20 to ≤ 64 years of age. Together with the primary efficacy analysis, this comparison was conducted in a hierarchical

manner to control for Type 1 error.

The analysis populations for this trial were as follows.

- The intent-to-treat infected population (ITTI) included all subjects who received the study drug and had a confirmed diagnosis of influenza virus infection based on RAT results. This population was analyzed according to treatment to which the subjects were randomized. The ITTI population was the primary population for all efficacy analyses.
- The safety population included all randomized subjects who receive at least one dose of study drug. This population was analyzed according to treatment received. The safety population was used for all safety analyses.
- The per-protocol set (PPS) includes all randomized subjects in the ITTI population who did not have any protocol violations, who met the study entry criteria and who had adequate follow-up. The PPS was used for a sensitivity analysis of the primary endpoint.

Protocol Amendments

The protocol was not amended.

6.2.2 Study Results

Compliance with Good Clinical Practices

The trial was not conducted under U.S. IND. The Applicant states that the trial was conducted in accordance with Good Clinical Practice guidelines, all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in FDA guidance for industry, "Financial Disclosure by Clinical Investigators." See Section 13.1 of this review for the NDA financial disclosure form. No clinical investigators or sub-investigators were employees of Shionogi, Incorporated. No investigators or sub-investigators had disclosable financial interests or arrangements. The trial design also minimizes potential bias, because it was a double-blind, randomized, placebo-controlled trial. Therefore, in the opinion of this reviewer, there was no bias due to the financial interests of investigators.

Patient Disposition

Trial 1518T0821 was conducted at 72 study sites in Japan. The first subject was enrolled on December 2, 2015, and the last subject completed the study on April 2, 2016.
A total of 400 subjects were randomized to receive one of three doses of baloxavir marboxil

(N=300) or placebo (N=100). The majority of study subjects (389/400 or 97%) completed the trial. The number of subjects who discontinued the trial prematurely and the reasons for premature discontinuation are shown in the following table.

Table 14. Trial 1601T0821 – Patient Disposition and Reasons for Premature Discontinuation

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	
Randomized*	100	100	100	100
Completed trial	98	95	99	100
Prematurely discontinued trial	2	5	1	3
Reason for premature discontinuation				
Consent withdrawn	0	1	1	2
Lost to follow-up	1	1	0	0
Lack of efficacy	0	2	0	0
Investigator discretion	1	1	0	1

*Because 100 subjects were randomized to each arm, the number and percentage of subjects are the same, and only the number of subjects is shown in this table.
Source: Clinical Study Report 1518T0821, Figure 10-1, page 72.

As shown in Table 14, the majority of subjects finished the trial, and the percentage of subjects who finished the trial was similar in the three study arms. The most common reasons for premature discontinuation were withdrawn consent and loss to follow-up. The reasons for withdrawal by investigator discretion were due to investigator's decision to use oseltamivir, use of prohibited medication to treat allergies (referred to as "pollinosis"), and for treatment of nasopharyngitis. The number of individual reasons for premature study discontinuation were small and were similar between arms except for lack of efficacy, which was reported in two subjects (2%) in the baloxavir marboxil 20 mg dose arm and in none of the other study arms. As shown in this review, the efficacy of baloxavir marboxil was similar in the three baloxavir marboxil arms, so the reason for lack of efficacy only in this arm is unclear. However, the number of subjects with lack of efficacy is small.

Protocol Violations/Deviations

A total of 400 subjects were randomized to one of the three baloxavir marboxil arms or the placebo arm. The number of subjects in the safety population, intent-to-treat infected population, and per protocol population and reasons for exclusion from the per protocol population are shown in the following table.

Table 15. Trial 1601T0821 – Study Populations and Reasons for Exclusion

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	
All Randomized	100	100	100	100
Safety population	100	100	100	100
Intent-to-treat infected population	100	100	100	100
Received prohibited medications	9	4	3	7
Insufficient follow-up	1	2	0	2
Violated entry criteria	1	2	1	0
Per protocol population	89	92	96	91

Source: Clinical Study Report 1518T0821, Table 11-1, page 74.

All randomized subjects received a dose of study drug and were included in the safety population. All subjects were diagnosed with influenza by a rapid antigen test prior to enrollment, therefore, all subjects were also included in the ITTI population. The majority of subjects were included in the per protocol (PP) population. The percentage of subjects excluded from the PP population was similar in the four treatment arms; there was no clear relationship between exclusion from the PP population and baloxavir marboxil dose. Based on the small numbers of protocol violations and low numbers of premature discontinuations, the trial appears to have been well conducted.

Table of Demographic Characteristics

Table 16. Trial 1518T0821 - Demographic Characteristics

Demographic Parameters	Control Group / Placebo (N=100)	Baloxavir marboxil			
		10 mg (N=100)	20 mg (N=100)	40 mg (N=100)	Total (N=300)
Sex					
Male	61	68	58	60	186 (62%)
Female	39	32	42	40	114 (38%)
Age					
Mean years (SD)	37.4	37.7	37.9	37.3	37.6
Median (years)	37	36	36.5	38	37
Min, max (years)	20, 64	20, 62	20, 60	20, 63	20, 63
Race					
Asian	100	100	100	100	300 (100%)

Source: Clinical Study Report 1518T0821, Table 11-2, page 75.

The majority of subjects in all four treatment arms were male, all subjects were Asian, and the median age of subjects in all four arms was 37 years. The demographic characteristics were similar in all four treatment arms, and no differences that could have affected the trial results were identified.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Additional baseline characteristics

The percentage of subjects who were smokers ranged from 31% to 33% in the baloxavir marboxil arms and was 33% in the placebo arm. Overall 30% of subjects in the baloxavir arms had received the influenza vaccine prior to study participation; the percentage was lower in the 20 mg arm (20%) compared to the 10 mg arm (34%) and the 40 mg arm (37 %). The percentage of subjects in the placebo arm who had received a seasonal influenza vaccine was 31%. Because inactivated influenza vaccine and baloxavir marboxil are unlikely to interact, the differences in vaccination rates probably did not affect the efficacy results.

Disease characteristics

All subjects were enrolled within 48 hours of onset of influenza symptoms. The duration of influenza symptoms prior to treatment by time period are shown in the table below.

Table 17. Trial 1518T0821 – Time from Influenza Symptom Onset to Treatment

Hours	Placebo (N=231) n (%)	Baloxavir marboxil		
		10 mg N=100	20 mg N=100	40 mg N=100
0 to ≤ 12 hours	11	7	15	12
> 12 to ≤ 24 hours	42	38	40	28
> 24 to ≤ 36 hours	22	30	18	36
> 36 to ≤48 hours	25	25	27	24

Source: Clinical Study Report 1518T0821, Table 11-2, page 106.

Most subjects were enrolled from 12 to 36 hours from onset of symptoms; fewer subjects were enrolled either within 12 hours of symptom onset or 36 hours or longer after symptom onset. Time from influenza symptom onset to treatment was similar across arms except that fewer subjects were enrolled in the baloxavir marboxil arm in the > 24 hour to ≤ 36 hour time period. This difference is mostly offset by the increased number of subjects in the 20 mg arm who were enrolled in the > 12 hour to ≤ 24 hour time period.

The influenza virus subtypes identified among enrolled subjects are shown in the following table. The total number of subjects in each treatment arm is the number of subjects who had influenza type identified.

Table 18. Trial 1518T0821 – Influenza Virus Types and Subtypes

	Placebo N=98	Baloxavir marboxil		
		10 mg N=100	20 mg N=99	40 mg N=97
A/H1N1	69 (70%)	66 (66%)	71 (72%)	61 (63%)
A/H3N2	6 (6%)	13 (13%)	5 (5%)	12 (12%)
B	23 (23%)	21 (21%)	23 (23%)	24 (25%)

Source: Clinical Study Report 1518T0821, Table 11-26, page 103.

The most common influenza subtype identified in the trial was A/H1N1, which was identified in 68% of subjects (67% of subjects in the baloxavir marboxil arms and 70% in the placebo arm). Influenza A/H3N2 was identified in 10% of subjects in the baloxavir marboxil arms and 6% in the placebo arm. Influenza B was identified in 23% of subjects in the baloxavir marboxil arms and in 23% of subjects in the placebo arm. The percentages of each subtype were generally similar across the treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance
Baloxavir marboxil and placebo were administered as a single oral dose, which was administered at the study site, so compliance with study treatment was 100%.

Concomitant medications
Concomitant medications were used during the first five study days by 74% of subjects in the placebo arm, 78% in the baloxavir marboxil 10 mg arm, 77% in the baloxavir marboxil 20 mg arm, and 78% in the baloxavir marboxil 40 mg arm. Use of paracetamol (acetaminophen) as a rescue medicine was allowed in the study protocol; use of other medications to treat influenza symptoms was not allowed and resulted in exclusion from the per protocol population. The majority of subjects used antipyretic or anti-inflammatory, such as paracetamol (acetaminophen) or an NSAID (74% of subjects in the placebo arm, 77% in the baloxavir marboxil 10 mg arm, 73% in the baloxavir marboxil 20 mg arm, and 77% in the baloxavir marboxil 40 mg arm). Use of cold medications was uncommon and was reported in ≤ 7% in each treatment arm. Use of antibiotics and antivirals, including other anti-influenza agents, also resulted in exclusion from the per protocol population. Antibiotic use was also uncommon and was reported in 2 subjects in the placebo arm, 3 in the baloxavir marboxil 10 mg arm, 1 in the baloxavir marboxil 20 mg arm, and 2 in the baloxavir marboxil 40 mg arm. Anti-influenza antivirals (laninamivir or peramivir) were administered to 3 subjects in the placebo arm, 3 in the baloxavir marboxil 10 mg arm, 2 in the baloxavir marboxil 20 mg arm, and 1 in the baloxavir marboxil 40 mg arm; all started the other antiviral drug on Day 2 or Day 3 of the study. Overall, the percentage of subjects using concomitant medications and the type of medications used

was similar in the four treatment arms. There was no difference in the need for antipyretics or the need for antibiotics between the baloxavir marboxil arms and the placebo arm. Acetaminophen was allowed as a rescue medication in this trial and in Trial 1601T0831. There was no correlation between the baloxavir marboxil dose and the need for any concomitant medication, for antipyretics, or for antibiotics.

Rescue medication use

If influenza symptoms were so severe that the subjects needed rescue therapy between Day 1 and Day 22, subjects were permitted to take paracetamol (acetaminophen). The proportion of subjects who used acetaminophen was similar in the four treatment arms (77% to 80%).

Efficacy Results – Primary Endpoint

Please see Dr. Fraser Smith's Biostatistics review for an additional discussion of efficacy.

The primary efficacy endpoint was the comparison of time to alleviation of symptoms between the baloxavir marboxil and placebo arms; the results are shown in the following table.

Table 19. Trial 1518T0821 – Results for Primary Efficacy Endpoint: Time to Alleviation of Symptoms (Intent-to-Treat-Infected Population)

	Baloxavir marboxil			Placebo N=100
	10 mg N=100	20 mg N=100	40 mg N=100	
Median in hours (95% CI*)	54 (47.7, 66.8)	51 (44.5, 62.4)	50 (44.5, 64.4)	78 (67.6, 88.7)
Difference in median vs. placebo in hours	-24	-27	-28	---
P-value by Cox proportional hazards model	0.0561	0.1488	0.1650	---
P-value by Generalized Wilcoxon test	0.0085	0.0182	0.0046	

*CI = confidence interval
Source: Clinical Study Report 1518T0821, Table 11-6, page 79.

The median time to alleviation of influenza symptoms was 54 hours in the baloxavir marboxil 10 mg arm, 51 hours in the 20 mg arm, and 50 hours in the 40 mg arm. The results were similar in the three baloxavir arms but the difference in median time to alleviation of symptoms vs. placebo only increased slightly with increasing baloxavir marboxil dose. The difference between the median time to alleviation of symptoms in the baloxavir arms and the placebo arm ranged from 24 to 28 hours. The protocol- defined statistical test for determination of statistical significance was the Cox proportional hazards model. Using this method, the results

for the primary endpoint were not statistically significant. However, Phase 2 trials are typically designed to identify the dose for use in Phase 3 trials based on safety and efficacy data and are not adequately powered to demonstrate superiority. Therefore, the lack of statistical significance is not necessarily indicative of lack of efficacy. In addition, the difference in the median time to alleviation of symptoms between the baloxavir marboxil arms and the placebo arm is similar to that seen with other FDA-approved anti-influenza antivirals. (See Tamiflu® and Rapivab® package inserts). In addition, the Cox proportional hazards model may not have been the ideal method to analyze these data. The Wilcoxon test is a better statistical test for influenza trials because the Wilcoxon test puts more weight on early events, which is appropriate for the study of a self-limited disease. (See Dr. Smith's Biostatistics review). When the data were analyzed using the generalized Wilcoxon test, the results for all three baloxavir marboxil arms reached statistical significance.

Although the median time to alleviation of symptoms was similar in the three treatment groups (50 to 54 hours), it was shortest in the 40 mg baloxavir marboxil arm, which supports the use of the 40 mg dose in the treatment of influenza in otherwise healthy subjects. As discussed previously in this review, baloxavir exposure varies by race with exposure approximately 35% lower in non-Asians as compared to Asians. Therefore, these efficacy data also support the use of an 80 mg dose since the exposure in non-Asians who received 80 mg would be similar to the exposure in Asians who received 40 mg.

Subgroup analyses
Analyses of the primary endpoint for different subpopulations are shown in this section of the review. Subgroup analyses for gender and race were not provided for this study but were provided for both pivotal trials in the Clinical Summary of Efficacy. These results will be discussed in the Integrated Summary of Efficacy section of this review.

Time to alleviation of symptoms using the Per Protocol population
The results for the time to alleviation of symptoms using the Per Protocol population were similar to the results using the ITTI population. The results were provided as hazard ratios for each group. The results for the primary endpoint are shown for both the ITTI and the Per Protocol population in the following table.

Table 20. Trial 1518T0821 – Results for Primary Efficacy Endpoint: Time to Alleviation of Symptoms using Cox Proportional Hazards Model for Intent-to-Treat-Infected Population and Per Protocol Population

Baloxavir marboxil arm	Hazard ratio comparing baloxavir marboxil arm to placebo			
	ITTI population		Per Protocol Population	
	Hazard ratio (95% CI*)	P value	Hazard ratio (95% CI*)	P value
10 mg	0.758 (0.571, 1.007)	0.165	0.742 (0.551, 1.000)	0.1494
20 mg	0.810 (0.608, 1.078)	0.165	0.779 (0.578, 1.050)	0.1843
40 mg	0.817 (0.614, 1.087)	0.165	0.819 (0.609, 1.100)	0.1843

*CI = confidence interval
Source: Clinical Study Report 1518T0821, Tables 11-4 and 11-5, page 79.

As shown in Table 20, the hazard ratios for the time to alleviation of symptoms were similar in the ITTI and PP study populations. As discussed previously, the results were not statistically significant when using the Cox proportional hazards model.

Time to alleviation of influenza symptoms by smoking status
Approximately one-third of the trial population were smokers. The time to alleviation of symptoms was analyzed for smokers compared to non-smokers, and the results are shown in the following table.

Table 21. Trial 1518T0821 –Median Time to Alleviation of Symptoms by Smoking Habits (Intent-to-Treat-Infected Population)

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	
Smokers				
Number of subjects	33	32	31	33
Median in hours (95% CI*)	53 (45.1, 69.1)	59 (36.1, 69.3)	50 (37.9, 69.4)	79 (64.9, 91.3)
Difference vs. placebo in hours	-26	-20	-29	---
P value by Generalized Wilcoxon test	0.2300	0.4900	0.0941	--
Nonsmokers				
Number of subjects	67	68	69	67
Median in hours (95% CI*)	55 (47.7, 69.8)	49 (43.0, 61.7)	50 (39.0, 65.5)	78 (64.2, 90.7)
Difference vs. placebo in hours	-23	-29	-28	---
P value by Generalized Wilcoxon test	0.0180	0.0237	0.0151	

*CI = confidence interval
Source: Clinical Study Report 1518T0821, Table 11-28, page 105.

Influenza disease is often more severe in patients who smoke compared to those who do not; therefore, one would expect the time to alleviation of symptoms to be shorter in nonsmokers compared to smokers in this trial. On comparison of results for nonsmokers to smokers, in this trial, time to alleviation of symptoms was shorter for nonsmokers than smokers in the 20 mg arm (49 hours for nonsmokers compared to 59 hours for smokers). However, the number of subjects who smoked was small, so it is hard to reach any definitive conclusions regarding this analysis. In addition, the median time to alleviation of influenza symptoms was shorter in the baloxavir marboxil arms compared to the placebo arm regardless of dose, both for smokers and non-smokers.

Time to alleviation of symptoms by time of last food consumption
Blood samples were collected for the measurement of plasma drug concentrations once on Days 2 and 6. If "circumstances permitted," blood for PK measurements was also obtained on Days 1, 3, and 15. The primary endpoint was analyzed for three time periods: dosing of baloxavir marboxil more than 4 hours before or after food intake, dosing within 2 to 4 hours before or 2 to 4 hours after food intake, and dosing less than 2 hours before or less than 2 hours after food intake. The results are shown in the following table.

Table 22. Trial 1518T0821 –Time to Alleviation of symptoms by Time since Food Consumption (Intent-to-Treat-Infected Population)

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	N=100
Dosing >4 hours before or > 4 hours after food intake				
Number of subjects	31	32	25	30
Median in hours (95% CI*)	56 (43.1, 83.5)	52 (30.5,104.8)	54 (37.6,90.3)	91 (66.4,105.8)
Difference vs. placebo in hours	-35	-39	-37	---
P value#	0.0813	0.0099	0.0069	---
Dosing within 2-4 hours before or 2-4 hours after food intake				
Number of subjects	39	40	34	35
Median in hours (95% CI*)	51 (46.2, 71.0)	51 (44.2,68.0)	46 (28.7, 69.0)	69.0 (53.3, 88.7)
Difference vs. placebo in hours	-18	-18	-23	---
P value#	0.0778	0.1961	0.0286	---
Dosing < 2 hours before or < 2 hours after food intake				
Number of subjects	30	28	41	35
Median in hours (95% CI*)	55 (45.9, 73.2)	49 (31.2, 62.3)	53 (37.9, 68.9)	79 (63.4, 84.2)
Difference vs. placebo in hours	-24	-30	-26	--
P value#	0.4101	0.1722	0.4327	---

*CI = confidence interval
#P value was calculated using the stratified Generalized Wilcoxon test.
Source: Clinical Study Report 1518T0821, Table 11-29, page 106.

The median time to alleviation of influenza symptoms was shorter in the baloxavir marboxil arm compared to the placebo arm for all three baloxavir marboxil doses regardless of the timing of dosing relative to food intake. Overall, the results for median time to alleviation of symptoms were similar by dose for each time period. Therefore, food consumption did not appear to interfere with the efficacy of baloxavir marboxil and the package insert will state that baloxavir marboxil may be taken with or without food.

Time to alleviation of symptoms by influenza virus type or subtype
The median time to alleviation of influenza symptoms was analyzed by influenza type or subtype isolated. As shown in the following table, the majority of influenza types/subtypes isolated were influenza A/H1N1.

Table 23. Trial 1518T0821 –Time to Alleviation of Symptoms by Influenza Type or Subtype (Intent-to-Treat-Infected Population)

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	N=100
Influenza A/H1N1				
Number of subjects	66	71	61	69
Median in hours (95% CI*)	53 (45.9, 65.6)	47 (39.4,55.3)	48 (35.2, 65.5)	71 (64.9, 89.9)
Difference vs. placebo in hours	-18	-24	-23	
P value#	0.0084	0.0083	0.0049	---
Influenza A/H3N2				
Number of subjects	13	5	12	6
Median in hours (95% CI*)	66 (28.1, 83.5)	66 (21.3,188.5)	45 (23.5,113.4)	100 (18.9, 113.1)
Difference vs. placebo in hours	-34	-34	-55	---
P value#	0.1254	0.4913	0.2689	---
Influenza B				
Number of subjects	21	23	24	23
Median in hours (95% CI*)	63 (44.5, 82.3)	65 (46.4, 73.2)	63 (43.3, 69.8)	83 (58.1, 92.8)
Difference vs. placebo in hours	-20	-18	-20	--
P value#	0.2152	0.6608	0.1604	---

*CI = confidence interval
#P value was calculated using the stratified Generalized Wilcoxon test.
Source: Clinical Study Report 1518T0821, Table 11-26, page 103.

Of all subjects with the type or subtype of influenza isolated, 68% were infected with influenza A/H1N1, 23% with influenza B, and 9% with influenza A/H3N2. The median time to alleviation of symptoms was shorter in subjects who received baloxavir marboxil than in subjects who received placebo for all baloxavir marboxil doses and for all three influenza types or subtypes. This difference reached statistically significance for all three doses of baloxavir marboxil only in subjects infected with influenza A/H1N1. The time to alleviation of symptoms for the influenza B subgroup was somewhat higher compared to the influenza A subgroups for the 40 mg baloxavir dose but was still shorter than in the placebo group.

In Trial 1601T0831, in subjects infected with influenza B, the median time to alleviation of symptoms was longer in the baloxavir marboxil arm compared to the placebo arm. In the Phase 2 trial (1518T0821), the median time to alleviation of symptoms was shorter in the baloxavir marboxil arms compared to the placebo arm for subjects with influenza A and with influenza B. During the 2015/2016 influenza season in which Trial 1518T0821 was conducted, 56% of circulating influenza B strains were from the Yamagata lineage and 44% were from the

Victoria lineage (National Institute of Infectious Disease in Japan, www.niid.go.jp). In the following influenza season (2016/2017), in which 1601T0831 was conducted, the circulating influenza B lineage was reversed with 44% of circulating influenza B from the Yamagata lineage and 56% from the Victoria lineage (www.niid.go.jp). Influenza B lineage was not identified in the two pivotal trials, and efficacy by influenza B lineage could not be assessed. The discordant results for influenza B in the two pivotal trials could have been related to differences in B lineages.

Data Quality and Integrity

No issues were noted by Applicant audits of study sites or by FDA Office of Scientific Investigations that necessitated censoring of data or sensitivity analyses.

Efficacy Results – Secondary and other relevant endpoints

Time to alleviation of individual symptoms
Subjects with clinical influenza and a positive RAT were enrolled in the trial; clinical influenza was defined as axillary temperature ≥ 38.0° C with the presence of one respiratory symptom (nasal congestion, cough, or sore throat) of moderate or severe intensity and one general symptom (muscle or joint aches, fatigue, feverishness or chills, or headache) of moderate or severe intensity. The seven influenza symptoms were then followed daily for 14 days. The median time to alleviation of each individual symptom is shown in the following table. The most commonly reported respiratory influenza symptom was cough, which was reported in 75% of subjects; the most commonly reported generalized influenza symptom was feverishness or chills, which was reported in 95% of subjects.

Table 24. Trial 1518T0821 –Time to Alleviation of Individual Influenza Symptoms (Intent-to-Treat-infected population)

	Baloxavir marboxil			Placebo
	10 mg	20 mg	40 mg	
Nasal congestion				
Number of subjects	49	38	45	47
Median in hours (95% CI*)	25 (19.0, 47.2)	22 (13.4,30.5)	22 (16.0, 28.7)	43 (22.9, 68.3)
Difference vs. placebo in hours	-18	-21	-21	---
P value#	0.1500	0.0199	0.0081	---
Sore throat				
Number of subjects	56	64	55	46
Median in hours (95% CI*)	35 (21.2, 49.8)	28 (19.9,32.1)	32 (17.3, 43.0)	26 (16.5, 45.2)
Difference vs. placebo in hours	+9	+2	+6	---
P value#	0.1800	0.8047	0.6602	---
Cough				
Number of subjects	74	74	78	75
Median in hours (95% CI*)	31 (21.3, 41.5)	30 (21.9,32.9)	25 (16.1, 29.4)	31 (20.9, 51.4)
Difference vs. placebo in hours	0	-1	-6	---
P value#	0.6643	0.8536	0.1551	---
Muscle or joint aches				
Number of subjects	73	77	71	71
Median in hours (95% CI*)	31 (24.9, 39.9)	30 (22.8, 37.0)	25 (20.5, 28.9)	42 (28.7, 48.6)
Difference vs. placebo in hours	-11	-12	-17	---
P value#	0.2153	0.0346	0.0048	---
Fatigue				
Number of subjects	82	82	77	79
Median in hours (95% CI*)	32 (29.2, 39.9)	31 (26.7, 42.4)	31 (24.6, 38.6)	43 (30.3, 53.2)
Difference vs. placebo in hours	--11	-12	-12	---
P value#	0.1221	0.0594	0.0224	---
Feverishness or chills				
Number of subjects	97	93	94	95
Median in hours (95% CI*)	25 (21.3, 28.4)	29 (22.0, 34.8)	23 (19.8, 28.6)	29 (21.1, 33.4)
Difference vs. placebo in hours	-4	0	-6	---
P value#	0.0602	0.3774	0.0258	---

Headache				
Number of subjects	61	58	54	57
Median in hours (95% CI*)	42 (29.8, 47.3)	37 (28.5, 43.5)	38 (28.6, 44.5)	44 (29.7, 53.6)
Difference vs. placebo in hours	-2	-7	-6	---
P value#	0.6846	0.7741	0.0904	---

*CI = confidence interval
#P value was calculated using the stratified Generalized Wilcoxon test.
Source: Clinical Study Report 1518T0821, Table 11-8, page 83.

The trial was not powered to demonstrate differences between the baloxavir marboxil arms and the placebo arm for individual symptoms. Although the median time to alleviation of individual influenza symptoms was shorter in the 10 mg baloxavir marboxil arm compared to placebo for five of the seven symptoms, none of the comparisons between the baloxavir marboxil 10 mg arm and placebo reached statistical significance. In the 20 mg baloxavir marboxil arm, the time to alleviation of individual influenza symptoms was also shorter for five of the seven individual influenza in the baloxavir marboxil arm compared to placebo. The time to alleviation of two individual symptoms (nasal congestion and muscle or joint aches) was statistically significantly shorter in the baloxavir marboxil 20 mg arm compared to the placebo arm. In contrast, the median time to alleviation of individual influenza symptoms was shorter in the 40 mg baloxavir marboxil arm compared to placebo for six of the seven symptoms, and the median time to alleviation of four symptoms (nasal congestion, muscle and joint aches, fatigue, and feverishness or chills), was statistically significantly shorter in baloxavir marboxil 40 mg arm compared to placebo. The demonstration of efficacy against individual symptoms was dose-dependent, and the efficacy versus placebo was demonstrated most often in the baloxavir marboxil 40 mg arm. This supports the use of the baloxavir marboxil 40 mg dose for the treatment of influenza.

Time to alleviation of fever
The median time to alleviation of fever is shown in the following table.

Table 25. Trial 1518T0821 – Median Time to Alleviation of Fever (Intent-to-Treat-Infected Population)

	Baloxavir marboxil			Placebo N=100
	10 mg N=100	20 mg N=100	40 mg N=100	
Median in hours (95% CI*)	33 (26.9, 38.1)	32 (26.9, 35.8)	29 (24.5, 34.7)	45 (35.6, 54.0)
Difference vs. placebo in hours	-12	-13	-16	---
P value by Generalized Wilcoxon test	0.0128	0.0034	0.0003	---

*CI = confidence interval
Source: Clinical Study Report 1518T0821, Table 11-9, page 84.

The median time to alleviation of fever was statistically significantly shorter in all three baloxavir marboxil arms compared to the placebo arm.

Time to cessation of viral shedding
Nasopharyngeal swabs were sent for viral culture daily on Days 2, 3, 6 and Day 9. Results were compared to examine the proportion of subjects with viral shedding. On Day 2, virus was isolated in 48% of subjects in the baloxavir marboxil arm compared to the 96% of subjects in the placebo arm ($p < 0.0001$). There was also a statistically significant decrease in the proportion of subjects with viral shedding in the baloxavir marboxil arm compared to the placebo arm on Day 3 (22% compared to 71%), Day 4 (17% compared to 56%), and Day 5 (14% compared to 30%). On Day 6, there was no longer a statistically significant difference in the proportion of subjects with influenza virus isolated in the baloxavir marboxil arm (8%) compared to the placebo arm (13%).

Table 26. Trial 1518T0821 –Proportion of Subjects with Positive Influenza Virus Titer by Time Point in Subgroup of Subjects 20 Years of Age and Older (Intent-to-Treat-Infected Population)

	Baloxavir marboxil Arms			Placebo N=99
	10 mg N=99	20 mg N=100	40 mg N=98	
Day 2				
Proportion with influenza isolated	87%	72%	51%	94%
P value	0.0882	<0.0001	<0.0001	---
Day 3				
Proportion with influenza isolated	42%	37%	29%	82%
P value	<0.0001	<0.0001	<0.0001	---
Day 6				
Proportion with influenza isolated	11%	11%	11%	24%
P value	0.0204	0.0243	0.0250	---
Day 9				
Proportion with influenza isolated	0	0	1%	1%
P value	0.3115	0.3173	0.9730	---

Source: Clinical Study Report 1518T0821, Table 11-11, page 87.

Influenza viral shedding has not been clearly associated with clinical resolution of symptoms; and the decrease in viral shedding in the 40 mg arm does not correlate with clinical superiority of the baloxavir marboxil 40 mg arm compared to the 10 and 20 mg dose. In addition, there are issues regarding the methodology of the assays used and about the possibility of false negatives in the baloxavir marboxil arm due to carryover of baloxavir marboxil (Please see Dr. Ince's Virology review). Therefore, the clinical significance of these data is uncertain.

Incidence of influenza-related complications

Influenza-related complications were reported in only two subjects. One subject in the baloxavir marboxil 40 mg arm was diagnosed with bronchitis and otitis media, and one subject in the placebo arm was diagnosed with sinusitis. There were too few subjects with influenza-related complications to assess the difference between treatment arms and placebo.

Results of Quality of Life questionnaires

In the EQ-5D-5L quality of life questionnaire, no differences were observed between any of the three baloxavir marboxil arms and placebo. In addition, there was no difference between the time to resumption of normal activities between the baloxavir marboxil arms and the placebo arm using the protocol-specified analysis. In a post-hoc analysis using a different statistical method, there was a statistically significant shorter time to resumption of normal activity in the baloxavir marboxil 20 mg arm only compared to the placebo arm.

Results for household infection substudy

No statistically significant difference was observed in the proportion of household contacts with influenza between any of the three baloxavir marboxil arms and the placebo arm.

Dose/Dose Response

Trial 1518T0821 was a Phase 2 dose finding study comparing a single 10 mg, 20 mg or 40 mg dose of baloxavir marboxil to placebo. The primary endpoint was the median time to alleviation of symptoms. Using the Wilcoxon statistical test, the median time to alleviation of symptoms was statistically significantly shorter in all three baloxavir marboxil arms than in the placebo arm. Although the median time to alleviation of symptoms was similar in the three baloxavir marboxil arms, it was shortest in the baloxavir marboxil 40 mg arm. The proportion of subjects with viral shedding was considerably smaller in the baloxavir marboxil 40 mg arm compared to the 10 mg and 20 mg arms at Day 2 and 3. Although the viral shedding does not correlate with clinical outcome, it does provide support for increased virologic activity of the baloxavir marboxil 40 mg dose compared to lower doses. While antiviral activity and clinical efficacy were observed for all three baloxavir doses, the use of the 40 mg dose is also supported by the shorter overall median time to alleviation of symptoms and the shorter median time to alleviation of symptoms for four of the seven influenza symptoms followed in this study.

7 Integrated Review of Effectiveness

7.2 Assessment of Efficacy Across Trials

The efficacy of baloxavir marboxil was studied in two pivotal trials, 1518T0821 and 1601T0831. Trial 1518T0821 was a Phase 2, dose-finding, PK, safety, and efficacy trial in 400 otherwise healthy adult subjects with influenza. The dose identified in this Phase 2 trial for further study in Phase 3 was a single oral 40 mg dose. Trial 1601T0831 was a Phase 3, PK, safety and efficacy trial of 1432 otherwise healthy adolescent and adult subjects with influenza. In 1601T031, subjects in the baloxavir marboxil arm received a single 40 mg dose if they weighed less than 80 kilograms and a single 80 mg dose if they weighed 80 kilograms or more. The recommended dose of baloxavir marboxil in the proposed package insert is the same as that used in Phase 3. Section 14 of the package insert includes the efficacy results from the baloxavir marboxil 40 mg arm in Trial 1518T0821 and from efficacy results from Trial 1601T0831. The clinical efficacy described in this section will be limited to efficacy at the doses recommended in the package insert.

7.2.1.1 Primary Endpoints

The primary endpoint, the median time to alleviation of symptoms, was identical in both pivotal

trials. The primary endpoint was met in both trials. Trial 1518T8021 was not conducted under US IND. The protocol for Trial 1601T0831 was submitted to FDA prior to initiation of the trial, and FDA reviewers agreed with use of this primary endpoint.

The use of median time to alleviation of symptoms was also consistent with FDA guidance. FDA recommendations for clinical trial design in the development of drugs for the treatment of influenza are provided in FDA Guidance for Industry, "Influenza: Developing Drugs for Treatment and/or Prophylaxis." According to the guidance, the primary endpoint in treatment trials of otherwise healthy adults should be the time to a pre-defined level of symptom improvement. The components of the primary endpoint should include fever with a constellation of symptoms such as cough, coryza, headache, body aches and sore throat. The primary endpoints used in the pivotal trials of baloxavir marboxil are consistent with the guidance. The components of the primary endpoint in these trials included all recommended components plus an additional two components (feverishness or chills and fatigue). Therefore, the primary endpoint used in these trials was consistent with FDA guidance regarding the primary endpoint for studies of influenza treatment.

The primary endpoints used in the two pivotal trials of baloxavir marboxil were also consistent with the primary endpoint used in trials of other FDA-approved direct acting, anti-influenza drugs. Time to alleviation of defined influenza symptoms was used as the primary endpoint in registrational trials for all three direct-acting anti-influenza drugs since 1999. The individual components comprising the symptom complex were identical in the baloxavir marboxil trials and the pivotal trials of oseltamivir and peramivir registrational trials, while the pivotal trials supporting zanamivir approval included four of the seven influenza symptoms.

The results for the primary endpoints of the two pivotal trials are shown in the two following tables.

Table 27. Time to Alleviation of Symptoms Subjects with Acute Uncomplicated Influenza in Phase 2 Trial 1518T0821 (Median Hours)

	Baloxavir marboxil 40 mg (95% CI[1]) N=100	Placebo (95% CI) N=100
Adults (20 to 64 Years of Age)	50 hours (45, 64)	78 hours (68, 89)

[1]CI: Confidence interval

Table 28. Time to Alleviation of Symptoms in Subjects with Acute Uncomplicated Influenza in Phase 3 Trial 1601T0831 (Median Hours)

	Baloxavir marboxil 40 mg or 80 mg[1] (95% CI[2]) N=455	Placebo (95% CI[2]) N=230
Subjects **(≥** 12 Years of Age)	54 hours (50, 59)	80 hours (73, 87)

[1]Dosing was based on weight. Subjects weighing <80 kg received a single 40 mg dose and subjects ≥ 80 kg received a single 80 mg dose.
[2]CI: Confidence interval

The results reached statistical significance in both trials.

The subgroup analysis of the primary efficacy endpoint in the adolescent population of Trial 1601T0831 is included in the package insert for baloxavir marboxil. In adolescent subjects (age 12 to < 18 years of age) in Trial 1601T8031, the median time to alleviation of symptoms for subjects who received baloxavir marboxil (N=63) was 54 hours (95% CI of 43, 81) compared to 93 hours (95% CI of 64, 118) in the placebo arm (N=27).

The median time to alleviation of symptoms was 54 hours in the baloxavir marboxil arm and in the oseltamivir arm. The results for this comparison will also be included in the package insert.

7.2.1.2 Secondary and Other Endpoints

The results of important secondary endpoints are discussed in this section of the clinical review. The two pivotal trials were conducted in different influenza seasons (2015/2016 and 2016/2017). Influenza seasons vary by attack rate, duration of influenza season, the predominant influenza strain circulating, and co-circulation pathogens. Therefore, the efficacy results for the two pivotal trials cannot be pooled across the pivotal trials and are discussed individually for the two trials. See Section 6.0 of this review for a discussion of addition secondary endpoints in each trial.

Median time to alleviation of symptoms by influenza strain
There are typically three strains (influenza A/H1N1, influenza A/H3N2, and influenza B) that circulate during each influenza season. Although all three strains circulate, a single strain usually predominates during a single influenza season. Because many patients will not have a test for influenza or a test to identify the strain of influenza, it is preferable that anti-influenza drugs are active against all three influenza strains that commonly circulate. However, DAVP does not usually recommend powering studies of influenza drugs to determine efficacy against

each influenza strain. Since it is difficult to predict which influenza strains will circulate in any particular season, it is difficult to plan a trial to determine efficacy against all three strains. In addition, determination of efficacy against all three strains would require multiple influenza seasons and delay the approval of efficacious drugs. Therefore, most influenza drug trials are driven by results against a single strain, but results against all three strains are assessed.

During the 2015/2016 influenza season, in which Trial 1518T0821 was conducted, the predominant strain circulating was influenza A, subtype H1N1. Influenza A/H1N1 was isolated in 67% of subjects who received the 40 mg dose of baloxavir marboxil and who had their influenza strain identified; this compared to influenza A/H3N2 which was isolated in 10% of subjects and influenza B which was isolated in 23% of subjects. The predominant strain in the 2016/2017 influenza season, in which Trial 1601T0831 was conducted, was A/H3N2, which was isolated in 90% of subjects in the baloxavir marboxil arm who had their influenza strain identified. This compared to influenza A/H1N1 which was only identified in 2% of subjects, and influenza B, which was identified in 9% of subjects. Efficacy results by strain in the two trials are shown in the following table.

Table 29. Median Time to Alleviation of Symptoms (in Hours) by Influenza Strain in the Pivotal Trials of Baloxavir Marboxil (Intent-to-Treat-Infected Population)

	Trial 1601T0831 40 mg or 80 mg#		Trial 1518T0821 40 mg Arm	
	Baloxavir marboxil	Placebo	Baloxavir marboxil	Placebo
Influenza A/H1N1	N=7	N=7	N=61	N=69
Median time in hours (95% CI)	44 (2.0, 109.1)	141 (82.1, --)	48 (35.2, 65.5)	71 (64.9, 89.9)
Influenza A/H3N2	N=392	N=195	N=12	N=6
Median time in hours (95% CI)	52 (47.0, 56.8)	80 (69.5, 86.8)	45 (23.5, 113.4)	100 (18.9, 113.1)
Influenza B	N=38	N=20	N=24	N=23
Median time in hours (95% CI)	93 (53.4, 135.4)	77 (46.8, 189.0)	63 (43.3, 69.8)	83 (58.1, 92.8)

Weight based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg
Source: Clinical Study Reports 1601T0831, Table 11-32, pages 153-154 and 1518T0821, Table 11-26, page 103.

As shown in the table, the efficacy of baloxavir marboxil was demonstrated against the predominant strain in each trial (A/H3N2 in 1601T0831 and A/H1N1 in 1518T0821). In both trials, the time to alleviation in the baloxavir marboxil arm was shorter against the other, less common influenza A subtype compared to placebo. However, the median time to alleviation of symptoms against influenza B was shorter in the baloxavir marboxil arm than placebo in 1518T0821 but not in 1601T0832. The numbers of subjects with influenza B are smaller

compared to the predominant influenza A strain in both studies. As a result, the 95% confidence intervals are wide and overlapping. This may partially explain the discordant efficacy results for influenza B. The results may also be in part due to the lack of statistical power in the assessment of efficacy by strain. However, the results for efficacy are of concern because the EC_{50} values for influenza type B viruses were generally 5- to 10-fold above those for type A viruses, as measured in cell culture. For these reasons, reference to efficacy by influenza type and subtype was added to the limitations of use statement in the section 1 of the package insert and the results for influenza B were added to Section 14, Clinical Studies section.

The Applicant pooled the results of the two pivotal trials to demonstrate a trend toward efficacy against influenza B; in this analysis the median time to alleviation of symptoms was 65 hours in the baloxavir marboxil arm compared to 82 hours in the placebo arm. However, we disagree with pooling the efficacy data. Different influenza strains circulate during each influenza season and influenza B strains of two different lineages may circulate. In the two influenza seasons in which these trials were conducted, different percentages of the two influenza B lineages did circulate. In the 2015/2016 influenza season, there was a slight predominance of influenza B of the Victoria lineage and in the 2016/2017 influenza season, influenza B of the Yamagata lineage predominated. In addition, the Phase 3 trial included subjects from the U.S. and Canada, while the Phase 2 study was conducted solely in Japan. Pharmacokinetic exposures for baloxavir vary by race. Finally, the Applicant included the results for all three doses studied in the Phase 2 study; two of the doses included in the analysis are lower than the doses to-be-marketed in the United States.

The concerns about efficacy against influenza B are based on the discordant results in two trials. The Applicant plans to submit the results of several more efficacy studies both in adults and pediatric patients; therefore, there will be additional opportunities to assess baloxavir marboxil efficacy by influenza strain.

Time to resolution of fever
FDA recommends inclusion of time to resolution of fever as a secondary endpoint in trials of influenza drugs (FDA Guidance for Industry, "Influenza: Developing Drugs for Treatment and/or Prophylaxis"). Temperature of 38° C or higher was an entry criterion for both studies, and time to resolution of fever was a secondary endpoint in both pivotal efficacy trials. The median time to alleviation of fever in Trial 1601T0831 was 25 hours (95% CI of 22.6, 26.6) in the baloxavir marboxil arm compared to 42 hours (95% CI of 37.4, 44.6) in the placebo arm. In Trial 1518T0821, the median time to alleviation of fever was 29 hours (95% CI of 24.5, 34.7) in the baloxavir marboxil arm compared to 45 hours (95% CI of 35.6, 54.0) in the placebo arm. The result was statistically significant in both trials.

Time to cessation of viral shedding
Another secondary endpoint assessed in both pivotal trials was time to cessation of viral

shedding. The percentages of subjects with viral shedding on Days 2, 3, 6, and 9 were measured in both trials and are shown in the following table.

Table 30. Percentages of Subjects with Viral Shedding in the Pivotal Trials of Baloxavir Marboxil (Intent-to-Treat Population)

	Trial 1601T0831 40 mg or 80 mg#		Trial 1518T0821 40 mg Arm	
	Baloxavir marboxil N=610	Placebo 309	Baloxavir marboxil N=100	Placebo N=100
Day 2	44%*	96%	72%*	94%
Day 3	18%*	69%	29%*	82%
Day 6	9%	9%	11.3%*	24%
Day 9	3%	5%	1%	1%

Weight based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg
*Statistically significant difference between baloxavir marboxil and placebo arm
Source: Clinical Study Reports 1601T0831, Table 11-8, pages 118 and 1518T0821, Table 11-11, page 87.

The rate of shedding on Days 2 and 3 was higher in the baloxavir marboxil arm in Trial 1518T0821 than in Trial 1601T0831. This may be related to the different influenza strains that predominated in the trials; influenza A/H1N1 was the predominant strain isolated in subjects in 1518T0821 and influenza A/H3N2 was the predominant strain isolated in 1601T8031. However, the difference in the percentage of subjects with detectable virus on Days 2 and 3 was statistically significantly shorter in the baloxavir marboxil arm than in the placebo arm in both trials.

The clinical significance of this finding is limited. Viral shedding has not been shown to correlate with clinical symptoms of influenza, and its utility in the assessment of efficacy is negligible. While a decrease in viral shedding may lead to a decrease in the transmission of clinical influenza, that association has not been proven in a clinical trial.

The methodology used to conduct the assays may have influenced the results. See Dr. Ince's Virology review. The impact of baloxavir marboxil carryover in nasal swab specimens may have affected the results and lowered the number of positive samples in the baloxavir marboxil arms. Therefore, the utility of these results is unclear.

7.2.2 Subpopulations

See Section 4.0 of Dr. Fraser Smith's Biostatics review for additional information on subgroup analyses.

Time to alleviation of influenza symptoms by sex
The time to alleviation by sex is shown for each pivotal trial in the following table.

Table 31. Median Time to Alleviation (in Hours) by Sex in the Pivotal Trials of Baloxavir Marboxil (Intent-to-Treat-Infected Population)

	Trial 1601T0831 40 mg or 80 mg#		Trial 1518T0821 40 mg Arm	
	Baloxavir marboxil	Placebo	Baloxavir marboxil	Placebo
Females	N=224	N=111	N=40	N=39
Median time in hours	62	85	52	89
Male	N=232	N=120	N=60	N=61
Median time in hours	47	73	48	69

Weight based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg
Source: Created by reviewer from time to event datasets for each pivotal trial

As shown in the table, the median time to alleviation of symptoms was shorter in the treatment and placebo arms in both studies for males compared to females. Although there have been studies describing differences in the incidence of influenza and the severity of influenza by sex, there is little if any information regarding differences in the duration of influenza by sex. Despite these differences, treatment differences (e.g., shorter time to alleviation of symptoms in baloxavir marboxil arms compared to placebo arms) for both sexes were observed in both trials.

Time to alleviation of influenza symptoms by race/ethnicity
In Trial 1518T0821, all subjects in the baloxavir marboxil 40 mg arm and in the placebo arm were Asian. In Trial 1601T0831, 77% of baloxavir marboxil and placebo subjects were Asian; 19% of subjects in the baloxavir arm and 17% in the placebo arm were White. As a result, only 5% of subjects in 1601T0831 were not Asian or White, and results will only be shown for the Asian and White subgroups. Less than 5% of subjects who received either baloxavir marboxil or placebo in 1601T0831 were Hispanic or Latino; therefore, results by ethnicity will not be provided.

Table 32. Median Time to Alleviation (in hours) by Race in the Pivotal Trials of Baloxavir Marboxil (Intent-to-Treat-Infected Population)

	Trial 1601T0831 40 mg or 80 mg#		Trial 1518T0821 40 mg Arm	
	Baloxavir marboxil	Placebo	Baloxavir marboxil	Placebo
Asians	N=349	N=178	N=100	N=100
Median time in hours	46	75	50	78
Whites	N=85	N=40	0	0
Median time in hours	93	121	--	--

#weight-based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg
Source: Created by reviewer from time to event datasets for each pivotal trial

The time to alleviation of influenza symptoms was shorter in both the baloxavir marboxil and placebo arms in Asians than in Whites. The reason for this finding is unclear but may be related to difference by influenza strains circulating in Japan compared to those circulating in the United States and Canada, or to cultural differences in reporting symptoms. However, the difference in median time to alleviation of symptoms was shorter in the baloxavir arms than in the placebo arm in both Asians and Whites, and the results for differences in median time to alleviation of symptoms were similar for both races (-28 or -29 hours).

Time to alleviation of influenza symptoms by region of the world
Trial 1518T0821 was conducted only in Japan, while Trial 1601T0831 was conducted in Japan and North America (US and Canada). The analysis for time to alleviation of influenza symptoms for subjects in Japan compared to those in the United States and Canada is shown in the following table.

Table 33. Median Time to Alleviation (in Hours) by Region of the World in the Pivotal Trials of Baloxavir Marboxil (Intent-to-Treat-Infected Population)

	Trial 1601T0831 40 mg or 80 mg#		Trial 1518T0821 40 mg Arm	
	Baloxavir marboxil	Placebo	Baloxavir marboxil	Placebo
Japan	N=343	N=175	N=100	N=100
Median time in hours	46	75	50	78
U.S. and Canada	N=113	N=56	N/A	N/A
Median time in hours	83	110	--	--

Weight-based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg
Source: Created by reviewer from time to event datasets for each pivotal trial

The time to alleviation of influenza symptoms was shorter in both the baloxavir marboxil and placebo arms in Japan than in U.S./Canada in trial 1601T0831. As with the analysis of race, the reason is unclear but may be related to difference by influenza strains circulating in Japan compared to those circulating in the United States and Canada, or to cultural differences in reporting symptoms. Again, the difference between the median times to alleviation of symptoms between the baloxavir marboxil arm and the placebo arm was similar in the analyses by region (-29 hours for Japan and -27 for U.S./Canada).

Time to alleviation of influenza symptoms by age
Subjects from 12 to < 65 years of age were enrolled in Trial 1601T0831, while subjects from 20 to < 65 years of age were enrolled in Trial 1518T0821. The Applicant provided an analysis of efficacy for Trial 1601T0831 for subjects 18 years and old and those younger than 18 years of age. The median time to alleviation of symptoms for subjects ≥ 18 years of age was 54 hours in the baloxavir marboxil arm compared to 79 hours in the placebo arm. The median time to alleviation of symptoms for adolescents (12 to < 18 years old) was 54 hours in the baloxavir

marboxil arm compared to 93 hours in the placebo arm. The results for both age groups reached statistical significance. There was a considerable difference for median time to alleviation of symptoms in the placebo arms in the two age groups. The reason for this difference is unclear but may be related to the small number of subjects in the adolescent placebo arm (N=27).

7.2.2.1 Dose and Dose-Response

The dose recommended in the proposed baloxavir marboxil package insert is a single, oral 40 mg dose for patients weighing less than 40 kg and a single, oral 80 mg dose for patients weighing 80 kg or more.

Nonclinical studies to support dose selection
See. Dr. Ince/s Virology review for a full discussion of these studies. The target plasma concentrations for clinical studies were derived from nonclinical studies. The studies were conducted using baloxavir, the major metabolite of baloxavir marboxil. The Applicant studied inhibition of influenza replication by baloxavir in MDCK cells. Multiple seasonal influenza viruses including clinical and laboratory isolates were evaluated. The 50% effective concentration (EC_{50}) of baloxavir for influenza viruses was 0.20 to 1.87 nmol/L, and the EC_{50} for influenza B viruses was 3.33 to 13.0 nmol/L.

The potential clinical dose was further explored in PK/PD studies in mice. Mice were infected with influenza and treated with baloxavir five days later. Mice treated with oseltamivir were used as an active control. Virus titers in the lung were measured 24 hours after dosing with baloxavir. Pharmacokinetic parameters were also measured. The study objective was to identify the baloxavir marboxil dose that resulted in a 10-fold *lower* virus titer in the lung compared to oseltamivir. The objective was met against influenza A at a baloxavir marboxil dose of 3 mg/kg/day and against influenza B at a dose of 30 mg/kg/day. The target dose in mice was determined to be 30 mg/kg/day in order to be active against both influenza A and B viruses. The plasma concentration 12 hours (C_{12}) after dosing with 30 mg/kg/day was 6.85 ng/mL. Because the concentration of radioactivity in the lung was higher than in the plasma in rat studies of radiolabeled baloxavir, the Applicant believes the plasma C_{12} of 6.85 ng/mL will result in baloxavir levels that inhibit influenza A and B replication in the lungs.

Clinical pharmacokinetic studies to support baloxavir marboxil doses
Please see Dr. Hassan's Clinical Pharmacology review.
In a Phase 1, single ascending dose study conducted in Japan, baloxavir had a geometric mean elimination half-life of 75 hours after a single 40 mg dose and of 86 hours after an 80 mg dose. Plasma concentrations at 72 hours post dose exceeded the *in vitro* EC_{50} in all study subjects for both the 40 mg and 80 mg doses. In a different PK study, which was conducted in the U.S., plasma concentrations 72 hours after an 80 mg dose exceeded the *in vitro* EC_{50} in all study subjects. These results supported the use of a single dose of baloxavir marboxil to treat

influenza.

The Applicant conducted a Phase 2, dose-finding study in Japan, Trial 1518T0821, to identify the dose for use in Phase 3 studies of baloxavir marboxil. Subjects were randomized to receive a single dose of baloxavir marboxil (10 mg, 20 mg, or 40 mg) or a single dose of placebo. PK, safety, and efficacy were assessed. Efficacy was measured by the median time to alleviation of influenza symptoms, and the results for all three dosing arms reached statistical significance. Although the median times to alleviation of symptoms (the primary endpoint) were very similar in all three baloxavir marboxil arm, the median time to alleviation of symptoms was highest in the 40 mg arm. In addition, there was a dose-dependent response for the median time to alleviation of individual influenza symptoms. The median times to alleviation of each individual symptom of influenza (see Table 19 in Section 6.2.2) were statistically significantly shorter than placebo for four of the seven individual symptoms in subjects who received 40 mg of baloxavir marboxil. The percentage of subjects with influenza virus detected in nasal swab samples was lower on Days 2 and 3 in the baloxavir marboxil 40 mg arm compared to the 10 mg and 20 mg arms. These findings together with the lack of dose-related safety findings supported the use of the 40 mg dose in Phase 3.

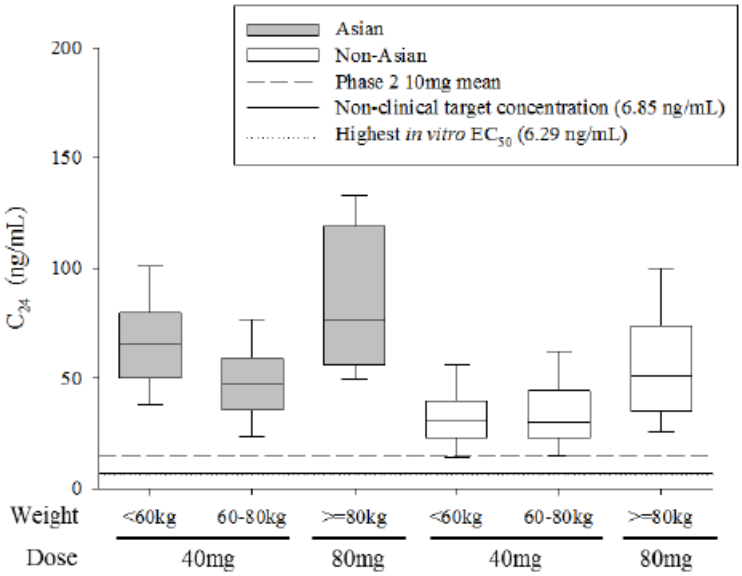
After review of Phase 1 and 2 study results, DAVP requested that the Applicant study weight-based dosing of baloxavir marboxil in the Phase 3 study. This request was based on the Phase 1 finding of decreasing exposures with increasing weights, on decreased plasma concentrations observed after a medium fat meal in a Phase 1 study, and on reduced plasma exposure in U.S. subjects as compared to Japanese subjects across Phase 1 studies. In the Phase 1, food effect study, plasma concentrations of baloxavir after a medium fat meal were compared to those after fasting. The C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ decreased by 18%, 31%, and 30%, respectively, after a medium fat meal. Although the Applicant had not directly compared the PK of baloxavir marboxil in Japanese and U.S. subjects, after PK studies were conducted in the U.S., the exposures in U.S. subjects were observed to be approximately 35% of what had been reported in Japanese subjects. As a result of these concerns, the Phase 3 trial of baloxavir marboxil in otherwise healthy subjects was conducted using weight-based dosing with a single 40 mg dose for subjects weighing less than 80 kg and a single 80 kg dose for subjects weighing 80 kg or more.

Population PK analyses along with the results of Phase 1, 2, and 3 studies were further used to support the proposed dosing of baloxavir marboxil. The proposed dose is a single 40 mg dose for subjects weighing less than 80 kg and a single 80 kg dose for subjects weighing 80 kg or more, as studied in the Phase 3 trial. Population PK analyses were performed using 8,310 concentrations from 1,109 subjects in studies of baloxavir marboxil. Of the 1,109 subjects, 799 were Asians, 254 were White, and 56 were Other. In the evaluation of covariates body weight and race were found to be the most influential covariates on baloxavir pharmacokinetics.

An exposure-response analysis by influenza strain was conducted by the Applicant using pooled data from Phase 2 and 3 trials. In the Phase 2 trial, the median time to alleviation of symptoms was shorter in the baloxavir arms compared to placebo for all three influenza strains. In the Phase 3 trial, the median time to alleviation of symptoms was shorter in the baloxavir arm than in the placebo arm for both influenza A subtypes but not for influenza B. The reason for efficacy against influenza B in one trial but not the other trial is unclear. When times to alleviation of symptoms for the three different influenza strains were plotted against the C_{24}, no clear exposure-response relationships were found for the time to alleviation of symptoms. However, time to alleviation of symptoms did correlate with C_{24} when the data were analyzed using linear regression. When the correlation between viral titer on Day 2 and C_{24} were analyzed, the reduction in virus titer was greater with increasing C_{24} for all three virus types/subtypes. The reductions in virus titer on Day 2 were less for influenza B compared to influenza A. The reduction in viral titer was considerably lower for influenza B in the baloxavir marboxil arm than for placebo or for oseltamivir. In addition, the C_{24} in both pivotal trials was higher than the *in vitro* EC_{50} values. These data support the use of the proposed doses of baloxavir marboxil for both influenza A and influenza B.

In Phase 1 studies and in population PK analyses, weight and race were important covariates for baloxavir pharmacokinetics. Weight-based dosing was used in the Phase 3 trial and is proposed as the to-be-marketed dose. Time to alleviation of symptoms in the Phase 3 trial was analyzed by weight. The median time to alleviation of symptoms in subjects weighing < 80 kg and who received a single 40 mg dose of baloxavir marboxil was 51 hours (95% CI of 46.4, 55.3) compared to 79 hours (69.5, 87.1) in subjects who received placebo. The median time to alleviation of symptoms in subjects weighing ≥ 80 kg was 67 hours (95% CI of 53.5, 82.6) in the baloxavir marboxil arm and 85 (95% CI of 69.0, 148.5) in the placebo arm. The median time to alleviation of symptoms was 28 hours shorter in the baloxavir arm than the placebo arm for subjects weighing less than 80 kg and 19 hours shorter in the baloxavir arm than in the placebo arm for subjects weighing 80 kg or more. Results for median time to alleviation by race are shown in Table 34 in Section 7.2.2 of this review. The Applicant compared weight and race to estimated C_{24} using data from the Phase 3 trial and their population PK model. Weight was divided into three strata, < 60 kg, 60-80 kg, and ≥ 80 kg; race was analyzed as Asian and non-Asian. The results are shown in Figure 1.

Figure 1: Comparison of C24 by Race and Weight using a Population PK Model



As shown in Figure 1, the median C_{24} was higher for Asian subjects than non-Asian subjects in each weight stratum. While the C_{24} values were lowest for non-Asian subjects weighing < 60 kg and non-Asian subjects weighing from 60 to 80 kg, the 10th percentiles for C_{24} values for these groups were still higher than the mean C_{24} value observed in the baloxavir marboxil 10 mg arm, which was demonstrated to be efficacious in the Phase 2 trial. In addition, the 10th percentiles for C_{24} for all subgroups are also higher than the EC_{50} value from nonclinical studies. Therefore, in spite of differences in PK by weight and race, these data support use of the proposed weight-based doses of baloxavir marboxil in the U.S. package insert.

In a Phase 1 study of the effect of a medium fat meal on baloxavir PK, decreased baloxavir exposures were demonstrated in the fed condition compared to fasted. Subjects in the Phase 2 and 3 trials were instructed to take baloxavir marboxil without regard to food. Subjects were to report whether dosing with baloxavir marboxil was ≥ 4 hours before or ≥ 4 hours after food intake (fasted), 2 to 4 hours before or 2 to 4 hours after food intake (intermediate), or < 2 hours before or < 2 hours after food intake (fed). The effect of food intake on C24 is shown in the following table.

Table 34. Effect of Food Intake on C24 of Baloxavir Marboxil in the Pivotal Trials

	C_{24} (ng/mL)			Ratio of C_{24} to that after Dosing in Fasted State		
	Phase 2 Trial	Phase 3 Trial		Phase 2 Trail	Phase 3 Trial	
	40 mg	40 mg	80 mg	40 mg	40 mg	80 mg
Fasted	62	46	58	--	--	--
Intermediate	57	47	63	0.92	1.01	1.08
Fed	56	41	54	0.91	0.89	0.93

Source: ISE, Table 2.7.3-70, page 192

As shown in the preceding table, the intermediate and fed C_{24} values were similar to those observed in the fasted state. The median time to alleviation of symptoms by food intake for Trial 1601T0831 is shown in Table 10 in Section 6.1.2 in this review. In this study, the median times to alleviation of symptoms were 25 to 27 hours shorter in the baloxavir marboxil arm compared to placebo arm in all three subgroups (fasted, intermediate, and fed). Therefore, food intake did not influence the C_{24} in Phase 2 and 3 and had no effect on the primary endpoint. The recommendations to take baloxavir marboxil without regard to food are appropriate and supported by these data.

7.2.2.2 Onset, Duration, and Durability of Efficacy Effects

Influenza is a self-limited disease; symptoms generally last from 3 to 7 days. In the placebo arms of the two pivotal trials symptoms of influenza were mild or absent in 78 hours in one trial and 80 in the other trial. Because influenza is self-limited, the duration and durability of efficacy effect are not applicable to the treatment of influenza.

7.3 Additional Efficacy Considerations

7.3.1.1 Considerations on Benefit in the Postmarket Setting

Baloxavir marboxil was studied in two pivotal of otherwise healthy subjects with influenza. The diagnosis of influenza was based on the presence of fever, one respiratory symptom and one general symptom plus confirmation of influenza by rapid diagnostic test or RT-PCR. A single dose of baloxavir marboxil was administered within 48 hours of symptom onset.

The proposed package insert states that baloxavir marboxil is to be used in patients with symptoms of influenza for less than 48 hours. In the postmarket setting, baloxavir marboxil may be administered in patients who have had influenza symptoms for longer than 48 hours, and baloxavir marboxil is likely to be less efficacious in this setting. However, it is difficult to control for off-label use.

The majority of subjects enrolled in the pivotal trials were Japanese. The pharmacokinetics of

baloxavir marboxil differ for Japanese subjects and non-Japanese subjects, but efficacy was demonstrated in both subgroups. Efficacy was also demonstrated by geographic region, Japan versus U.S./Canada. Overall, the efficacy in the U.S. population should not differ from that demonstrated in the Phase 3 trial. The number of Blacks (N=18) and Hispanics or Latinos (N=32) who received baloxavir marboxil in the pivotal trials was low. In the Late Cycle meeting agenda, which was shared with the Applicant on September 21, 2018, the Applicant was asked to enroll sufficient numbers of Blacks and Hispanics or Latinos in the trials which were requested as postmarketing requirements and commitments. The Applicant reiterated their commitment to enrolling under-represented races and ethnic groups in future trials in their October 4, 2018 correspondence to the FDA.

Baloxavir marboxil is a single oral dose. Adherence is not expected to be an issue, and baloxavir marboxil use should be the same in the postmarket setting as in the pivotal trials.

7.3.1.2 Other Relevant Benefits

One of the most important benefits of baloxavir marboxil is that it is administered as a single oral dose. Oseltamivir is the only other oral drug recommended for the treatment of influenza and is administered twice daily for five days. Baloxavir will also provide an alternate treatment against influenza strains that are oseltamivir-resistant. In addition, unlike oseltamivir, the dose of baloxavir marboxil does not need to be adjusted in subjects with renal impairment. Finally, baloxavir has in vitro activity against a wide range of influenza strains including avian influenza viruses with pandemic potential such as influenza A/H5N1 and A/H7N9.

7.4 Integrated Assessment of Effectiveness

The efficacy of baloxavir marboxil has been demonstrated in two adequate and well-controlled trials of more than 1800 subjects. The primary endpoint used to demonstrate efficacy in both trials was identical to the primary endpoint recommended by the FDA influenza guidance. The primary efficacy endpoint reached statistical significance against placebo in both trials using the statistical method recommended by DAVP. The efficacy of baloxavir marboxil was compared to a FDA approved anti-influenza drug, oseltamivir, and the efficacy results were similar for the two drugs. In addition, the effect of baloxavir marboxil was consistent across multiple secondary endpoints and subgroups in both pivotal trials. Therefore, these data provide confidence in the efficacy of baloxavir marboxil for the treatment of influenza in otherwise healthy patients.

8 Review of Safety

8.2 Safety Review Approach

The evaluation of baloxavir marboxil safety in support of this application was based primarily on clinical trial data from the 40 mg arm of the Phase 2 trial and the results of the Phase 3 trial conducted in otherwise healthy subjects with influenza. The results of these studies support the safety of the to-be-marketed doses of baloxavir marboxil and therefore will be discussed in detail. The results will be described for each trial individually. Because the designs of the pivotal trials were almost identical, the results were pooled for some analyses. However, due to differences in baloxavir exposure by race and weight and because of the different age entry criteria in the two studies, the results will not be pooled for all analyses.

Although the safety analysis for this review focused on the results for the 40 mg arm of the Phase 2 trial and the results of the Phase 3 trial, safety information from the overall baloxavir marboxil development program was also taken into account. This included information from 11 Phase 1 trials and from one non-IND, open-label study in Japanese pediatric subjects. In addition, limited postmarking information reported from Japan was reviewed.

The methods used to assess safety in the individual trials and in the integrated summary of safety were considered appropriate. For the FDA review, ADAM and SDTM datasets for Trial 1601T8031 and 1518T0821 were analyzed using JMP. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and are unlikely to impact the overall assessment of the safety profile of baloxavir marboxil. All of the safety assessments and conclusions in this review are those of the FDA clinical reviewer unless otherwise specified.

As agreed upon at the pre-NDA meeting, the Applicant submitted a Safety Update Report on August 22, 2018. The report was reviewed thoroughly, and important findings were incorporated into the review that follows.

8.3 Review of the Safety Database

8.3.1 Overall Exposure

The exposure to baloxavir marboxil across Phase 1, 2, and 3 trials is summarized in the following table.

Table 35. Baloxavir Marboxil Safety Database

Clinical Trial Groups	Baloxavir marboxil Any Dose N	Baloxavir marboxil Dose **≥40** mg* N	Active Control N	Placebo N
Healthy volunteers - Japan	219	113#	0	10
Healthy volunteers – US / UK	66	54	0	0
Controlled trials conducted for this indication[1]	910	710	513	409
Phase 1 study in subjects with hepatic impairment^	16	16	0	0
Open-label study in Japanese pediatric subjects with influenza	107	8	0	0
Total	1318	901	513	419

*This column includes the subset of subjects who received baloxavir at a dose of 40 mg or higher (the to-be-marketed dose)
#of the 113 subjects who received a dose of baloxavir marboxil ≥ 40 mg, 6 received a 60 mg single dose and the remaining subjects received either a 40 mg or 80 mg dose.
^The PK and safety study enrolled 8 subjects with moderate hepatic impairment and 8 matched healthy controls. All subjects received a single dose of baloxavir marboxil

In total, 1,318 subjects were exposed to any dose of baloxavir marboxil. Of these, 710 subjects received a baloxavir marboxil dose of 40 mg to 80 mg in the phase 2 and 3 trials. Race is a covariate for baloxavir PK, and drug exposure is higher in Asian subjects compared to non-Asians. As a result, the exposure observed in Asian subjects who receive a 40 mg dose of baloxavir marboxil is similar to the exposure observed in non-Asian subjects who receive an 80 mg dose. Similarly, the exposure observed in Asian subjects who receive a 20 mg dose is similar to the exposure after a 40 mg dose in non-Asians. Therefore, 185 additional Japanese subjects who received a 20 mg dose of baloxavir marboxil in clinical studies had exposures similar to those expected in non-Asian U.S. subjects who receive baloxavir marboxil at the recommended doses of 40 mg or 80 mg. The size of the safety database for appropriate exposures for the doses recommended for the U.S then increases to 1,086. Only subjects in Trial 1601T0831 were dosed by weight.

All subjects in the preceding table received a single dose of baloxavir marboxil. However, some of the PK studies were two- or three-period studies or had a crossover design, and subjects received a second or third dose of baloxavir marboxil after a washout period. Baloxavir marboxil was administered as a single dose in all trials involving treatment of influenza.

Thirty-six subjects of the 1,318 subjects who received baloxavir marboxil, received the suspension formulation, which will not be marketed. The remaining subjects received either the 10 mg or 20 mg tablet. The 10 mg tablet will not be marketed. In a bioequivalence study

(1622T081F), the 10 mg tablet was not bioequivalent to the 20 mg tablet; the geometric least squares mean ratio for the C_{max} of two 10 mg tablets to one 20 mg tablet was 0.76, which was lower than the predefined 90% CI of 0.80 to 1.25. However, the results for AUC were within the predefined 90% CI. Therefore, safety results for the 10 mg tablet are included in the analysis of safety data.

8.3.1.1 Relevant characteristics of the safety population:

This safety review focuses on the two pivotal trials, 1601T0831 and 1518T0821. Trial 1518T0821, a Phase 2 dose-finding trial, was conducted in Japan in subjects from 20 to < 65 years of age. The ITTI and the safety populations were identical in 1518T0821. See the demographics and baseline characteristics described in Section 6.2.1 for details describing the population. Trial 1601T0831, the Phase 3 safety and efficacy trial, differed from 1518T0821 in what subjects were enrolled in Japan, the U.S. and Canada and 1601T0831 enrolled subjects from 12 to < 65 years of age. The demographic and baseline characteristics for the ITTI population for this trial are described in Sections 6.1.2. The demographics and baseline characteristics in the ITTI population and safety population were similar except for race/ethnicity and region of the world. These differences are shown in the following table.

Table 36. Differences in Proportion of Subjects by Race and Region of the World in the ITTI and Safety Populations of Trial 1601T0831

	ITTI Population			Safety Population		
	Placebo N=231	Baloxavir N=456	Oseltamivir N=377	Placebo N=309	Baloxavir N=610	Oseltamivir N=513
Race						
Asian	77%	77%	81%	60%	60%	62%
White	17%	19%	16%	32%	33%	33%
Black	5%	4%	2%	8%	7%	4%
Latino ethnicity	5%	7%	7%	15%	19%	18%
Region						
Japan	76%	75%	80%	58%	58%	60%
U.S./Canada	24%	25%	20%	42%	42%	40%

Source: Study 1601T031, Table 11-2, pages 105-106 and Table 14.1.3.2, pages 238-241

The proportion of Asians and the proportion of subjects enrolled in Japan were higher in the ITTI population than in the safety population. This is likely to be related to the frequent use of a rapid diagnostic test for influenza prior to enrollment at the study sites in Japan. Use of a rapid diagnostic test resulted in enrollment of Asian subjects who were more likely to be influenza positive when influenza infection was confirmed by RT-PCR.

The majority of subjects in the safety database were Japanese. Black and Hispanic subjects were underrepresented. The following comment was included in the Late Cycle Meeting background package, "We remind you that additional data are needed for safety and efficacy in the following population subgroups which were underrepresented in Trials 1518T021 and 1601T0831: Blacks/African Americans and Hispanics and Latino Americans. We strongly recommend that you ensure adequate enrollment of subjects from each of these populations in postmarketing trials." Other than these noted shortcomings, important subgroups appear well-represented within the baloxavir marboxil safety population.

8.3.1.2 Adequacy of the safety database:

The total number of subjects in the baloxavir marboxil safety database is lower than recommended in the FDA guidance regarding developing drugs for the treatment of influenza. However, DAVP agreed with the size of the database as documented in the pre-NDA meeting minutes. The agreement was based on the robust evidence for efficacy together with the lack of safety signals observed thus far in the clinical and preclinical development program. In addition, the safety database for baloxavir marboxil will be supplemented with the results from a second Phase 3 trial, which was recently completed, in subjects at high risk of complications with influenza infection. A summary of the safety results of this trial were included in the Safety Update Report, and the full CSR for this trial will be included in a supplemental NDA expected to be submitted prior to the 2019/2020 influenza season.

8.4 Adequacy of Applicant's Clinical Safety Assessments

8.4.1.1 Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding data quality or the quality of the overall submission that had an effect on the safety review. After an internal audit, the Applicant observed irregularities at a single site; however, that site only enrolled 10 subjects in Trial 1601T0831. FDA conducted three inspections of clinical sites from the pivotal trials. The inspections were classified as No Action Indicated. Data included in this submission permitted a comprehensive review of baloxavir marboxil safety.

8.4.1.2 Categorization of Adverse Events

In the two pivotal trials, baloxavir marboxil was administered on Day 1, and all AEs were collected through Day 22. Adverse events were followed until resolution, stabilization, or until 35 days after the last dose of study drug.

There were no identified issues with respect to recording, coding, and categorizing AEs in either pivotal trial. AEs were classified by System Organ Class and Preferred Terms of the

MedDRA.system. The severity of AEs was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE version) 4.0. The causal relationship between adverse events and the study drug was based on the judgement of the investigator. Abnormal laboratory values were categorized as AEs if the investigator determined that the abnormal laboratory value was clinically relevant.

8.4.1.3 Routine Clinical Tests

In the two pivotal trials, AEs were followed from Day 1 to Day 22. Blood pressure, pulse rate, and respiratory rate were measured on Days 1, 2, 3, 5, 9, 15, and 22 in Trial 1601T0831. Blood pressure and pulse rate were measured on Days 1, 2, 6, 9, 15, and 22 in Trial 1518T0821. It is unclear why respiratory rate was not measured in the trial of a drug to treat a respiratory virus, but 1518T0821 was not conducted under U.S. IND. Electrocardiograms were obtained on Days 1, 2, and 22 in both studies. Clinical safety laboratory tests were obtained on Days 1, 5, 15, and 22 in Trial 1601T0831 and on Days 1, 6, 15, and 22 in Trial 1518T0821. Clinical laboratory tests in both pivotal trials included hematology (complete blood count with differential and platelet count), chemistry (ALT, AST, total, direct, and indirect bilirubin, alkaline phosphatase, GGT, LDH, BUN, creatinine, uric acid, calcium, electrolytes, total protein, albumin, and C-reactive protein), and urinalysis (dipstick for glucose, occult blood, protein, and urobilinogen). Pregnancy tests were obtained on Days 1 and 22 in both pivotal trials; an additional pregnancy test was obtained on Day 5 in Trial 1601T0831. The schedule of events was considered acceptable.

8.5 Safety Results

8.5.1.1 Deaths

No deaths were reported in the original NDA submission for baloxavir marboxil. A single death in a subject who received baloxavir marboxil was reported in the Safety Update Report (SUR). The SUR included high level safety results for a Phase 3 trial (Trial 1602T0832) comparing baloxavir marboxil, placebo, and oseltamivir in the treatment of influenza in subjects at high risk of influenza complications. The study design for the Phase 3 study in high risk subjects is almost identical to that of the Phase 3 trial, 1601T0831, which is included in the NDA. A total of 2178 subjects were randomized in a 1:1:1 ratio to receive a single dose of baloxavir (N=730), placebo (N=727), or oseltamivir (N=721). There was one death in the baloxavir arm and one death in the oseltamivir arm. The death of the subject in the baloxavir arm was judged as not related to baloxavir because the subject's symptoms began before he was given study drug. This subject, a 66 year old male, had a 12-lead ECG prior to receipt of baloxavir. His ECG was abnormal but was not read prior to dosing with baloxavir. He was referred to a cardiologist and underwent a coronary artery bypass graft. After surgery, he developed severe hypotension and right ventricular failure. His condition was further complicated by *Pseudomonas* bacteremia and pneumonia, and he died on Day 24. This reviewer agrees that his death was not related to baloxavir marboxil.

8.5.1.2 Serious Adverse Events

Two serious adverse events were reported subjects who received baloxavir marboxil in clinical trials. Both occurred in Trial 1601T0831. One SAE was an incarcerated inguinal hernia reported on Day 8. The other SAE was viral meningitis in a 24 year old White male who received a single 40 mg dose of baloxavir marboxil on Day 1. He had increased fever on Day 3. On Day 6, he presented to the emergency department with headache, nausea, and vomiting. A nasal swab was positive for influenza A on Day 6. He had a lumbar puncture; his cerebrospinal fluid had a white blood count of 112/mm^3 with 88% lymphocytes and a red blood cell count of 800/mm^3. No pathogens were identified. It does not appear that a viral culture or RT-PCR for influenza was obtained. In the opinion of this reviewer, the SAE of viral meningitis may represent progressive influenza complicated by influenza meningitis after treatment failure with baloxavir marboxil.

Serious adverse events were provided for Trial 1602T0832 in the Safety Update Report. In this Phase 3 study comparing baloxavir to placebo and oseltamivir in subjects at risk of influenza complications, SAEs were reported in 5 subjects (1%) in the baloxavir arm, 9 (1%) in the placebo arm, and 8 (1%) in the oseltamivir arm.

- A 36 year old female with morbid obesity received a single 80 mg dose of baloxavir marboxil on Day 1. On Day 8, she presented to the emergency department with right upper quadrant pain. Multiple bile duct stones were evident on ultrasound, and she underwent endoscopic bile duct stent placement. After surgery, the pain resolved.
- A 37 year old male with asthma, obesity and hypertension was treated with a single 80 mg dose of baloxavir marboxil. On Day 14, the subject presented with abdominal pain, and an ultrasound showed multiple gallstones. He underwent laparoscopic cholecystectomy on Day 15 due to chronic cholecystitis. The SAE resolved by Day 17.
- A 74 year old male with diabetes mellitus was treated with a single dose of baloxavir marboxil for influenza B. The subject presented to the emergency department on Day 15 with a pneumothorax and was hospitalized. He was subsequently lost to follow-up and the outcome is unknown.
- A 26 year old White male with a history of asthma and diabetes mellitus was enrolled in 1602T0832 and received a single dose of baloxavir marboxil on Day 1. Later than day, the subject developed difficulty breathing and was taken to the emergency room. His chest radiograph showed left lower lobe pneumonia and his rapid test for influenza was negative. He was admitted and treated with antibiotics and oseltamivir.
- A 62 year old White female with a history of diabetes mellitus received a single dose of baloxavir marboxil on Day 1. Her RT-PCR at baseline was positive for influenza B. On Day 3, she was observed to have a cough with pulmonary crackles and coarse breath sounds on exam. She was diagnosed with influenza pneumonia and admitted to the hospital. She was treated with antibiotics and oseltamivir and was discharged on Day 8.

None of these serious adverse events was attributed to baloxavir marboxil. In the opinion of

this reviewer, these serious adverse events were not related to baloxavir marboxil.

8.5.2 Dropouts and/or Discontinuations Due to Adverse Effects

Baloxavir marboxil is a single oral dose, therefore, no adverse events led to premature drug discontinuations in either open label trials or in trials in which a single oral dose of placebo was administered. In Trial 1601T0831, subjects who received a single dose of baloxavir also received oseltamivir placebo for five days. Therefore, subjects in this trial could discontinue the study prematurely, and two subjects did discontinue the trial. One subject in the 40 mg baloxavir marboxil arm discontinued due to bronchitis and pneumonia. Another subject in the 80 mg arm discontinued prematurely due to bronchitis. Neither adverse event was judged as related to the study drug. The percentage of subjects discontinuing prematurely in the baloxavir arm (0.3%) was similar to that observed in the placebo arm (0.3%) and the oseltamivir arm (0.4%).

8.5.2.1 Significant Adverse Events

No severe adverse events were reported in any of the 11 Phase 1 studies of baloxavir marboxil or in the Phase 2 trial, 1518T0821. A severe AE was defined as one that caused interruption of the subject's daily activities or had a clinically significant effect. Eight severe adverse events were reported in six subjects (0.7%) who received baloxavir marboxil in the Phase 3 trial, 1601T0831. Four severe AEs were reported in 4 subjects who received placebo (1%), and one severe AE was reported in a subject who received oseltamivir (0.2%). The eight severe AEs reported in subjects who received baloxavir marboxil were diarrhea, nausea, vomiting, viral meningitis, otitis media, polydipsia, headache, and incarcerated inguinal hernia. All except for the inguinal hernia occurred during the six days after treatment with baloxavir marboxil; five occurred within 2 days of receiving baloxavir marboxil (diarrhea, nausea, vomiting, polydipsia, and otitis media). Diarrhea, nausea, vomiting and polydipsia were judged as treatment-related. All eight severe AEs were reported in subjects enrolled in U.S. and Canada. No severe AEs or SAEs were reported in Japanese subjects in any study of baloxavir marboxil. This may be due to chance or may be related, in part, to cultural practices regarding symptom/AE reporting.

8.5.2.2 Treatment Emergent Adverse Events and Adverse Reactions

The following table displays all adverse events reported in at least 1% of subjects who received baloxavir marboxil in the two pivotal trials. This only includes subjects who were exposed to the to-be-marketed doses of 40 mg and 80 mg. There were no treatment-emergent adverse events reported in more than 5% of subjects in any arm in the pivotal trials.

Table 37. Number of Subjects with Treatment-Emergent Adverse Events Reported in 1% or More of Subjects Who Received Baloxavir Marboxil in Pivotal Trials

	Trial 1518T0821		Trial 1601T0831			Combined Baloxavir Subjects (%) N=710	Combined Placebo Arm N=409
	Baloxavir marboxil 40 mg N=100	Placebo N=100	Baloxavir marboxil N=610	Placebo N=309	Oseltamivir N=513		
Diarrhea	2 (2%)	5 (5%)	18 (3%)	14 (5%)	11 (2%)	20 (3%)	19 (5%)
Bronchitis	1 (1%)	0	16 (3%)	17 (6%)	18 (4%)	17 (2%)	17 (4%)
Nasopharyngitis	1 (1%)	2 (2%)	9 (2%)	2 (1%)	4 (1%)	10 (1%)	4 (1%)
Nausea	0	1 (1%)	8 (1%)	4 (1%)	16 (3%)	8 (1%)	5 (1%)
Headache	4 (4%)	3 (3%)	5 (1%)	3 (1%)	4 (1%)	9 (1%)	6 (1%)

Source: CSR 1518T0821, Table 12-4, page 120 and CSR 1601T8031, Table 12-6, page 207

The AEs reported in > 2% of subjects in the baloxavir marboxil arm were diarrhea and bronchitis. The Applicant analyzed the incidence of diarrhea by baloxavir C_{max} and exposure. There was some evidence of increasing incidence of diarrhea with increasing C_{max} and exposure. For example, in an analysis performed by the Applicant, the incidence of diarrhea was 0.5% in subjects with a C_{max} of < 40 ng/mL, 2% in subjects with C_{max} ≥ 40 to < 80 ng/mL, 4.3% in subjects with a C_{max} of ≥ 80 to < 120 ng/mL, and 3.4% in subjects with a C_{max} of ≥ 120 ng/mL. This suggests that diarrhea may increase with increasing plasma concentrations of baloxavir; however, the number of subjects with diarrhea was low making the utility of this analysis uncertain.

In the pooled results, there were no treatment-emergent adverse events reported in more than 5% of subjects in any arm in the pivotal trials. The only AEs reported in at least 2% of subjects in the baloxavir marboxil arm were diarrhea and bronchitis. Diarrhea was reported more frequently in the placebo arms in both trials compared to the baloxavir marboxil arms. Bronchitis was reported more frequently in the placebo arm than the baloxavir marboxil arm in the Phase 3 trial. In the Phase 2 trial, only one AE of bronchitis was reported in the baloxavir marboxil 40 mg arm and no AEs of bronchitis were reported in the placebo arm. There was no single AE reported more frequently in the combined baloxavir marboxil arms than in the combined placebo arm.

Only one drug –related adverse event, diarrhea, was reported in 1% or more subjects who received baloxavir marboxil. Drug-related diarrhea was reported in 11 subjects (1.5%) in the combined baloxavir marboxil arms in the two pivotal trials compared to six subjects (1%) of subjects in the combined placebo arms.

Adverse drug events and treatment-related adverse events in the 11 Phase 1 studies were reviewed. A total of 301 subjects were enrolled in these studies. The only treatment-related

adverse event (or adverse reaction) reported in more than two subjects was headache, which was reported in 13 subjects (4%). The majority of these studies were open-label and uncontrolled and in some of the studies, baloxavir marboxil was co-administered with another drug; therefore, the usefulness of this analysis is limited.

The Applicant defined an adverse drug reaction as one that was reported in at least 2% of subjects who received baloxavir marboxil, occurred at a higher incidence than placebo in the pooled pivotal trials, and was attributed to the study drug by the investigator. Using that definition, no ADRs would be listed in Section 6 Adverse Reactions section of the package insert. In the opinion of this reviewer, stating that there were no ADRs associated with baloxavir marboxil might mislead health care providers and patients about the risks and benefits associated with taking baloxavir marboxil. Therefore, the adverse events reported in at least 1% of subjects in the pivotal trials, as shown in Table 37, will be included in the package insert.

8.5.2.3 Laboratory Findings

The ISS and laboratory datasets provided for the ISS were reviewed for Grade 3 and Grade 4 laboratory abnormalities. No Grade 4 laboratory abnormalities were reported. One subject who received baloxavir marboxil in the pivotal trials had a Grade 3 value for ALT (352 U/L) and for AST (206 U/L) on Day 6. This subject had hepatic steatosis, and her baseline AST and ALT values were more than 3 times the upper limit of normal. The subject did not meet the entry criteria and should not have been enrolled. No other subjects who received baloxavir marboxil had Grade 3 laboratory values.

On examination of changes in laboratory values from baseline, there were no increases over time observed in liver function tests. An increase in both white blood cell count and lymphocytes was observed as would be expected in subjects with viral respiratory illnesses. Overall, there was no evidence of abnormal laboratory findings after treatment with baloxavir marboxil.

8.5.2.4 Vital Signs

In the pivotal trials, vital signs were measured prior to study treatment and at each study visit. The mean changes from baseline were relatively consistent across the baloxavir marboxil and placebo arms. No clinically meaningful changes in vital signs were observed in association with baloxavir marboxil use.

8.5.2.5 Electrocardiograms (ECGs)

Twelve-lead ECGs were performed on Days 1, 2, and 22 in both pivotal trials. The ECG was assessed to determine whether the ECG was normal or abnormal. If an ECG was deemed

abnormal and clinically significant, the results were recorded as an adverse event. The results of all abnormal ECGs were also reviewed by the medical monitor.

Marked increases in QTc from baseline (> 60 ms) were uncommon, occurring in three subjects who received baloxavir marboxil and two who received placebo. Marked prolonged QTc values (> 500 msec) were also uncommon and were observed in nine subjects who received baloxavir marboxil compared to five who received placebo. These changes did not appear to be dose-related as the three subjects with QTcF greater than 500 msec received baloxavir marboxil doses of 10 mg or 20 mg.

ECG changes were reported as an adverse event in five subjects who received baloxavir marboxil. Three subjects had the same ECG abnormalities at baseline. One subject had an ECG change observed at Day 22 that was reported as an AE but which was also reported as clinically insignificant. The remaining subject was a 26 year old female with sinus bradycardia with onset at Day 15; which resolved by Day 22.

In the opinion of this reviewer, baloxavir marboxil was not associated with meaningful ECG changes in the pivotal trials or in the thorough QT study (see Section 8.5.2.6).

8.5.2.6 QT

The Applicant conducted a thorough QT/QTc study (Study 1527T0816) in which 63 healthy Japanese subjects received the following single-dose treatments in a randomized order: 1) baloxavir marboxil single 40 mg oral dose, 2) baloxavir marboxil single 80 mg oral dose, 3) placebo, and 4) 400 mg oral moxifloxacin.

A QT-IRT consult was requested and the review was submitted on September 21, 2017. The reviewer concluded that baloxavir marboxil was not associated with significant QTc prolongation in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between baloxavir marboxil (single dose of 40 mg and 80 mg) and placebo were below 10 msec, the threshold for regulatory concern as described in ICH E14 guidelines. The mean exposure observed in this study with the 80 mg baloxavir marboxil dose adequately covered the exposures of baloxavir marboxil for the to-be-marketed dose of 40 mg for patients weighing less than 80 kg and 80 mg for subjects weighing 80 kg or more. Further, the exposure-response analysis did not show a statistically significant concentration-QTc relationship for the drug. The moxifloxacin control established the assay sensitivity, as intended.

8.5.2.7 Immunogenicity

As baloxavir marboxil is a small molecule, there is limited concern regarding the potential for immunogenicity. Therefore, studies assessing the formation of anti-drug antibodies were not conducted for baloxavir marboxil.

8.6 Analysis of Submission-Specific Safety Issues

8.6.1.1 Hepatic adverse events

In nonclinical repeat dose oral toxicity studies in rats, liver effects were observed at the high baloxavir marboxil dose. Abnormal findings were noted on gross and microscopic examination of the liver, but findings were minimal or mild and resolved during recovery. 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, hepatic adverse events were considered adverse events of special interest.

No cases of drug-induced liver injury or Hy's Law were reported in the clinical development program for baloxavir marboxil. No hepatic adverse events, other than increases in liver enzymes, were reported. Abnormalities in liver enzymes in the pivotal trials are shown in the following table. The liver tests included in the table were obtained between Day 2 and Day 22 after dosing with baloxavir marboxil. This table includes subjects who received any dose of baloxavir marboxil in the dose-finding, Phase 2 trial.

Table 38. Number of Subjects with Abnormal Liver Enzymes in Pivotal Trials of Baloxavir Marboxil (Safety Population)

	Category	Baloxavir marboxil N=910	Placebo N=409
ALT	≤ 3 x ULN*	897 (99%)	400 (99%)
	> 3 to ≤ 5 x ULN	5 (1%)	2 (1%)
	>5 to ≤ 20 x ULN	1 (0.1%)	1 (0.2%)
	>20 x ULN	0	0
	Total	903	403
AST	≤ 3 x ULN*	900 (99%)	400 (99%)
	> 3 to ≤ 5 x ULN	4 (0.4%)	2 (0.5%)
	>5 to ≤ 20 x ULN	1 (0.1%)	1 (0.2%)
	>20 x ULN	0	0
	Total	905	403
Total bilirubin	≤ 1.5 x ULN*	899 (99.6%)	399 (100%)
	> 1.5 to ≤ 3 x ULN	4 (0.4%)	0
	>3 to ≤ 10 x ULN	0	0
	>10 x ULN	0	0
	Total	903	399

The ≤ 3 x ULN categories for ALT and AST and the ≤ 1.5 x ULN category for total bilirubin include subjects with normal laboratory values.
Source: ISS, Table 2.7.4-40, page 56

As shown in the preceding tables, the proportion of subjects with increased liver enzyme tests was similar in the baloxavir marboxil and placebo arms. All changes in ALT and AST were 5-fold or less than the upper limit of normal except for in one subject who was discussed previously in the laboratory AE section of this review. This subject had hepatic steatosis with abnormal ALT and AST at baseline (>3 x ULN) and had Grade 3 ALT and AST values on Day 6.

The Applicant conducted a PK and safety study (Study 1611T081B) in eight subjects with moderate hepatic impairment (Child-Pugh Class B) and eight matched controls. All subjects received a single 40 mg dose of baloxavir marboxil and were followed for 21 days post-dose. There were three AEs in subjects with moderate impairment (headache in two subjects and pruritus in one). There were two AEs in control subjects (headache and somnolence). No changes in liver enzyme tests were judged as clinically relevant and classified as adverse events. On review of the line listings, only one subject had an abnormal ALT (Grade 3) that was higher than the screening value (Grade 2). The increased ALT in this subject resolved after Day 8.

In the opinion of this reviewer, no hepatoxicity was associated with baloxavir marboxil use in the pivotal trials, and a single dose of baloxavir marboxil did not appear to worsen pre-existing liver disease in a small safety and PK study in subjects with moderate liver disease.

8.6.1.2 Neuropsychiatric adverse events

Abnormal behavior has been reported in patients infected with influenza. In addition, cases of neuropsychiatric adverse events have been reported postmarketing in patients who have received oseltamivir and laninamivir. These cases have primarily been observed in pediatric patients and adolescents. The mechanism of these neuropsychiatric AEs is unknown. The Applicant conducted an analysis of the system organ class AEs in the pivotal trials. The results for the 40 mg baloxavir marboxil arm in 1518T0821 and the baloxavir marboxil arms, the placebo arms from both trials, and the oseltamivir arm in 1601T0821 are shown in the following table. Of note, adolescents were enrolled in Trial 1601T0831 but were randomized to baloxavir marboxil or placebo and did not receive oseltamivir.

Table 39. Number and Percentage of Subjects with Neuropsychiatric Adverse Events in the Pivotal Trials of Baloxavir Marboxil (Safety Population)

	Baloxavir marboxil N=710	Placebo N=409	Oseltamivir N=513
Number (%) of subjects with any neuropsychiatric AE	11 (2%)	12 (3%)	8 (2%)
Psychiatric AEs	0	2 (1%)	1 (1%)
Euphoric mood	0	0	1 (1%)
Insomnia	0	0	1 (1%)
Nightmare	0	2 (1%)	0
Abnormal behavior	0	1 (0.2%)	0
Nervous system AEs	11 (2%)	10 (2%)	6 (1%)
Headache	4 (1%)	6 (1%)	4 (1%)
Dizziness	3 (0.4%)	4 (1%)	1 (0.2%)
Dsygeusia	2 (0.3%)	0	0
Hypoesthesia	1 (0.1%)	0	0
Parosmia	1 (0.1%)	0	0
Syncope	1 (0.1%)	0	0
Migraine	0	0	1 (0.2%)

Source: ISS, Table 2.7.4-44, page 61 and ISS AE dataset

Overall psychiatric adverse events were uncommon in these trials, and none were reported in the baloxavir marboxil arms. The most frequently reported neurologic AE was headache, which is common in patients with influenza. Other neurologic AEs were very uncommon. There was no clear association of neuropsychiatric AEs with any treatment arm in these trials.

8.7 Safety Analyses by Demographic Subgroups

Results for subgroups analyses are shown in this section; however, these analyses were limited because of the small percentage of subjects with adverse events in the baloxavir marboxil arms of the pivotal trials.

Safety analysis by age
A total of 117 adolescents (8% of all subjects) were enrolled in Trial 1601T0831 and randomized to either baloxavir marboxil (N=76) or placebo (N=41). Adverse events reported at least two adolescents are shown in the following table.

Table 40. Adverse Events Reported in ≥ 2 Adolescent Subjects in Either Arm in Trial 1601T0831

	Baloxavir marboxil N=76	Placebo N=41
Subjects with any AE	13 (17%)	14 (34%)
Diarrhea	3 (4%)	2 (5%)
Bronchitis	1 (1%)	2 (5%)
Otitis media	0	2 (5%)
Nightmares	0	2 (5%)
Headache	1 (1%)	2 (5%)

Source: CSR 1601T0831, Table 14.3.2.8, pages 2727-2731

As shown in Table 40, the percentage of adolescent subjects with any adverse event was 17% in the baloxavir marboxil arm and 34% in the placebo arm. Adverse events were reported in 21% of subjects 18 years of age and older (adults) who received baloxavir marboxil and in 23% who received placebo. The most frequently reported AEs in the overall population and in subjects 18 years of age and older were the identical. In subjects 18 years of age and older, diarrhea and bronchitis were both reported in 3% of subjects. There were no severe or serious adverse events reported in the adolescent subject population. In the opinion of this reviewer, there was no increase in the incidence or severity of adverse events in adolescents, and the types of adverse events was similar to those observed in adult subjects.

Safety analysis by race
Adverse events reported by race are shown in the following table. The table is limited to AEs observed in Asians and Whites because of the small number of other races enrolled in the pivotal trials

Table 41. Number of Subjects with Adverse Events in the Pivotal Trials by Race (Asian and White)

	Baloxavir marboxil		Placebo		Oseltamivir	
	Asian N=463	White N=198	Asian N=284	White N=98	Asian N=316	White N=170
Diarrhea	12 (3%)	8 (4%)	16 (7%)	2 (2%)	10 (3%)	1 (1%)
Bronchitis	11 (2%)	3 (2%)	13 (5%)	2 (2%)	9 (3%)	9 (5%)
Nausea	6 (1%)	1 (1%)	2 (1%)	3 (3%)	4 (1%)	11 (7%)
Sinusitis	5 (1%)	1 (1%)	4 (1%)	3 (3%)	2 (1%)	3 (2%)

Source: ISS, Table 2.7.4-58, page 84 and ISS AE dataset

The percentage of subjects with each adverse event in the Asian demographic subgroup was similar to that in the White subgroup. No significant difference in baloxavir marboxil safety was

observed by race. Blacks and Hispanics were underrepresented in the study population. The Applicant was encouraged to enroll more Blacks and Hispanics in their postmarketing trials. However, there is no rationale for a difference in safety by race, and on review of data from the pivotal trials, there are no concerns regarding safety differences by race.

Safety analysis by sex
Adverse events by sex are shown in the following table.

Table 42. Number of Subjects with Adverse Events in the Pivotal Trials by Sex

	Baloxavir marboxil		Placebo		Oseltamivir	
	Male N=355	Female N=355	Male N=207	Female N=202	Male N=275	Female N=238
Diarrhea	9 (3%)	11 (3%)	7 (3%)	12 (6%)	5 (2%)	6 (3%)
Bronchitis	10 (3%)	7 (2%)	6 (3%)	11 (5%)	10 (4%)	8 (3%)
Nausea	2 (1%)	6 (2%)	2 (1%)	3 (2%)	4 (2%)	12 (5%)
Sinusitis	3 (1%)	8 (2%)	2 (1%)	6 (3%)	2 (1%)	3 (1%)

Source: ISS, Table 2.7.4-54, page 80 and ISS AE dataset

The safety profile of baloxavir marboxil was similar in males and females. No safety differences by sex were observed.

8.8 Specific Safety Studies/Clinical Trials

No studies were conducted for assessment of a specific safety issue. No subjects were powered to identify or quantify a safety concern. However, safety data were collected in each study of baloxavir marboxil.

8.9 Additional Safety Explorations

8.9.1.1 Human Carcinogenicity or Tumor Development

The assessment for oncologic events is limited, because baloxavir marboxil was administered as a single dose and subjects were followed for 21 days after dosing. In addition, because baloxavir marboxil is administered as a single dose, the potential for human carcinogenicity seems low.

Nonclinical carcinogenicity studies were not conducted because baloxavir marboxil is to be used as a single dose for this indication. All genotoxicity studies were negative.

8.9.1.2 Human Reproduction and Pregnancy

Females who were pregnant were excluded from all clinical trials. No pregnancies were reported in the clinical development for baloxavir marboxil.

In the nonclinical program for baloxavir marboxil-related, embryo-fetal studies were conducted in rats and rabbits. A slight decrease in maternal body weights and food intake were observed in both species. Abortions and fetal skeletal variations (cervical rib and supernumerary ribs) were also observed in rabbits. However, the baloxavir exposures in the animal studies were 5 to 7 times the exposure at the recommended clinical doses; adverse effects were not observed at exposures similar to the exposures in humans at the recommended dose. Therefore, animal studies suggest that the possibility of fetal harm in humans is remote. See Dr. Diggs's Pharmacology/Toxicology review.

8.9.1.3 Pediatrics and Assessment of Effects on Growth

Study of baloxavir marboxil in subjects younger than 12 years of age
The results of a single non-IND pediatric study conducted in Japan were submitted with the NDA. This study, 1618T0822, was an open-label, single arm, safety, PK, and efficacy study of baloxavir marboxil in otherwise healthy Japanese pediatric patients with uncomplicated influenza. Subjects from the age of 6 months to < 12 years of age were enrolled and treated with a single oral baloxavir dose by weight as shown below. The tablet formulation of baloxavir marboxil was used for all subjects in this study.

Table 43. Baloxavir Marboxil Dose by Weight in Study 1618T0822

Weight at Screening	Dose	Tablet
5 to < 10 kg	5 mg	½ of a 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: CSR 1618T0822, Table 9-1, page 41.

Most patients younger than 5 years of age cannot swallow a tablet, and it is not known whether subjects younger than 5 years of age in this study had any difficulties in swallowing the baloxavir marboxil tablet. It is unclear whether all study subjects were able to tolerate the tablet formulation and thus received the intended dose of baloxavir marboxil.

Subjects were followed for efficacy for 14 days and for safety for 21 days. Blood samples for determination of baloxavir plasma concentrations on Days 1, 2, and at one visit from Day 6 to 22. Additional blood samples for PK were collected in a subgroup of subjects.

A total of 107 subjects were randomized: 105 in the age 2 to 12 year old cohort and 2 subjects in the 6 months to < 2 years old cohort. Since only two subjects were younger than 2 years of age, conclusions regarding efficacy, PK and safety cannot be reached in this age group.

Baloxavir C_{24} values for pediatric subjects in this trial were compared to C_{24} values obtained in adults who received 40 mg baloxavir marboxil in Trial 1518T0821. Mean C_{24} values in pediatric

subjects who received 40 mg (86.4 ng/mL) were slightly higher compared to those observed in adults in 1518T0821 who received 40 mg (61.5 ng/mL). However, C_{24} values in subjects who received 10 or 20 mg were lower than expected. DAVP Clinical Pharmacology reviewers discussed these results with the Applicant and higher doses of baloxavir marboxil will be studied in pediatric trials requested in the initial pediatric study plan (iPSP) submitted under the U.S. IND.

The median time to alleviation of symptoms was 45 hours. In the Phase 3 trial conducted in adults and adolescents, the median time to alleviation of symptoms in the baloxavir marboxil arm was 54 hours. Therefore, based on cross-study comparison, baloxavir marboxil appears to be efficacious in pediatrics, with the caveat that there appears to be some variability in the time to alleviation of symptoms across trials (and in placebo arms). However, the appropriate dose has yet to be identified for specific pediatric weight bands or age ranges.

No deaths, SAEs, or AEs leading to premature study discontinuation were reported in this study. Adverse events were reported in 37 subjects (35%). Adverse drug reactions were reported in 4 subjects (4%). The four treatment-related AEs were diarrhea or soft feces (N=3) and increased ALT (N=1). The increase in ALT was Grade 1 in severity, so it is unclear why this value was judged to be clinically significant and categorized as an AE. Three AEs were reported in at least 2% of subjects: vomiting (8%), diarrhea (3%), and pharyngitis (3%).

Overall, the efficacy and safety results reported in this pediatric trial were similar to that reported in the pivotal trials in adults. However, an appropriate formulation was not used in the pediatric study, the appropriate dose was not identified, and safety needs to be studied using the appropriate dose of baloxavir marboxil. In addition, only two subjects younger than two years of age were studied in 1618T0822, and additional information about baloxavir marboxil PK, safety, and efficacy is needed in this age group.

Study of baloxavir marboxil in adolescents
Subjects from 12 to < 18 years of age were included in the Phase 3 trial, 1601T0831. Safety and efficacy in adolescents was similar to that observed in adults. These results are shown in the section of this review describing efficacy by subgroup and the section of this review describing safety by demographic subgroup. In the package insert, efficacy results for the primary endpoint in adolescents will be included in Section 8.4, Pediatric Use. This section of the PI will also contain a sentence stating that the adverse events reported in adolescents were similar to those reported in adults.

The Applicant has completed a Phase 3 study of baloxavir marboxil in subjects with influenza who are at increased risk of influenza complications. This study enrolled subjects 12 years of age and older. The Applicant plans to conduct a Phase 3 study in seriously ill/hospitalized subjects with influenza. This study will also enroll subjects 12 years of age and older. The

results of both studies will be submitted as supplements to the NDA. Additional information regarding safety and efficacy in adolescents will most likely be added to the package insert after review of these trials.

Postmarketing safety reports
Limited postmarketing safety data were submitted from the time period this year (March 14, 2018 to May 31, 2018) that baloxavir marboxil was marketed and distributed in Japan. There were three serious AEs reported in pediatric patients.

- A 2 year received a single dose of baloxavir marboxil for influenza and was also begun on a cephalosporin for otitis media. Two days later, he was still febrile, and a laboratory work-up revealed a low white blood cell count of 2200/μL) and thrombocytopenia (97,000/μL). The abnormal laboratory values resolved and were likely due to influenza or to use of a cephalosporin.
- An 8 year old with influenza A was treated with 20 mg of baloxavir marboxil and reported delirium, diarrhea, and headache afterwards. The delirium resolved the same day; diarrhea and headache resolved two days later.
- A 10 year old male was treated with a single 40 mg dose of baloxavir marboxil for influenza and woke during each of the next three nights with abnormal behavior (feeling scared and hiding in the bathroom). This behavior resolved.

Two of these reports describe abnormal behavior and may represent neuropsychiatric AEs that have been observed in patients with influenza. Neuropsychiatric adverse events have been described in postmarketing reports for other anti-influenza drugs.

Initial Pediatric Study Plan
The Applicant and FDA agreed upon an initial Pediatric Study Plan (iPSP) on May 5, 2017. The Applicant plans to study pediatric patients in all age ranges (birth to < 18 years old). Pharmacokinetic, safety and efficacy data for adolescents was included in the NDA and are described in this review. The Applicant was granted a deferral for studies in pediatric patients from birth to < 12 years of age, because the results of adolescent and adult were available prior to completion of studies in pediatric patients < 12 years of age. (b) (4)

The Applicant agreed to conduct a Phase 1 bioequivalence study to compare the baloxavir marboxil (b) (4) formulation to the 20 mg tablet. This study will have two parts, a bioequivalence (BE) part and a food effect (FE) part. In the BE part, 50 healthy adults will receive a single 20 mg tablet of baloxavir marboxil and 20 mg (b) (4) Pharmacokinetic parameters will be measured to determine if the (b) (4) is bioequivalent to the tablet formulation. In order for BE to be demonstrated, the 90% confidence intervals for C_{max} and $AUC_{0\text{-last}}$ of the (b) (4) formulation to the 20 mg tablet should be included within the range of 0.80 and 1.25. Fourteen

subjects will be enrolled in the FE part of the study to assess the effect of food on the PK of baloxavir (b) (4) The effect of food will be assessed using the PK parameters of baloxavir by ANOVA. Safety in both parts of the study will be assessed by collection of adverse events and summarizing them by treatment and incidence. This study was recently completed, but the results have not been submitted to FDA.

The Applicant has agreed to conduct a randomized, (b) (4)-controlled, safety, PK, and efficacy study of baloxavir marboxil in otherwise healthy subjects 1 to < 12 years of age with influenza-like symptoms. (b) (4)

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(b) (4)

The Applicant has also agreed to conduct a third study. This study will be a (b) (4) safety, PK, and efficacy study of baloxavir marboxil in otherwise healthy pediatric subjects from birth to < 1 year of age with influenza-like symptoms. (b) (4)

8.9.1.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses and no reports of drug abuse occurred in the clinical development program for baloxavir marboxil. Based on baloxavir marboxil's mechanism of action, no withdrawal or rebound effects are anticipated.

8.10 Safety in the Postmarket Setting

8.10.1 Safety Concerns Identified Through Postmarket Experience

Baloxavir marboxil was approved in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA) on February 23, 2018 for the treatment of influenza in otherwise healthy patients weighing at least 20 kilograms. Baloxavir marboxil is not approved for use in any other country. Commercial distribution in Japan began on March 14, 2018 and continued to the end of the Japanese 2017/2018 influenza season (May 31, 2018). The Applicant estimates from drug sales that 384,970 patients received baloxavir marboxil during this time period.

During the first six months after approval of new drugs in Japan, Market Authorization Holders are responsible for collecting adverse drug reaction reports from all medical institutions where the drug is used. Sales representatives visit every facility in which the drug is used and encourage submission of postmarket AE reports. Sales representatives visit health care providers every two weeks for the first two months, then monthly for the remaining six months after drug approval. As a result, AE reports are solicited and not spontaneous, but the AE report is submitted in the same format as spontaneous AEs, and no additional information to clarify missing information about AEs is sought.

During the reporting period from the time baloxavir marboxil was first distributed in Japan and the database closure on September 13, 2018, there were non-serious AE reports for 303 patients and serious AE reports for 19 patients. These reports described 385 non-serious AEs and 28 serious AEs. The CIOMS forms were submitted for all serious AE reports.

The most commonly reported non-serious AEs were gastrointestinal (202 AEs) including 113 AE

reports of diarrhea, 39 of vomiting, 20 of nausea, and 7 of soft feces. Headache was reported in 30 patients. No other non-serious AEs were reported in 20 patients or more. Possible allergic reactions to baloxavir marboxil reported as non-serious AEs included 8 AEs of swelling of lips, face, or eyelids; 8 AEs of urticaria; 16 AEs of rash; and 4 AEs of drug eruption.

Serious adverse events reported in more than one patient were anaphylactic shock (N=2), decreased blood pressure (N=2), erythema multiforme (N=2), melena (N=2), loss of consciousness (N=2), seizures (N=2), and pneumonia (N=2). Other serious AEs were reported in a single subject each: death, multiple organ dysfunction syndrome, septic shock, acute kidney injury, rhabdomyolysis, diarrhea, delirium, abnormal behavior, thrombocytopenia, hyponatremia, decreased white blood cell count, fall, subarachnoid hemorrhage, and tendon rupture.

Serious AEs resulted in death in two patients and the serious AE was reported as death in a third patient.

- Report 201804957 – This was a 90 year old Japanese male who presented to his health care provider (HCP) with a fever to approximately 39° C and nasopharyngitis. Although his rapid influenza test was negative, he was prescribed one 20 mg dose of baloxavir marboxil. Two days later, the patient experienced loss of consciousness and died. His past medical history was significant for a pacemaker placed four years previously. No other information was provided, but the HCP concluded that his death was related to baloxavir marboxil.
- Report 2018000698 – This was a spontaneous report from a consumer who stated that an elderly relative had taken a single dose of baloxavir marboxil for influenza and had developed an anaphylactic shock-like syndrome. The patient was taken to a hospital and died. No other information was provided. No information from medical personnel or the hospital was obtained.
- Report 20180819 – This was a 77 year old Japanese male who was diagnosed with influenza B and treated with a single 40 mg dose of baloxavir marboxil. The next morning, the patient reported respiratory discomfort and wheezing and was hospitalized. The subject was diagnosed with septic shock and multi-organ failure due to pneumococcal pneumonia and died that day.

There is insufficient information available to determine relationship between death and baloxavir marboxil for either of the first two serious adverse events described. In this reviewer's opinion, the third death was clearly related to bacterial sepsis and not to baloxavir marboxil.

Insufficient information to evaluate these serious AEs was an issue for multiple reports. In other AE reports, an adequate reason, besides administration of baloxavir marboxil, was provided for the etiology of the serious AE. Serious AE reports that, in the opinion of this reviewer, might be related to baloxavir marboxil or in which an association with baloxavir

marboxil cannot be ruled out, include the following reports.

- Erythema multiforme in an 80 year old patient with influenza B - This patient presented with a rash the day after receiving a single dose of baloxavir marboxil and was diagnosed with erythema multiforme by a dermatologist. He subsequently developed fever and ataxia and was hospitalized for treatment with steroids. He also received paracetamol, carbocisteine (a mucolytic agent), and ebastine (antihistamine); however, these drugs were unlikely to cause allergic reactions and his erythema multiforme was probably due to treatment with baloxavir marboxil.
- Diarrhea and hyponatremia in an 80 year old female – The patient began having approximately 10 stools one day after a single 40 mg dose of baloxavir marboxil. After three days of diarrhea, she was diagnosed with hyponatremia and treated with intravenous fluids. Her diarrhea and hyponatremia resolved. She was also diagnosed with empty sella syndrome; however, empty sella syndrome is not typically associated with diarrhea.
- Acute renal failure due to rhabdomyolysis in a 67 year old female – The patient was treated with a single dose of baloxavir marboxil for influenza and was seen by her HCP for left thigh pain five days later. At the time of the HCP visit, she was hospitalized for rhabdomyolysis and acute renal failure. She required hemodialysis and remained in the hospital for approximately six weeks. She had been receiving a statin for hypercholesterolemia for 10 years. Her HCP diagnosed her with acute renal failure due to rhabdomyolysis and considered rhabdomyolysis due to either influenza or baloxavir marboxil. The renal failure resolved, and the patient recovered. Although a relationship of rhabdomyolysis to baloxavir marboxil cannot be ruled out, statin use was also a confounding factor in this case.
- Seizures, loss of consciousness, and vomiting in a 40 year old female – A patient with no history of seizures had vomiting and three seizures associated with loss of consciousness approximately ten hours after receiving a single 40 mg dose of baloxavir marboxil for the treatment of influenza A. Her CT scan showed cerebrovascular stenosis, which is not typically associated with seizures. The seizures were thought possibly to be due to fever or influenza itself, but a relationship to baloxavir marboxil could not be ruled out.
- Anaphylactic shock – A 31 year old male was diagnosed with influenza B and treated with a single 40 mg dose of baloxavir marboxil. Six days later, the patient presented to the emergency department with swelling of lips and eyelids, urticaria, cold sweats, and respiratory discomfort. He was treated with intramuscular adrenaline x 3, intravenous steroids, and intravenous antihistamines in the emergency department and was admitted to the hospital. He continued on steroids and antihistamine, and his symptoms gradually improved. He was discharged after one day in the hospital. Allergy tests for the foods he had eaten prior to developing symptoms and screening for hereditary angioedema were negative. A relationship between anaphylactic shock and baloxavir marboxil cannot be ruled out because of the long half-life of baloxavir.

There were three serious AEs reported in pediatric patients. A 2 year received a single dose of baloxavir marboxil for influenza and was started on a cephalosporin for otitis media at the same time. Two days later, he was still febrile, and a complete blood count revealed leukopenia (white blood cell count of 2200/μL) and thrombocytopenia (97,000/μL). Both resolved and were more likely due to influenza or to use of a cephalosporin than to baloxavir marboxil. An 8 year old with influenza A was treated with 20 mg of baloxavir marboxil. On the day of treatment, he experienced delirium, diarrhea, and headache. The delirium resolved the same day; diarrhea and headache resolved two days later. A 10 year old male was treated with a single 40 mg dose of baloxavir marboxil for influenza and woke that night and the next two nights with abnormal behavior (feeling scared and hiding in the bathroom). The abnormal behavior resolved. These adverse events raise the possibility of neuropsychiatric AEs with baloxavir marboxil in pediatric patients; however, these AEs may have been related to influenza.

The majority of non-serious adverse events reported in the limited time period after the recent approval of baloxavir marboxil in Japan were gastrointestinal AEs, particularly diarrhea. Nausea and vomiting were also reported much more commonly than other AEs. Reports of serious AEs were uncommon, and the types of serious adverse events varied. It is difficult to reach any definitive conclusions regarding serious AEs observed post-marketing because of the low incidence of individual events reported during the very limited time period in which baloxavir marboxil was commercially available in Japan.

8.10.1.1 Expectations on Safety in the Postmarket Setting

Safety conclusions in this review are primary based upon data from two pivotal trials of baloxavir marboxil. The amount of postmarketing safety data from Japan was limited due to the short amount of time that baloxavir marboxil has been marketed there, and the type of postmarketing surveillance that was performed. Routine pharmacovigilance activities will be ongoing in the United States, as well as in Japan, to detect any potential new safety signals.

8.10.1.2 Additional Safety Issues From Other Disciplines

All safety issues from other disciplines have been incorporated into relevant sections elsewhere in this review.

8.11 Integrated Assessment of Safety

The overall safety database for baloxavir marboxil comes from the two pivotal trials of baloxavir, marboxil, 1601T0831 and 1518T0821, and is considered adequate. The safety findings from Trials 1601T0831 and 1518T0821 are described in detail in Sections 8.4 and 8.5 of this review.

Diarrhea and bronchitis were the only adverse event reported in ≥ 2% of subjects. Adverse events reported in 1% to < 2% of subjects who received baloxavir marboxil were nasopharyngitis, nausea, and headache. All of these AEs were reported at a similar or higher frequency in the placebo arms than in the baloxavir marboxil arms. Two serious adverse events were reported in the pivotal trials of baloxavir marboxil. One SAE was viral meningitis. This SAE was possibly due to influenza and may have been related to treatment failure with baloxavir marboxil. The other SAE, an incarcerated hernia, was clearly not related to baloxavir marboxil. No deaths were reported in the pivotal trials.

There were no deaths, no serious adverse events, and no severe adverse events reported in the 11 Phase 1 studies of baloxavir marboxil. The most commonly reported AE in these studies was headache.

Preliminary results from a second Phase 3 trial of baloxavir marboxil were submitted in the Safety Update Report. In this trial, subjects at increased risk of influenza complications were randomized to receive baloxavir marboxil, placebo, or oseltamivir. There was one death in a subject who received baloxavir marboxil in this trial. This subject had abnormalities noted on his screening ECG that resulted in the subject having coronary artery bypass graft surgery, and the subject died of complications from surgery. This SAE was clearly unrelated to baloxavir marboxil.

In summary, there are no concerning safety findings from Phase 1, Phase 2, or Phase 3 trials of baloxavir marboxil.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee or other external consultations were held to discuss this application.

10 Labeling Recommendations

10.2 Prescription Drug Labeling

Labeling negotiations with the Applicant are ongoing. Below are general clinical recommendations for proposed labeling.

Indications and Usage

- The indication was revised to specify that Xofluza was indicated for the treatment of *acute uncomplicated* influenza.
- The limitation of use was modified to include consideration of influenza types and subtypes when prescribing baloxavir marboxil. A reference to Section 14 Clinical Studies was also added. This was because of the discordant results for influenza B in the two pivotal trials, and a description of the efficacy of baloxavir marboxil against influenza B was added to Section 14.

Adverse Reactions

- The Applicant proposed a statement (b) (4)
- This section was revised to add a table describing adverse events observed 1% or more of subjects who received baloxavir marboxil in the two pivotal trials.
- The section contained the number of subjects who received any dose of baloxavir marboxil to describe the total number of subjects exposed to baloxavir marboxil, and the number of subjects exposed to the to-be-marketed dose was added.
- Sentences describing the study population of the two pivotal trials were added.

Pediatric Use

- (b) (4)
- Efficacy and safety information for adolescents was added.

Clinical Studies

- Demographic characteristics for the study populations in the two pivotal trials were added.

(b) (4)

- Information regarding self-assessment of influenza symptoms by study subjects was added to explain the study design.

(b) (4)

- Information on the percentage of subjects infected with each influenza strain was added to show that A/H3N2 was the predominant strain isolated in Trial 1601T0831 and

A/H1N1 was the predominant strain isolated in Trial 1518T0821.

- A description of the efficacy results against influenza B was provided for each of the pivotal trials.

(b) (4)

[redacted]

11 Risk Evaluation and Mitigation Strategies (REMS)

No safety issues were identified to necessitate a REMS.

12 Postmarketing Requirements and Commitments

The following clinical postmarketing studies are currently under consideration as Postmarketing Requirements or Postmarketing Commitments. Additional postmarketing requirements and commitments have been proposed by Clinical Pharmacology and Virology reviewers.

Postmarketing Requirements:

1. Conduct a randomized active-controlled clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric patients from 12 months to less than 12 years of age with acute uncomplicated influenza, to identify a safe and effective dose(s) of baloxavir marboxil. Include characterization of baloxavir resistance-associated substitutions in viral isolates from patients with prolonged viral shedding.

2. Conduct a single-arm, open-label clinical study to evaluate pharmacokinetics, safety and antiviral activity of baloxavir marboxil in pediatric patients from birth to less than 12 months of age with acute, uncomplicated influenza. Include characterization of baloxavir resistance-associated substitutions in viral isolates from patients with prolonged viral shedding.

3. Submit the clinical study report and datasets for the pharmacokinetics, safety, antiviral activity of baloxavir marboxil in Japanese pediatric patients who weigh less than 20 kg with acute, uncomplicated influenza. Include characterization of resistance-associated substitutions, including supportive datasets.

Postmarketing Commitments:

1. Submit the clinical study report and datasets for the completed phase 3 clinical trial which evaluated efficacy of baloxavir for treatment of acute, uncomplicated influenza in patients at high risk for influenza complications 12 years of age and older.

2. Conduct a randomized, double-blind, controlled clinical trial evaluating efficacy and safety of baloxavir marboxil in patients hospitalized with severe influenza.

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

4. Submit the clinical study report and datasets for the bioequivalence study comparing the tablet [redacted] (b) (4) formulations of baloxavir marboxil in healthy adult volunteers.

13 Appendices

13.1 Financial Disclosure

There were no financial disclosures of significant concern. The financial disclosures as described in this section do not affect the approvability of baloxavir marboxil.

Covered Clinical Study: Trial 1518T0821

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 226		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study: Trial 1601T0831

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 993		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		

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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

There were no investigators with disclosable financial interests which could potentially bias either of these trials.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELISSE S BAYLOR
10/16/2018

MARY E SINGER
10/16/2018
I concur with Dr. Baylor's review and recommendations.