CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Cross-Discipline Team Leader/Division Director/Deputy Office Director Summary Memo

Date	October 22, 2018
From	Mary Singer, M.D., Ph.D., CDTL, and Debra Birnkrant, M.D., Division Director, DAVP John Farley, M.D., M.P.H, Deputy Office Director, OAP
Subject	Treatment of Acute Uncomplicated Influenza
NDA/BLA # and Supplement#	NDA 210854/S-000
Applicant	Shionogi, Inc.
Date of Submission	April 24, 2018
PDUFA Goal Date	December 24, 2018
Proprietary Name	Xofluza™
Established or Proper Name	Baloxavir marboxil
Dosage Form(s)	Tablets 20 mg, 40 mg
Recommended 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
Recommended Dosing Regimen(s)	Single oral dose based on weight: • weight of 40 kg to < 80 kg: 40 mg • weight ≥ 80 kg: 80 mg
Recommendation on Regulatory Action	*Approval*

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Benefit-Risk Integrated Assessment

Baloxavir marboxil inhibits influenza virus polymerase acidic protein endonuclease resulting in inhibition of viral RNA synthesis. This is a new mechanism of action. Cross-resistance with other anti-influenza drugs is not anticipated, and baloxavir marboxil is expected to retain activity against influenza strains with amino acid substitutions conferring resistance to the neuraminidase inhibitor class of influenza antiviral drugs. 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. The CDC estimates that there are between 140,000 and 170,000 hospitalizations each year for influenza and that there are 12,000 to 56,000 deaths each year due to influenza. In the 2017/2018 influenza season, 30,453-laboratory confirmed influenza-related hospitalizations were reported from October 1, 2017 to April 30, 2018 at hospitals in the CDC surveillance system, although the estimated total number of influenza-related hospital admissions in the US was approximately 900,000 in 2017-2108 influenza season (https://www.bmj.com/content/363/bmj.k4136). CDC tracks pneumonia and influenza-attributed deaths each year, and during the 2017/2018 season, the proportion of deaths attributed to pneumonia and influenza was at or above the epidemic threshold for 16 weeks from December, 2017 through April, 2018, accounting for approximately 10% of all deaths in the US during January 2018. The estimated number of influenza-related deaths was 80,000 in 2017 to 2018 season.

Two classes of influenza antiviral drugs currently available in the United States, neuraminidase inhibitors and adamantanes. 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. Adamantanes, including amantadine and rimantidine comprise the other class of influenza antiviral drugs. Use of the adamantanes is not currently recommended because of widespread adamantine resistance among influenza virus strains. In contrast, resistance to neuraminidase inhibitors is uncommon, but isolated instances of increased rates of resistance among influenza A virus isolates have been reported, and more widespread NAI resistance was reported in 2007.

Two clinical trials were conducted to support the safety and efficacy of baloxavir marboxil for treatment of acute, uncomplicated influenza in adults and adolescents. 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 the same in the baloxavir marboxil and oseltamivir arms. A treatment effect was also observed 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 in the subgroup with influenza B virus. In the Phase 2, dose-ranging trial, 1518T0821, 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 in the influenza B subgroup was observed. The median time to alleviation of symptoms for subjects with influenza B virus infection was 63 hours in the baloxavir marboxil arm and 83 hours in the placebo arm. Thus, efficacy results for treatment of influenza B virus -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, influenza antiviral 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 virus (Yamagata or Victoria) may be the predominant influenza strain in circulation. It is difficult to predict which strains will circulate each season, and influenza antiviral drug efficacy may vary by strain. A person's response to influenza may also be affected by pre-existing immunity to the same or similar influenza virus strain. Therefore, some variation in efficacy is expected by season. The discordant influenza B response observed in the two clinical trials may be related to differences in the circulating influenza B virus strains in the two seasons. However, neither study was powered to analyze efficacy by influenza type/subtype, so the influenza B results also may have been affected by the smaller number of subjects with influenza B. The concerns regarding the discordant results for influenza B were discussed with the Applicant, and a summary of efficacy results for a third trial, a recently completed Phase 3 trial 1601T0832, conducted in subjects at high risk of influenza complications was submitted 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 Limitation of Use specifically for influenza B was not included in product labeling 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 trial and in a Phase 2 trial, 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 virus is circulating in the community. A Limitation of Use statement was included encouraging providers to, "Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use" baloxavir marboxil."

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 combined baloxavir marboxil arms was diarrhea (2%) compared to 1% in pooled placebo arms. Note however, that none of the drug-related diarrhea was reported in the 40 mg baloxavir marboxil arm in the Phase 2 trial or the baloxavir marboxil arm (weight-based dosing) in the Phase 3 trial. 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 was 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 NDA for baloxavir marboxil will receive a 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 influenza cases 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. In the 2017/2018 influenza season, a total of 30,453-laboratory confirmed influenza-related hospitalizations were reported in hospitals in the CDC surveillance system, and the	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
	proportion of influenza-related deaths was at or above the epidemic threshold for 16 consecutive weeks during December 2017-April 2018.	
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. o 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 virus. o Majority of circulating seasonal influenza A virus strains are resistant to adamantanes, so use is not recommended.	There is a need for additional antiviral drugs for treatment of influenza that are safe, effective and available in an oral formulation. Amino acid substitutions conferring resistance has been reported with the available influenza antiviral drugs. There remains an unmet need for antiviral drugs with new mechanisms 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 (n=456) compared to 80 hours in the placebo arm (n=231). • 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	A large Phase 3 trial and a smaller Phase 2 trial demonstrated that baloxavir marboxil was 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 Phase 3 trial in acute, uncomplicated influenza, subjects who were at high risk for influenza complications were

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	subjects who received placebo. • 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. The median time to alleviation of symptoms in subjects with influenza B virus 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 710 who received the to-be-marketed dose in Phase 2 and 3 trials. • 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. The Applicant was asked 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 Phase 2 and 3 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. Resistance data will be collected from all future clinical trials, including pediatric studies.

2. Background

Baloxavir marboxil is a new molecular entity (NME) with a new 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.

The Division recommended that the NDA be submitted with the completed Phase 2 and 3 trials, 1518T0821and 1601T0831, respectively, after the robust demonstration of efficacy in the Phase 3 trial, and demonstration of superiority over placebo for each of the baloxavir marboxil doses tested in the Phase 2 trial. The Applicant had originally planned to complete their Phase 3 trial, 1602T0832, in subjects at high risk for influenza complications to submit with the NDA along with the Phase 3 trial in otherwise healthy subjects, 1601T0831. However, enrollment in the former trial was slower than expected, and rather than delay the submission for a drug with potential public health benefit, the Division encouraged the Applicant to submit data from the Phase 3 "high risk" trial later.

Influenza results in significant morbidity and mortality worldwide, as noted above. Currently available antiviral drugs recommended for treatment of acute, uncomplicated influenza in the U.S. include only drugs from the neuraminidase inhibitor (NAI) class, including oseltamivir (oral), peramivir (intravenous), and zanamivir (inhaled). Clinical trials for each of these drugs in the class have demonstrated clinical benefit measured as reduction in the time to alleviation of symptoms (approximately 1 day reduction in time to alleviation of symptoms compared to placebo). Baloxavir marboxil clinical trials used the same primary endpoint as for the NAI trials, and showed similar benefit, i.e. approximately 1day reduction in time to alleviation of influenza symptoms compared to placebo. The adamantanes, amantadine and rimantadine, although approved for influenza treatment, are no longer recommended, due to widespread influenza resistance to these drugs.

Baloxavir has activity in cell culture against neuraminidase inhibitor-resistant influenza virus, and cross-resistance between baloxavir and neuraminidase inhibitors or M2 proton pump inhibitors (adamantanes) is not expected. Baloxavir is active in cell culture against a broad range of influenza virus types and subtypes, including influenza A and B viruses (although EC_{50} value is higher for influenza B than for influenza A virus), and the avian influenza viruses, A/H7N9 and A/H5N1, which have the potential for causing influenza pandemics.

The Applicant, Shionogi, Inc., transferred the ownership of IND 126653 to Roche/Genentech, Inc., on May 17, 2018. Under the agreement with Roche/Genentech, Shionogi and Co., Ltd. will supply baloxavir marboxil (Xofluza™) bulk tablets and Roche/Genentech is responsible for (b) (4) distribution in the US.

Baloxavir marboxil is currently marketed in Japan since February, 2017 as a single dose for treatment of acute, uncomplicated influenza in adults and adolescents.

3. Product Quality

There are no unresolved product quality issues. The following section summarizes the product quality assessment from the OPQ reviews, as summarized by Dr. Stephen Miller.

- General product quality considerations:

Drug Substance
Baloxavir marboxil is a prodrug that is converted to the active form, baloxavir, through hydrolysis. The structure and absolute stereochemistry of baloxavir marboxil was verified by single crystal x-ray determination. For the drug substance, baloxavir marboxil, the process, specifications and controls, and stability data were considered acceptable from a product quality perspective. The proposed acceptance criteria for the specified impurities in the drug substance specification were considered appropriate from the product quality perspective, and were qualified from the toxicology perspective. (b) (4) is an elemental impurity (b) (4) controlled at not more than (b) (4) ppm in the (b) (4) . The Applicant submitted a thorough risk assessment for mutagenic impurity control, which was deemed appropriate. Mutagenic impurities most likely to advance to the drug substance, including (b) (4)

Drug Product
The proposed drug product, baloxavir marboxil (XOFLUZA™), is a solid, immediate-release film-coated product which will be marketed in the US as 20 mg and 40 mg tablets. The product is packaged in blister packs as two or four 20 mg tablets, and one or two 40 mg tablets. The drug product specifications were considered acceptable to support the identity, strength, purity and quality of the product from a product quality perspective. The submitted analytical methods and validation reports were reviewed and found acceptable. The submitted stability data for the drug product was consistent with that requested by OPQ at the pre-NDA meeting (October 31, 2017). The 24 months expiration date was considered acceptable for both tablet strengths (at 25° (b) (4) No drug product specific impurities were described, and elemental impurities, including (b) (4) acceptable limits.

The NDA described a single primary container closure system for the drug product: (b) (4) From the OPQ perspective, either container closure system was considered acceptable; however, the Applicant informed DAVP at the mid-cycle meeting on August 18, 2018, that the DosePak passed (b) (4) and only the DosePak will be used for US launch supplies.

- Facilities review/inspection: The Applicant provided information for 9 facilities involved in the manufacture of the drug substance, drug product, release testing, stability testing, drug substance intermediate testing, primary packaging/labelling, bulk product storage, final packaged product storage, and drug product release.

Pre-approval inspections (PAIs) were scheduled for the drug product manufacturing site, Shionogi and Co., Ltd., and the drug product analytical testing site, Shionogi Analytical Center Co., Ltd, both of which had not been previously inspected by the FDA. The outcomes of these inspections were VAI and NAI for Shionogi & Co. Ltd. and Shionogi Analytical Center Co. Ltd., respectively. There were no objectionable conditions found at either site and both facilities are able to support the acceptability of this application. For the remaining facilities, it was determined that no additional PAIs were required based on reviewing the most recent inspections for each facility, acceptable profiles, and their intended use. Thus, all facilities were determined to be acceptable for this NDA.

- Biopharmaceutics: The provided pharmacokinetics (PK) information for the lower strength 20 mg tablet, (b) (4) and 40 mg strengths, and PK linearity over a dose range of 6 mg to 80 mg, are appropriate and support the approval of the biowaiver request for the proposed higher 40 mg strength, and therefore the request for a waiver of conducting a bioequivalence study, comparing the 40-mg tablet with the 20-mg tablet which was used in the Phase 3 pivotal study, was granted July 31, 2018. The proposed dissolution method and the revised acceptance criterion for batch release and stability testing are acceptable.

- Environmental Assessment: The applicant claimed categorical exclusion from the requirement to submit an Environmental Assessment (EA) according to 21 CFR 25.31(b), which is applicable to this NDA.

4. Nonclinical Pharmacology/Toxicology

For full details see Pharmacology/Toxicology review by Drs. Deacqunita Diggs and Hanan Ghantous.

- Pharmacokinetics

In both rats and monkeys, the prodrug, baloxavir marboxil was metabolized rapidly to the active form, baloxavir. Increasing doses of baloxavir marboxil resulted in less than dose-proportional increases in exposure (AUC and C_{max}) of baloxavir in both rats and monkeys under fed conditions. Baloxavir exposure was greater in both species under fasted conditions. In cynomolgus monkeys, concomitant dosing of baloxavir marboxil with minerals (calcium, magnesium, aluminum, and iron) resulted in decreased baloxavir exposures. Protein binding was 92% in rats, and 85-89.5% in monkeys. Baloxavir was widely distributed, but was found mainly in the intestinal mucosa and liver between 1-2 hours post-dose in rats, and was below the limit of quantification in tissues at 24 hours post-dose. Baloxavir marboxil metabolites were primarily products of glucuronidation and oxidation of baloxavir in rats and monkeys. Radioactivity was primarily excreted in the feces via the bile, following a single oral administration of [^{14}C]-baloxavir marboxil in rats and monkeys. Baloxavir and its related metabolites were detected in milk from lactating rats. Maximum milk concentration of baloxavir was reached 2 hours post dosing and maximum plasma concentration was reach 1 hour post dosing. After 24 hours, baloxavir was undetectable in plasma and milk.

- Toxicology

Repeat-dose toxicology studies (one month exposure with a one month recovery period) were performed in rats and cynomolgus monkeys. The liver and thyroid were identified as target organs of toxicity. In rats, liver findings included increased liver weight, accentuated lobular pattern, liver enlargement, and histopathology findings of minimal centrilobular hypertrophy, minimal to mild macrovesicular fatty change in periportal

hepatocytes, and a mild increase in Kupffer cell phagocytosis at the high dose. These effects resolved during the recovery period. In cynomolgus monkeys, increases in AST, ALT, alkaline phosphatase, GGT, and glutamate dehydrogenase were reported, but these changes were not detected at the end of the recovery period. No histopathological findings in the liver were noted in monkeys.

In the thyroid, minimal diffuse follicular epithelial hyperplasia and minimal to mild decrease in colloid were observed at the mid and high dose in rats at the end of dosing; but these effects resolved during recovery. In monkeys, increased thyroid weights were observed in males at the end of dosing at the high dose and remained during recovery. Thyroid histopathology findings in monkeys included slight to moderate dilatation of follicles and follicular macrophages in all doses and controls which resolved during recovery.

There were testicular findings in one high dose male monkey who had an adhesion on the right testis/epididymis, with marked fibrosis and seminiferous tubule degeneration/necrosis and decreased prostate weight. One mid-dose male had fibrosis and necrosis/degeneration in the seminiferous tubule. However, these findings were not attributed to baloxavir because there was no clear dose-response, and similar findings were observed in historical controls with cynomolgus monkeys. Additionally, these findings were not seen at the end of recovery in the one month toxicology study, and were not observed in a 2-week repeat dose toxicology study at higher doses in the same species.

Based on the liver and thyroid findings, safety margins at the NOAELs in rats (20 mg/kg/day) and monkeys (10 mg/kg/day) were 0.6 and 2.5 times the exposure at the recommended clinical dose, respectively. However, these findings were considered mild and reversible, and because clinical trials had already been conducted in Japan without any safety issues identified with similar baloxavir exposures, these safety margins were not a major clinical concern when the IND was opened and clinical trials were initiated in the US.

All safety pharmacology (cardiovascular, neurological, respiratory, and skeletal muscles) and all genotoxicity studies (Ames, micronucleus and clastogenesis tests) were negative. Effect on the potassium channel current was evaluated in hERG-transfected CHO cells, and no significant effect was seen up to 10 µmol/L baloxavir in one assay, but a decrease in hERG currents was observed at 8.44 µmol/L in a second assay. No significant effects on cardiovascular parameters, including ECG parameters, were observed in cynomolgus monkeys given a single oral dose of baloxavir marboxil up to 400 mg/kg. Baloxavir marboxil was not phototoxic to the skin or cause skin reactions in *in vivo* studies but showed phototoxic potential in *in vitro* assays.

- Reproductive toxicology

In a fertility and early embryonic development study in rats was performed and no drug-related effects were observed. Embryofetal studies conducted in rats and New Zealand White (NZW) rabbits showed a decrease in maternal body weights and food intake. In rats, there were no drug-related effects on any parameter of the cesarean section for external and placental morphologies of live fetuses, and there were no drug-related effects on fetal visceral or skeletal alterations (malformation and degree of ossified bone). In NZW rabbits, abortions and fetal skeletal variations (cervical rib and supernumerary ribs) were observed. Exposure multiples at the maternal and fetal NOAELs in rats and rabbits were 5- and 7- times the baloxavir exposure at the recommended clinical dose, respectively.

In prenatal and postnatal development studies in rats, ocular abnormalities were noted in the F1 generation, including lens opacity, corneal opacity, and other findings. However, because of the low incidence of these findings relative to historical controls, these effects were not considered related to baloxavir marboxil.

- Carcinogenicity: Carcinogenicity studies were not conducted because the intended clinical use is for a single dose.

5. Clinical Pharmacology

See Clinical Pharmacology review by Drs. Hazem Hassan, Simbarashe Zvada, Luning (Ada) Zhuang, Su-Young Choi, and Shirley Seo, for full details.

Baloxavir marboxil (S-033188) is a prodrug that is rapidly metabolized to its active form, baloxavir (S-033447). In brief, following a single oral administration of baloxavir marboxil, the time to achieve the peak plasma concentration (T_{max}) is 4 hours. The absolute bioavailability of baloxavir marboxil has not been established. Baloxavir marboxil is rapidly hydrolyzed by esterases in the intestinal lumen and epithelium, liver and blood to form baloxavir. Baloxavir is highly protein-bound (93-94%). Elimination half-life is 79.1 (CV: 22.4%) hours. Baloxavir is metabolized by UGT1A3 with a minor contribution from CYP3A4. Approximately 80% of the administered dose is excreted in the feces, with urinary excretion contributing to < 15% of the administered dose.
In the Phase 3 clinical trial, 1601T0831, at the recommended dose of 40 mg for otherwise healthy patients weighing less than 80 kg, the mean (CV%) baloxavir C_{max} and AUC were 96.4 ng/mL (45.9%) and 6160 ng·hr/mL (39.2%), respectively. At the recommended dose of 80 mg for otherwise healthy patients weighing ≥ 80 kg, mean (CV%) baloxavir C_{max} and AUC were 107 ng/mL (47.2%) and 8009 ng·hr/mL (42.4%), respectively.

Dose proportionality assessment indicated that baloxavir exposure increases in a dose proportional manner over the proposed dose range of 40 to 80 mg. No bridging is needed for the 20 mg to-be-marketed formulation since it is identical to the formulation used in the pivotal study. The 40 mg to-be-marketed formulation was not used in any clinical study. Therefore, a waiver of bioavailability evaluation between the to-be-marketed 20-mg formulation and the to-be-marketed 40-mg was requested and granted by the FDA based on the available data, reviewed by the OPQ Biopharmaceutics reviewers, Drs. Qi Zhang and Elsbeth Chikhale.

Effect of Race
Based on a population pharmacokinetic analysis, race, in addition to body weight, is a covariate for oral drug clearance (CL/F) of baloxavir. After accounting for the weight differences, AUC_{inf} values were approximately 35% lower in Non-Asians as compared to Asians. No dose adjustment based on race is recommended since body weight-based dosing is considered sufficient to provide appropriate drug exposure levels, although it did not completely eliminate the effect of race.

Effect of Weight

Body weight had a significant effect on pharmacokinetics of baloxavir. As body weight increased, baloxavir exposure decreased.
Weight-based dosing was recommended by clinical pharmacology reviewers based on the Phase 2 dose-ranging trial, 1518T0821, which was conducted in Japan, in which there was no significant difference in efficacy by baloxavir marboxil dose (10, 20 or 40 mg), and on two key co-variates associated with the overall US population (weight and race). Non-Asian race and higher body weight both were associated with a decrease in baloxavir exposure, and thus weight-based dosing was recommended for use in the Phase 3 trial, 1601T0831, and subsequently for labeling. Weight-based dosing, as proposed, resulted in no clinically relevant exposure differences between subjects with relatively lower or higher body weight.

Food effect
Administration with food decreased the C_{max} and AUC of baloxavir by approximately 48% and 36%, respectively. However, in the Phase 2 and 3 clinical trials in which baloxavir marboxil was administered without regard to food, no clinically relevant differences in efficacy were observed when baloxavir marboxil was administered with or without food. Baloxavir plasma concentrations at 24 hours post dosing (C_{24}) would still be on the plateau of the exposure-response curve for efficacy after a ~ 50% decrease in exposures following the administration of 40 and 80 mg doses.

The clinical pharmacology reviewers agreed with the proposed labeling that baloxavir marboxil can be administered with or without food, but also proposed labeling to recommend that taking baloxavir marboxil with dairy products (milk) or calcium-fortified beverages should be avoided because of the potential interaction of baloxavir marboxil with calcium, resulting in chelate formation and reduced baloxavir exposure. In addition, co-administration of baloxavir marboxil with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g. calcium, iron, magnesium, selenium, or zinc) should be avoided due to a potential drug interaction resulting in decreased baloxavir exposures. This finding was observed in a non-human primate study. A clinical study to evaluate this potential drug interaction was proposed as a postmarketing commitment, but the Applicant declined to conduct this study, stating in the Late Cycle Meeting that this study would not be needed if the proposed language in the Dosage and Administration section (recommendation to avoid dairy products, calcium-fortified beverages and polyvalent-cation containing medications) were included in product labeling.

Exposure-Response Relationships
In the Phase 2 and 3 clinical trials 1518T0821 and 1601T0831, for the baloxavir marboxil doses administered, no change in exposure-response relationship was observed for efficacy based on the primary endpoint, time to alleviation of symptoms, or the secondary viral shedding endpoints for both type A and B influenza. Additionally, there was no clear relationship between baloxavir exposure and treatment-emergent resistance substitutions. An evaluation for an exposure-response relationship for adverse events was not conducted because of the low frequency of adverse events in the clinical trials.

A thorough QT (TQT) study was reviewed by the QT-IRT. See consultation dated 9/21/17 in DARRTS under IND 126653. The TQT study, a randomized, blinded, 4-period crossover study was conducted in an Asian population with a mean body weight of 59 kg (range of 46 to 77 kg). Subjects were dosed with baloxavir marboxil (40 mg and 80 mg), placebo, and a single dose of moxifloxacin, 400 mg. No significant QT prolongation was observed at the 40 mg or 80 mg baloxavir marboxil doses in this study; but the expected QT prolongation was observed with moxifloxacin, indicating that assay sensitivity was established.

Recommended Dosing Regimen
Baloxavir marboxil is to be taken orally as a single dose with or without food within 48 hours of onset of influenza symptoms. The recommended dose of baloxavir marboxil in patients 12 years of age or older is a single weight-based dose of 40 mg for patients weighing 40 kg to less than 80 kg; and 80 mg for patients weighing at least 80 kg. No dose adjustment is needed based on sex, race, age, hepatic impairment, or renal impairment. Baloxavir marboxil and baloxavir exposure was not evaluated in subjects older than 65 years of age, less than 40 kg body weight, with severe hepatic impairment, or with severe renal impairment. The safety and effectiveness of baloxavir marboxil have not been established in pediatric patients less than 12 years of age.

Drug-Drug Interactions
As noted above, co-administration of baloxavir marboxil with laxatives, antacids, and supplements containing polyvalent cations should be avoided as they could decrease its solubility and permeability and hence decrease its absorption. This recommendation is based on the chemical structure of baloxavir marboxil, as well as the non-human primate study discussed above, and no clinical studies have been done to confirm the interaction. No clinically significant changes in the pharmacokinetics of baloxavir marboxil and baloxavir were observed when co-administered with itraconazole (a strong CYP3A and P-gp inhibitor), probenecid (UGT inhibitor), or oseltamivir (antiviral agent). No clinically significant changes in the pharmacokinetics of the following drugs were observed when co-administered with baloxavir marboxil: midazolam (CYP3A4 substrate), digoxin (P-gp substrate), rosuvastatin (BCRP substrate), or oseltamivir.

Based on in vitro studies, baloxavir marboxil and its active metabolite, baloxavir, did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Baloxavir marboxil and its active metabolite, baloxavir, did not induce CYP1A2, CYP2B6, or CYP3A4. Both baloxavir marboxil and baloxavir are substrates of P-glycoprotein (P-gp). Baloxavir did not inhibit organic anion transporting polypeptides (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT) 1, OAT3, multidrug and toxin extrusion (MATE) 1, or MATE2K.

6. Clinical Microbiology

For full details, see clinical Virology review by Drs. William Ince, Michael Thomson, and Julian O'Rear.

Baloxavir selectively inhibits the influenza virus polymerase acidic (PA) subunit of the influenza virus polymerase complex which primes viral mRNA transcription using 5' 7-methylguanosine cap-containing oligomers cleaved from host mRNAs by the endonuclease activity of PA. Baloxavir marboxil inhibits this "cap-snatching" activity and thereby prevents viral mRNA transcription necessary for viral replication. In an endonuclease inhibition assay, the 50% inhibitory concentration (IC_{50}) value of baloxavir ranged from 1.4 to 3.1 nM (n=4) for influenza A viruses, and 4.5 to 8.9 nM (n=3) for influenza B viruses. Baloxavir inhibited a wide variety of influenza virus strains in cell culture, included many geographically distinct strains of influenza A and B viruses, including several animal strains and zoonotic subtypes, including A/H5N1 and A/H7N9. In a plaque reduction assay using MDCK cells, the median EC_{50} value of baloxavir against different influenza virus strains was 0.75 nM (range: 0.20-1.85 nM, n=21) for subtype A/H1N1 strains, 0.67 nM (range: 0.35-1.87 nM, n=20) for subtype A/H3N2 strains, and 5.97 nM (range: 3.33-13.00 nM, n=18) for type B strains. The antiviral activity of baloxavir was assessed in combination with oseltamivir, peramivir and zanamivir in MDCK cells infected with A/H1N1 virus. Baloxavir was not antagonistic in any combination of drugs tested. The antiviral

activity of baloxavir was not assessed in combination with adamantanes. The cell culture antiviral activity of baloxavir was not reduced against influenza virus strains harboring known neuraminidase inhibitor substitutions. Influenza virus harboring substitutions that caused reduced susceptibility to baloxavir retained sensitivity to the neuraminidase inhibitor oseltamivir. Cross-resistance to adamantanes was not evaluated but is not expected because baloxavir and adamantanes target different viral proteins with distinct functions.

In the Phase 2 and 3 clinical trials submitted in support of the NDA, 1518T0821 and1601T0831, treatment with baloxavir marboxil had a statistically significant impact on the primary endpoint, time to alleviation of symptoms overall in both trials, but efficacy (based on the primary endpoint) in subsets of subjects infected with influenza B virus was inconsistent between the Phase 2 and 3 trials, as discussed in section 7, Clinical/Statistical-Efficacy below for discussion of efficacy by influenza virus types/subtypes.
Based on virologic endpoints, antiviral activity of baloxavir was reduced against influenza B virus compared to type A influenza viruses in both 1518T0821 and 1601T0831. See Table 6 in section 7, Clinical/Statistical-Efficacy.

Influenza Virus Shedding
The proportion of subjects positive for influenza virus by nasopharyngeal swab culture was assessed post-treatment. Overall, the proportion of subjects who were influenza virus positive at each time point was significantly reduced in the baloxavir marboxil arm compared to placebo on Days 2-5, and compared to oseltamivir at Days 2, 3 and 5 (treatment initiated on Day 1). Similarly, treatment with baloxavir marboxil resulted in a median 4.8 $\log_{10}$ reduction in tissue culture infective dose $(TCID)_{50}$/mL compared to a 1.3 $\log_{10}$ reduction in the placebo arm and a 2.75 $\log_{10}$ reduction in the oseltamivir arm at Day 2. Viral shedding, measured by either infectivity assay or RT_PCR was reduced for influenza B compared to influenza A strains in subset analysis. See Virology review for detailed analyses of these endpoints.

Resistance Analysis
Resistance analyses were supported by data from the Phase 2 and 3 trials, 1518T0821 and 1601T0831, and a single-arm, non-IND Phase 3 pediatric study, T0822, conducted in Japan. Among these three trials, treatment-emergent resistance occurred in 2.7-11% of adults and adolescents and in 25.6% of pediatric subjects. As discussed in the Virology review, the increased rate of resistance observed in pediatric subjects is consistent with what has been observed for neuraminidase inhibitors, and may be related to increased viral load, prolonged viral shedding, or to distinct immunological responses in pediatric patients in comparison to adults. Note also that in the non-IND Japanese pediatric study (1618T0822), baloxavir marboxil doses were different than those that will be evaluated in pediatric studies agreed upon in the initial pediatric study plan under the US IND 126653, and which will be required postmarketing requirements under PREA regulations. The reasons for difference in frequency of treatment-resistant isolates between the Phase 2 and 3 trials is not known, but could be due to differences in influenza strains, virologic methods, study population, or other factors.

In the Phase 2 and 3 trials, 1518T0821 and 1601T0831, influenza A and B viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were observed as shown in the following table which will be included in the prescribing information. The overall incidence of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir in Trials 1518T0821 and 1601T0831was 2.7% (5/182) and 11% (39/370), respectively. None of the treatment-emergent substitutions associated with reduced susceptibility to baloxavir were identified in virus from pre-treatment respiratory specimens in the clinical studies.

Table 1. Treatment-Emergent Amino Acid Substitutions in PA Associated with Reduced Susceptibility to Baloxavir

Influenza Type/Subtype	A/H1N1	A/H3N2	B
Amino Acid Substitution	E23K/R, I38F/T	E23G/K, A37T, I38M/T, E199G	I38T

In a pooled analysis of subjects with type A virus infections in studies 1518T0821 and 1601T0831, treatment-emergent resistance-associated substitutions were associated with an increase in the primary endpoint, time to alleviation of symptoms (TTAS) in baloxavir marboxil treatment arms. The medians of the TTAS for subjects with and without a treatment-emergent resistance associated substitution were 63.32 (n=44) and 49.63 (n=413) hours, respectively, and the difference was statistically significant (p=0.0198, Mann-Whitney test). However, compared to placebo, the TTAS still remained shorter in subjects with RAS treated with baloxavir marboxil. The presence of a resistance-associated substitution was associated with viral rebound and prolonged viral shedding (beyond Day 5) among baloxavir marboxil-treated subjects.

7. Clinical/Statistical- Efficacy

See Clinical Review by Dr. Melisse Baylor and Statistical Review by Drs. Fraser Smith and Thamban Valappil for full details.

The efficacy of baloxavir marboxil in patients with acute uncomplicated influenza was supported by the results of a Phase 2 and a Phase 3 trial, 1518T0821 and1601T0831, respectively. 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 the US. 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. Initially the Applicant had intended to complete two Phase 3 trials in acute, uncomplicated influenza, one in otherwise healthy subjects (Trial 1601T0831) and the second in subjects at high risk for influenza complications (Trial 1601T0832). However, because 1601T0831 and 1518T0821 both demonstrated the superiority of baloxavir marboxil over placebo, DAVP encouraged the Applicant to submit an NDA based on the Phase 2 trial conducted in Japan (1518T0821) and the Phase 3 trial (1601T0831) conducted under the US IND. As requested, the Applicant submitted these two trials with the original NDA, and the summary efficacy and safety data from the now completed Phase 3 trial in subjects at high risk for influenza complications (Trial1601T0832) were submitted with the safety update report.

In Trials 1518T0821 and 1601T0831 and, the primary efficacy endpoint was time to alleviation of influenza signs and symptoms (TTAS), the same primary endpoint that was used in oseltamivir, peramivir, and inhaled zanamivir Phase 3 trials. Virologic endpoints were secondary endpoints, and in both trials, the comparator was placebo. In the Phase 3 trial, in addition to a placebo control, oseltamivir was an active control comparator; while the Phase 2 trial was a baloxavir marboxil dose-ranging study vs. placebo. Both trials were double blind, randomized, placebo-controlled trials which were considered adequate and well-controlled trials by the review team. No issues related to study design, study conduct or integrity, or major statistical issues were identified during the review. Most subjects completed the studies, and there were no major issues with missing data.

<u>Efficacy in Phase 2 Trial 1518T0821</u>

This was a randomized, double-blind, placebo-controlled dose-ranging trial conducted solely in Japan in otherwise healthy subjects ages 20 to 64 years old with acute, uncomplicated influenza. Subjects were included if they had fever (temperature ≥ 38° C (axillary), and at least one systemic symptom of moderate or greater severity (headache, feverishness or chills, muscle or joint pain, or fatigue), and at least one respiratory symptom of moderate or greater severity (cough, sore throat, or nasal congestion). Time interval from symptom onset to enrollment must have been ≤ 48 hours. Subjects were excluded if they had severe influenza requiring hospitalization, receipt of other antiviral medications for influenza within 7 days of enrollment, or baseline risk factors for severe or complicated influenza based on the definition of high risk by the Centers of Disease Control and Prevention. Influenza was diagnosed by rapid antigen-testing (RAT), which was not confirmed by RT-PCR. Subjects were randomized 1:1:1:1 to a single dose of baloxavir marboxil 10, 20, or 40 mg or placebo. Subjects recorded their temperature and influenza symptoms in an electronic diary (eDiary). A single dose of baloxavir marboxil or placebo was administered at the clinical site on study Day 1, and subjects were followed until Study Day 22.

The primary efficacy endpoint was TTAS, which 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 primary efficacy population was the intent to treat-infected (ITTI) population, which included all subjects who received the study drug and had a confirmed diagnosis of influenza virus infection based on RAT results.

A total of 400 subjects were randomized to one of the 4 arms noted above. The majority of subjects (97%) completed the trial. Protocol violations were uncommon, and the proportion of subjects who discontinued or who had a protocol violation was similar across arms. Most (62%) of subjects were male, all were Asian, and the median age was 37 years. The majority of subjects used acetaminophen or NSAIDs, as allowed by the protocol, but use was similar across treatment arms. Subjects were to take their temperature prior to or 4 hours after acetaminophen or NSAID use. This trial was conducted during the 2015/2016 influenza season. The most common influenza type/subtype isolated was A/H1N1 (63%), followed by influenza B (25%), and A/H3N2 (12%).

The following table shows the results for the primary efficacy analysis in this trial. The median time to alleviation of symptoms was 24 to 28 hours shorter in the baloxavir marboxil arms than in the placebo arm. Statistical significance was shown for each of the baloxavir marboxil doses vs. placebo using the generalized Wilcoxon test. Note that the Applicant had prespecified using the Cox proportional hazards model to assess the primary endpoint, and statistical significance was not met for any of the baloxavir treatment arms vs. placebo; however, the Wilcoxon test is the statistical method recommended by DAVP for analysis of acute, uncomplicated influenza trials because it puts more weight on earlier timepoints, as discussed in Drs. Smith and Valappil's statistical review. The difference in the medians, 24 to 28 hours for baloxavir in comparison to placebo is similar to that reported in similar trials of influenza neuraminidase inhibitors, oseltamivir, peramivir, and zanamivir. However the difference in medians overestimates the median difference of 17 to 20 hours. The median difference is recommended as a preferable way to estimate treatment effects. See Statistics review for further details regarding analysis of the primary endpoint.

Table 2: Trial 1518T0821 – Results for Primary Efficacy Endpoint in ITTI Population

Time to alleviation of symptoms	**Baloxavir marboxil†**			**Placebo**
	10 mg	**20 mg**	**40 mg**	**N=100**

	N=100	**N=100**	**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 medians for baloxavir vs. placebo (hours)	-24	-27	-28	---
Median difference (baloxavir vs. placebo) (hours)	-17	-18	-20	---

*CI = confidence interval
†Baloxavir marboxil treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Gehan-Breslow's generalized Wilcoxon test (p-value: 0.014, adjusted for multiplicity); The primary analysis of Cox Proportional Hazards Model did not reach statistical significance (p-value: 0.165)

The 40 mg baloxavir marboxil dose was chosen to go forward in the Phase 3 trial based on these results, although efficacy was demonstrated even with the 10 mg baloxavir marboxil dose in this trial. DAVP further recommended weight-based dosing for the Phase 3 trial because weight and race are significant covariates for baloxavir exposure, and agreed with using a 40 mg or 80 mg dose based on weight to ensure that baloxavir exposures would be sufficient to inhibit influenza B.

Efficacy in Phase 3 Trial 1601T0831

Trial 1601T0831 was a Phase 3, randomized, controlled, pharmacokinetic, safety, and efficacy trial of baloxavir marboxil in otherwise healthy subjects from 12 to ≤ 64 years of age with acute uncomplicated influenza. The trial was conducted in Japan and the US. Inclusion and exclusion criteria were the same as for the Phase 2 trial, 1518T0821, except that adolescents (12 to < 18 years of age) were enrolled in this trial, and based on DAVP advice, subjects were included based on the clinical diagnosis of influenza. A rapid influenza diagnostic test (RIDT)was performed, but subjects could be enrolled whether the RIDT was either positive or negative, and influenza diagnosis was confirmed by RT-PCR. Subjects had to meet the same criteria for influenza as the Phase 2 trial and had to be enrolled within 48 hours of symptom onset. Subjects 20 to ≤ 64 years of age were randomized 2:2:1 to baloxavir marboxil, oseltamivir, or placebo; while subjects 12 to < 20 years of age were randomized 2:1 to receive baloxavir marboxil or placebo.
The trial was conducted in a double-blind, double-dummy fashion by using two different placebos, one matching baloxavir marboxil and one matching oseltamivir. Subjects received a single dose of baloxavir marboxil on day 1 followed by placebo twice daily to complete 5 days of dosing, or 5 days of oseltamivir 75 mg twice daily or 5 days of placebo twice daily. Baloxavir marboxil was dosed by weight in this trial, 40 mg single dose for subjects weighing less than 80 kg, and 80 mg single dose for subjects weighing more than 80 kg.

The primary efficacy endpoint, time to alleviation of symptoms of influenza was the same as that used in the Phase 2 trial, and subjects recorded temperature and influenza symptoms as discussed above. Subjects were followed for 14 days for efficacy and 22 days for safety. The primary efficacy population was the intent to treat-infected (ITTI) population, which included all subjects who received the study drug and had a confirmed diagnosis of influenza virus infection based on confirmed influenza by RT-PCR.
The primary efficacy analysis was comparison of time to alleviation of influenza symptoms for baloxavir marboxil vs. placebo. Comparison of the primary endpoint for baloxavir marboxil vs. oseltamivir was a secondary comparison.

A total of 1436 subjects were enrolled at 141 clinical sites in Japan and 149 in the US between December, 2016 and April, 2017. The majority (95%) of subjects completed the trial and protocol violations were uncommon

and similar across arms. Approximately one-half of the study population was male and one-half female. The majority of subjects were Asian (mostly Japanese) (78%), 17% were White, 4% were Black/African American, < 2% were Native Hawaiian/Pacific Islander, and 6% were of Hispanic/Latino ethnic origin. and the median age was 32 to 35 years old. Influenza A/H3N2 was the most common influenza type/subtype (90%), followed by influenza B (9%), and A/H1N1(2%). The proportion of subjects who used antipyretic agents was similar across the treatment arms (12-13% subjects).

The primary efficacy analysis is shown in the following table. The median time to alleviation of symptoms was 54 hours in baloxavir marboxil arm compared to 80 hours in the placebo arm, resulting in a 26.5 hours shorter median time to alleviation of symptoms in the baloxavir arm (weight-based dosing) than in the placebo arm (difference in medians). However the difference in medians overestimates the median difference of -21 hours, as shown below. The median difference is recommended as a preferable way to estimate treatment effects. The shorter TTAS in the baloxavir marboxil arm was statistically significant using either the generalized Wilcoxon or log-rank tests.

Table 3: Trial 1601T0831 – Results for Primary Efficacy Endpoint in ITTI population)

Time to Alleviation of Symptoms	**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 in medians vs. placebo in hours (95% CI*)	-26.5 (-35.8, -17.8)	---
Median Difference (baloxavir vs. placebo) in hours (95% CI*)	-21 (-28, -13)	---

*CI = confidence interval
†Baloxavir marboxil treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Peto-Prentice's generalized Wilcoxon test (p-value: <0.001);

Comparison with Oseltamivir
In a secondary comparison, when the primary endpoint was compared for baloxavir marboxil vs. oseltamivir, there was no difference in the median time to alleviation of symptoms (median 54 hours for each arm).

Secondary Endpoints

Time to Resolution of Fever
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.

Subgroup Analysis

Efficacy by Age
In the Phase 3 trial, 1601T0831the 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. For adolescent subjects (age 12 to 17) in the Phase 3 trial, 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).

Efficacy by Sex
Time to alleviation of influenza symptoms by sex in the Phase 2 and 3 trials is shown in the following table. For both males and females, time to alleviation of symptoms was shorter in the baloxavir marboxil than placebo arms, although TTAS was longer for females than males in general.

Table 4. Median TTAS by Sex in Trials 1518T0821 and 1601T0831 (ITTI Population)

Time to Alleviation of Symptoms	**Trial 1601T0831 40 mg or 80 mg#**		**Trial 1518T0821 40 mg Arm**	
	Baloxavir marboxil	**Placebo**	**Baloxavir marboxil**	**Placebo**
Females	N=224	N=110	N=40	N=39
Median time in hours	63	87	54	93
Males	N=231	N=120	N=60	N=61
Median time in hours	48	74	48	69

Weight based dosing: 40 mg dose for subjects < 80 kg and 80 mg dose for subjects ≥ 80 kg

Efficacy by Race
In the Phase 3 trial, 1601T0831, TTAS varied by race. In the Phase 2 trial, only Asian (Japanese) subjects were enrolled. As shown in the following table, median time to alleviation of influenza symptoms was shorter in both Asian and White subjects treated with baloxavir marboxil than in those who received placebo, but TTAS was shorter for Asians than Whites in the baloxavir marboxil group in the Phase 3 trial. The reasons for the differences between Asians and Whites is not clear, but could be related to cultural differences in symptom reporting, in time to enrollment and administration of study drug from onset of symptoms, in baloxavir marboxil pharmacokinetics, in influenza strains, or to other reasons. There were insufficient numbers of Black/African American subjects or Hispanic/Latino subjects in these trials to make analyze these subsets. This is discussed in section 13, Postmarketing Recommendations.

Table 5. Median TTAS by Race Marboxil in Trials 1518T0821 and 1601T0831 (ITTI Population)

Time to Alleviation of Symptoms	**Trial 1601T0831 40 mg or 80 mg#**		**Trial 1518T0821 40 mg Arm**	
	Baloxavir marboxil	**Placebo**	**Baloxavir marboxil**	**Placebo**
Asians	N=348	N=177	N=100	N=100
Median time in hours	46	78	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

Efficacy by Influenza Type/Subtype across Trials
As shown in the following table, there was noteworthy variation in efficacy by influenza strains within and across trials. These trials were not powered for subset analysis, but some concern was raised by the review team because of the higher EC_{50} of baloxavir for influenza B in cell culture, and the discordant results for influenza B

in the Phase 2 and 3 trials. These conflicting results may be explained, in part, by small numbers, or the different influenza B lineage identified in the two trials. See Dr. Baylor's clinical review for further details.

Table 6. Median TTAS by Influenza Type/Subtype in Trials 1518T0821 and 1601T0831 (ITTI 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

These data, along with the higher EC_{50} in cell culture for influenza B, brought up the issue of whether a Limitation of Use for influenza B should be included in the Indications section of product labeling. However, the summary data, including data from the influenza B subgroup from the recently completed Phase 3 trial 1601T0832, in subjects at high risk was complications was submitted with the safety update report on August 22, 2018, and showed that the time to improvement of symptoms was shorter in subjects treated with baloxavir marboxil compared to placebo in this subgroup (which comprised approximately 40% of the population in that trial), providing some reassurance that the discordant findings may have been due to chance or small numbers.

In the Phase 3 trial, 1601T0832, in subjects at high risk for complications, in the overall ITTI population, the time to improvement of symptoms was shorter with baloxavir marboxil, 73.2 hours, 95% CI(67.2, 85.1) than with placebo, 102.3 hours, 95% CI (92.7, 113.1), a finding consistent with that observed in the Phase 3 trial, 1601T0831. In the influenza B subgroup in this trial, the difference in the median, time to improvement of symptoms, was 26 hours shorter with baloxavir marboxil, 74.6 hours, 95% CI (67.4, 90.2), than with placebo, 100.6 hours, 95% CI (82.6, 115.8), consistent with findings seen for influenza B in the Phase 2 trial (1518T0821). It should be noted that only summary data from this trial was reviewed as datasets were not submitted at the time of the safety update report (at the Division's request) because this was designated as a priority review. Submission of the full Clinical Study Report and datasets for the Phase 3 trial1601T0832 has been agreed to by the applicant as a PMC.

Conclusions on the Substantial Evidence of Effectiveness: The Applicant has provided substantial evidence of effectiveness in two adequate and well-controlled trials, the Phase 2 and Phase 3 trials, 1518T0821and 1601T0831, to support approval of baloxavir marboxil for the treatment of adults and adolescents with acute, uncomplicated influenza. Baloxavir marboxil was superior to placebo for the primary endpoint, time to alleviation of symptoms for the proposed dosing regimen. In the Phase 3 trial, the efficacy of baloxavir

marboxil was similar to that of oseltamivir, an influenza neuraminidase inhibitor approved for this indication. In subset analyses, reduced activity of baloxavir was shown for influenza B in comparison to influenza A, based on both clinical and virologic endpoints. Time to alleviation of symptoms for the influenza B subgroup remained shorter than that observed with placebo in the Phase 2 trial but was longer than that observed with placebo in the Phase 3 trial, although the data were limited. Summary data submitted to the NDA from a recently completed trial in subjects at high risk for complications of influenza, demonstrated that time to improvement of symptoms was shorter in subjects treated with baloxavir marboxil than those who received placebo in the influenza B subgroup, providing additional support for not limiting use of baloxavir marboxil for treatment of influenza A.

Some limitations are noted for these trials, namely, Blacks/African Americans, and Hispanics/Latinos and other ethnic groups were underrepresented. In addition, these trials did not include subjects ages 65 and older, a group considered at high risk for influenza complication. However, the Phase 3 trial, 1601T0832, in subjects at high risk for complications of influenza, including elderly subjects was recently completed, and summary data from that trial submitted with the NDA demonstrated similar efficacy with baloxavir marboxil in the overall population.

8. Safety

See Clinical Review by Dr. Melisse Baylor for full details.

- Adequacy of Safety Database

Overall, in Phase 1, 2, and 3 trials, a total of 1318 subjects received any dose of baloxavir marboxil, including 910 subjects in the Phase 2 and 3 placebo-controlled trials who received a single dose of baloxavir, 710 of whom received baloxavir marboxil at the doses recommended in the package insert. An additional 185 Japanese subjects received baloxavir marboxil in Phase 2 and other trials at doses which would provide similar baloxavir exposures to that with the 40 mg dose in non-Asians. Although the 2011 *FDA Guidance for Industry, Influenza: Developing Drugs for Treatment and/or Prophylaxis*, recommends a larger safety database for this indication (1500 patients at the dose and duration proposed for marketing), DAVP agreed with the size of the safety database at the pre-NDA meeting with the Applicant based on the robust data demonstrating efficacy in the baloxavir marboxil development program, and apparent lack of any safety signal with the proposed dosing regimen. Overall the safety database was considered acceptable.

- Key Safety Results

The Safety Population included all subjects in the Phase 2 and 3 trials, 1518T0821and 1601T0831, who received baloxavir marboxil at the recommended dose, i.e. a single dose of 40 mg or 80 mg based on weight (n=710). No dose-related safety findings were observed in the Phase 2 trial in which subjects received 10, 20 or 40 mg baloxavir marboxil or placebo; and safety data for the 10 and 20 mg doses are not presented in this review.

No deaths were reported in the Phase 2 and 3 trials submitted with the original NDA. In the safety update report, one death was reported in a subject from the recently completed Phase 3 trial, 1602T0832, in subjects at

high risk for influenza complications. This death was reviewed in detail in Dr. Baylor's clinical review, and is not considered related to baloxavir. The subject had an abnormal ECG on hospital admission and underwent coronary artery bypass surgery which was complicated by severe hypotension, right heart failure, as well as *Pseudomonas* pneumonia and bacteremia, resulting in death.

Two serious adverse events (SAEs) were reported in the Phase 3 trial, 1601T0831, and none was reported in Phase 2 (1518T0821). The two SAEs were incarcerated inguinal hernia, not related to baloxavir, and viral meningitis. The latter SAE was not attributed to baloxavir marboxil by the investigator; however, cerebrospinal fluid (CSF) white blood count of 112/mm^3 with 88% lymphocytes and a red blood cell count of 800/mm^3. No pathogens were identified. CSF viral culture or RT-PCR for influenza was not obtained. This SAE could represent a complication of influenza, i.e. influenza meningitis, potentially due to baloxavir treatment failure.

Baloxavir marboxil is administered as 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 baloxavir marboxil or placebo was dispensed. In Trial 1601T0831, subjects who received a single dose of baloxavir also received oseltamivir placebo for five days. Two subjects prematurely discontinued this trial. One subject in the 40 mg baloxavir marboxil arm discontinued due to bronchitis and pneumonia. Another subject in the 80 mg baloxavir marboxil arm discontinued due to bronchitis. Neither adverse event was judged as related to the study drug by the investigator. The percentage of subjects who discontinued prematurely in the baloxavir arm (0.3%) was similar to that observed in the placebo arm (0.3%) and the oseltamivir arm (0.4%).

In the safety update report, SAEs were reported in 5 (1%) subjects in the baloxavir marboxil arm, 9 (1%) in the placebo arm, and 8 (1%) in the oseltamivir arm in Trial 1602T0832, the recently completed trial in subjects at high risk for influenza complications. None of the SAEs was attributed to baloxavir marboxil by the investigator, and upon review of the narratives, Dr. Baylor agreed.

Treatment-Emergent Adverse Events
The following table displays all adverse events reported in at least 1% of subjects who received baloxavir marboxil in the two pivotal trials, separately and combined. This only includes subjects who were exposed to the to-be-marketed doses of 40 mg and 80 mg. The combined baloxavir arm includes subjects in the Phase 3 trial who received 40 or 80 mg baloxavir marboxil based on weight, and only the 40 mg baloxavir marboxil arm from the Phase 2 trial. In the latter trial, the majority of subjects weighed < 80 kg. Pooling of the Phase 2 and 3 data was considered appropriate because of the similar dosing, and adverse event monitoring. There were no treatment-emergent adverse events reported in more than 5% of subjects in any arm in the Phase 2 and 3 trials. In the combined baloxavir marboxil treatment arm, none of these adverse events was reported at a higher frequency than in the pooled placebo arms.

Table 7. 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%)

Severe Adverse Events

Adverse events classified as severe were reported only in the Phase 3 trial in US subjects; while none was reported in the Japanese subjects in the Phase 2 or the Phase 3 trial. No severe adverse events were reported in any of the 11 Phase 1 studies. In 1601T0831, 6/610 (0.9 %) subjects in the baloxavir arm experienced severe adverse events compared to 4/309 (1.3%) in the placebo arm, and 1/513 (0.2%) subjects treated with oseltamivir. Among subjects treated with baloxavir, severe adverse events included diarrhea, nausea, vomiting, viral meningitis (also reported as an SAE), otitis media, polydipsia, headache, and incarcerated inguinal hernia (also reported as an SAE). Diarrhea, nausea, vomiting and polydipsia were considered treatment-related. These data suggest that there may be some differences in the way that adverse events are perceived and reported by patients and/or investigators in Japan in comparison to the US, and the baloxavir marboxil safety profile may differ once more US patients are enrolled in these trials.

Adverse Reactions

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 (2%) in the combined baloxavir marboxil arms in the two pivotal trials compared to six subjects (1%) of subjects in the combined placebo arms. 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 were listed in Section 6 Adverse Reactions section of the package insert (see section 12, Labeling).

Laboratory and Electrocardiographic Abnormalities

Overall no significant laboratory abnormalities were identified in subjects treated with baloxavir in the Phase 2 and 3 trials. Additionally, there were no significant ECG abnormalities, including significant QT prolongation, associated with baloxavir marboxil in these trials.

Baloxavir Marboxil Safety in Adolescents

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. The most frequent AEs reported in adolescents (12 to ≤ 18 years old) were similar to those reported in adults (> 18 years old) and in the overall population in this trial. None of these events was reported at a higher frequency with baloxavir marboxil than with placebo. No serious or severe adverse events were reported in this subpopulation.

Table 8. 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%)

Safety Analysis by Race and Sex
No significant difference in adverse events (or frequency thereof) was found when Asians and non-Asians were compared. As noted previously, there were insufficient numbers of Blacks/African Americans or Hispanic/Latinos to analyze safety in these subpopulations. The safety profile of baloxavir marboxil was similar in males and females.

Postmarketing Experience
Baloxavir marboxil was approved in Japan on February 23, 2018 for treatment of acute, uncomplicated influenza in otherwise healthy patients weighing at least 20 kg. The Applicant estimates from drug sales that 384,970 patients received baloxavir marboxil during the 2017/2018 influenza season. Active postmarketing surveillance is done in Japan during the first 6 months after drug approval (i.e. safety reports are solicited rather than spontaneous). Postmarketing safety information was submitted to the NDA in the safety update report submitted to the NDA on August 22, 2018. The most common non-serious adverse events reported were nausea, vomiting, and diarrhea, and headache. A number of hypersensitivity non-serious adverse events were also reported, including swelling of the lips, face, or eyelids, urticarial, rash, and drug eruption. CIOMS reports for serious adverse events were reviewed, including 2 cases of anaphylaxis, but these had insufficient information to attribute causality to baloxavir marboxil or were confounded by concomitant medications or other factors. However, based on these reports, hypersensitivity to baloxavir marboxil will be included as a Contraindication in product labeling, as proposed by the Applicant.

9. Advisory Committee Meeting

No major issues were identified that would benefit from Advisory Committee advice; thus, an Advisory Committee was not convened.

10. Pediatrics

Extrapolation of Efficacy to Pediatric Population
Although the pathogenesis of influenza is the same in adults and children, severity of disease and the incidence of complications are inversely associated with age depending on immunologic maturity and lack of specific cell-mediated immunity in children. Maternal antibodies may provide some protection in the first 6 months of age. The Division agreed with the initial pediatric study plan proposed by Shionogi, Inc., which outlined a partial extrapolation approach. Adolescents were evaluated in the Phase 3 trial, 1601T0831, and efficacy and safety were demonstrated in this group (see sections 7 and 8 above). Although the proposed pediatric trials outlined below, are not powered for efficacy, efficacy will be a key secondary endpoint, and sufficient safety and pharmacokinetics data should be obtained to determine a safe and effective dose of baloxavir marboxil in pediatric patients from birth to < 12 years old.

Pediatric Study Plan and PREA Commitments
The Applicant and FDA agreed upon an initial Pediatric Study Plan (iPSP) on May 5, 2017. The iPSP was reviewed with the Pediatric Review Committee (PeRC), which was in agreement. The Applicant plans to study

pediatric patients in all age ranges (birth to < 18 years old). Pharmacokinetic, safety and efficacy data for adolescents were included in this NDA and are described in this review. The safety and efficacy data supporting an approval of baloxavir marboxil in adolescents were assessed by PeRC, which agreed with the Division's assessment. The Applicant was granted a deferral for studies in pediatric patients from birth to < 12 years of age, because the results of adolescents and adults were available prior to completion of studies in pediatric patients < 12 years of age. No pediatric waivers were granted. (b) (4) . These studies were agreed upon by the Applicant as postmarketing requirements under PREA, and are outlined below:

- (b) (4) subjects 12 months to < 12 years of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
- (b) (4) subjects from birth to < 1 year of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
- Submit the clinical study report and datasets for the pharmacokinetics, safety and efficacy trial of baloxavir marboxil in Japanese pediatric subjects who weigh less than 20 kg with acute, uncomplicated influenza. Include characterization of resistance-associated substitutions, including supportive datasets.

(b) (4) (b) (4) the clinical study report and datasets for the bioequivalence study comparing the 20 mg tablet and (b) (4) formulations of baloxavir marboxil in healthy adult volunteers.

Pediatric Written Request
A Proposed Pediatric Study Plan (PPSR) has not been submitted and Pediatric Written Request has not been issued at this time, although this was discussed with the Applicant at a type C meeting (b) (4) held on April 18, 2018.

11. Other Relevant Regulatory Issues

Financial disclosures: The Applicant has adequately disclosed financial agreements with clinical investigators . No clinical investigators or sub-investigators were employees of Shionogi, Incorporated. No investigators or sub-investigators had any disclosable financial interests or arrangements.

Good Clinical Practice (GCP): Although the Phase 2 trial, 1518T0821, was a non-IND study conducted only in Japan, the Applicant attested 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. The Phase 3 trial, 1601T0831, which was conducted under the US IND in Japan and the US was conducted in compliance with International Council for Harmonization Guidelines and Good Clinical Practice.

Office of Scientific Investigations (OSI) audits: 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.

Pre-Launch Activity Import Request (PLAIR): The Applicant submitted a PLAIR on August 27, 2018 for importation of the unapproved finished dosage form bulk drug product for final packaging at a US location to prepare for launch in the US. The Applicant certified that the packaged products will be held at the packaging or warehouse site in the US without selling or distributing the product until NDA approval. The PLAIR was discussed with the CDER Imports and Exports Compliance Branch (IECB) and the Division and OPQ recommended that the PLAIR should be granted to enable distribution of the product as early as feasible after the NDA action was taken. The PLAIR was granted on September 14, 2018 by IECB.

There are no other outstanding regulatory issues.

12. Labeling

- Product Name: The proprietary name, "Xofluza", was proposed by the Applicant and no concerns were identified upon review by DAVP, OPQ, OSE/DMEPA or OPDP. The proposed name for baloxavir marboxil was conditionally agreed upon June 1, 2018.

- INDICATIONS AND USAGE:

The Applicant proposed the following Indication and Limitations of Use:

Xofluza is indicated for treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

Limitations of Use

Influenza viruses change over time. [redacted] (b) (4)

DAVP agreed with the indication but proposed including "acute, uncomplicated influenza". DAVP initially proposed a Limitation of Use for influenza B, based on the discordant influenza B efficacy results in the two clinical trials (see section 7. Clinical-Statistical Efficacy above). The Applicant disagreed with this Limitation of Use based on the following:

a. In clinical practice, depending on the setting, influenza is diagnosed clinically rather than by using diagnostic tests for influenza A and B. Including a Limitation of Use for influenza B could discourage/delay the use of baloxavir marboxil for early treatment of influenza;
b. Efficacy of baloxavir for treatment of influenza B was based on analysis of small subgroups, and the trials were not powered for subgroup analysis;

c. In the recently completed Phase 3 trial of baloxavir marboxil for the treatment of influenza in patients at high risk for complications (trial 1601T0832), patients with influenza B infection comprised a higher proportion (40%) of the overall population than in trials 1518T0821 and 1601T0831, and based on time to alleviation of symptoms, baloxavir marboxil was found to be superior to placebo in the influenza B subgroup in the "high risk" trial. These summary data are discussed in section 7, Clinical-Statistical Efficacy, above.

Based on these considerations, DAVP agreed and proposed a more general Limitations of Use, which was accepted by the Applicant, as described below:

Indications and Usage

"XOFLUZA™ is indicated 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.

Limitations of Use:

Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs. Consider available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use XOFLUZA *[see Microbiology (12.4) and Clinical Studies (14.1)]*."

- DOSAGE AND ADMINISTRATION:

The proposed dosage regimen for the indication is appropriate for adults and adolescents. Baloxavir marboxil dosage will be based on weight, i.e. a single dose of 40 mg for patients weighing 40 kg to less than 80 kg; and a single dose of 80 mg for patients weighing at least 80 kg. The Applicant has agreed to include DAVP's proposed language in this section on avoiding co-administration of baloxavir marboxil with dairy products and calcium-fortified beverages, polyvalent-cation containing laxatives, antacids, or oral supplements (e.g. calcium, iron, magnesium, selenium, or zinc). The following language was agreed upon by the Applicant:

DOSAGE AND ADMINISTRATION

"Initiate treatment with XOFLUZA within 48 hours of influenza symptom onset. XOFLUZA is taken orally as a single dose and may be taken with or without food. However, co-administration of XOFLUZA with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*."

Adults and Adolescents (12 years of age and older)

"The recommended dose of XOFLUZA in patients 12 years of age or older with acute uncomplicated influenza is a single weight-based dose as follows:

Table 1 Recommended XOFLUZA Dosage in Adults and Adolescents 12 Years and Older

Patient Body Weight (kg)	Recommended Oral Dose
40 kg to less than 80 kg	Single Dose of 40 mg
At least 80 kg	Single Dose of 80 mg

- CONTRAINDICATIONS

The Applicant proposed a contraindication for hypersensitivity to baloxavir marboxil or any of its ingredients. Although there were no serious adverse events consistent with hypersensitivity reactions observed in the Phase 2 and 3 trials reviewed with this NDA, the postmarketing reports from Japan included reports of anaphylaxis, urticaria, rash and other hypersensitivity-type adverse events. DAVP agreed to include the proposed contraindication based on these reports; however, a Warning and Precaution for anaphylaxis was not considered necessary at this time because the postmarketing reports for these adverse events were incomplete or confounded, and attributability to baloxavir marboxil could not be clearly established.

- ADVERSE REACTIONS

The Applicant initially proposed including the following statement in this section:

(b) (4)

DAVP considered this statement to be somewhat misleading, and after some negotiation, the following language was agreed upon with the Applicant:

"The safety profile of XOFLUZA is based on data from 2 placebo-controlled trials, in which a total of 910 subjects received XOFLUZA: 834 (92%) were adults (18 years and older) and 76 (8%) were adolescents (12 to less than 18 years). Of these, 710 subjects received XOFLUZA at the recommended dose. In Trial 1, adult subjects 20 to 64 years of age received a single oral dose of XOFLUZA or placebo. In Trial 2, adult subjects 20 to 64 years of age received XOFLUZA, placebo as a single oral dose on Day 1, or oseltamivir twice a day for 5 days, and adolescent subjects 12 to less than 20 years of age received XOFLUZA or placebo as a single oral dose."

"Table 2 displays the most common adverse events (regardless of causality assessment) reported in at least 1% of adult and adolescent subjects who received XOFLUZA at the recommended dose in Trials 1 and 2."

Table 2 Incidence of Adverse Events Occurring in Greater Than or Equal to 1% of Subjects Receiving XOFLUZA in the Acute Uncomplicated Influenza Trials

Adverse Event	XOFLUZA (N =710)	Placebo (N = 409)
Diarrhea	3%	5%
Bronchitis	2%	4%
Nausea	1%	1%
Nasopharyngitis	1%	1%
Headache	1%	2%

- CLINICAL PHARMACOLOGY

Section 12.3 was extensively revised and agreed upon with the Applicant. See the OCP Clinical Pharmacology Review for details.

- CLINICAL STUDIES

The Applicant proposed the following tables in the Clinical Studies section:

(b) (4)

The major issue with this display of efficacy data raised by the statistical reviewers, Drs. Fraser Smith and Thamban Valappil, was that the difference between Xofluza (baloxavir marboxil) and placebo, or oseltamivir, as shown, (b) (4) The Division noted that there were some inconsistencies in labeling (display of difference in medians vs. median difference) across the older influenza antiviral drugs. However, the following labeling proposal was put forward by the Division, and was agreed upon with the Applicant:

"In both trials, XOFLUZA treatment at the recommended dose resulted in a statistically significant shorter time to alleviation of symptoms compared with placebo in the primary efficacy population (Tables 5 and 6)."

Table 5 Time to Alleviation of Symptoms after Single Dose in Adult Subjects with Acute Uncomplicated Influenza in Trial 1 (Median Hours)

	XOFLUZA 40 mg (95% CI[1]) N=100	**Placebo (95% CI[1]) N=100**
Adults (20 to 64 Years of Age)	50 hours[2] (45, 64)	78 hours (68, 89)

[1]CI: Confidence interval
[2]XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Gehan-Breslow's generalized Wilcoxon test (p-value: 0.014, adjusted for multiplicity). The primary analysis using the Cox Proportional Hazards Model did not reach statistical significance (p-value: 0.165).

Table 6 Time to Alleviation of Symptoms after Single Dose in Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 2 (Median Hours)

	XOFLUZA 40 mg or 80 mg[1] (95% CI[2]) N=455	**Placebo (95% CI[2]) N=230**
Subjects (≥ 12 Years of Age)	54 hours[3] (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
[3]XOFLUZA treatment resulted in a statistically significant shorter time to alleviation of symptoms compared to placebo using the Peto-Prentice's generalized Wilcoxon test (p-value: <0.001).

"In Trial 2, there was no difference in the time to alleviation of symptoms between subjects who received XOFLUZA (54 hours) and those who received oseltamivir (54 hours). For adolescent subjects (age 12 to 17) in Trial 2, the median time to alleviation of symptoms for subjects who received XOFLUZA (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)."

In addition, the influenza B subgroup data (referenced indirectly in the Limitations of Use section) was proposed by the Division and agreed upon by the Applicant as follows:

"The number of subjects who received XOFLUZA at the recommended dose and who were infected with influenza type B virus was limited, including 24 subjects in Trial 1 and 38 subjects in Trial 2. In the influenza B subset in Trial 1, the median time to alleviation of symptoms in subjects who received 40 mg XOFLUZA was 63 hours (95% CI of 43, 70) compared to 83 hours (95% CI of 58, 93) in subjects who received placebo. In the influenza B subset in Trial 2, the median time to alleviation of symptoms in subjects who received 40 mg or 80 mg XOFLUZA was 93 hours (95% CI of 53, 135) compared to 77 hours (95% CI of 47, 189) in subjects who received placebo."

(b) (4)

(b) (4)

- Patient labeling

The Patient Package Information is currently under review by the Patient Labeling Team, and OPDP, as well as DMEPA and DRISK in OSE.

- Carton and container labeling

Carton and container labeling was reviewed by OPQ and DMEPA, who agreed with the proposed labeling after some changes.

13. Postmarketing Requirements and Commitments

Risk Evaluation and Management Strategies (REMS)
A REMS is not recommended as no major safety issues were identified.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The following postmarketing requirements (PMRs) are PREA requirements discussed with the Pediatric Review Committee on September 19, 2018, and agreed upon with the Applicant at the Late Cycle Meeting for this NDA held on October 1, 2018:

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

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

3. Submit the clinical study report and datasets for the (b) (4) pharmacokinetics, safety, and efficacy trial of baloxavir marboxil in Japanese pediatric subjects who weigh less than 20 kg with acute, uncomplicated influenza. Include characterization of resistance-associated substitutions, including supportive datasets.

The following additional PMRs were discussed and agreed upon by the Applicant at the Late Cycle Meeting:

4. Evaluate the impact of the following substitutions on susceptibility of cloned virus in cell culture to baloxavir: A/H1N1 PA: A37S, I38L, E199D, E199K, P267S, A476S, and E677D; A/H3N2 PA: F35L, V62I, T162I, E199D, E199K, Y321H, V432I, K492R, M595I, A618S, and G684R; in type B PA: A37Q, I38V, G199R, K298R, T304A, V645A, and M682L; and A/H3N2 PB2: R209K.

5. Evaluate the incidence of transmission of virus carrying substitutions identified as associated with reduced susceptibility to baloxavir or otherwise potentially resistance-associated, including substitutions listed as resistance-associated in Section 12.4 of the USPI, in studies of subjects treated prophylactically with baloxavir marboxil, and from studies of influenza virus transmission.

The following postmarketing commitments (PMCs) were discussed and agreed upon with the Applicant at the Late Cycle Meeting on October 1, 2018:

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

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

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 20 mg tablet and (b) (4) formulations of baloxavir marboxil in healthy adult volunteers.

5. Provide an annual update of emergence of resistance to baloxavir marboxil as an integrated review of information from various sources such as national and international influenza drug resistance databases and sequence databases, data collected by the Applicant, and published literature. Substitutions of particular interest include all those listed as resistance-associated in the USPI, as well as identified substitutions that reduce susceptibility to baloxavir marboxil ≥3-fold in cell culture.

The following PMCs were proposed and discussed with the Applicant at the Late Cycle Meeting, but they were not agreed upon by the Applicant. After further discussion, DAVP accepted the Applicant's justification for not performing these studies/trials as PMCs:

(b) (4)

The Applicant was also reminded (see Late Cycle Background/Agenda) that additional data are needed for safety and efficacy in Blacks/African Americans and Hispanic/Latino Americans, which were under-represented populations in Trials 1518T0821 and 1601T0831. DAVP recommended that these underrepresented populations be adequately enrolled in postmarketing clinical trials.

14. Comments to the Applicant

There are no additional comments to the Applicant.

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/

MARY E SINGER
10/22/2018

DEBRA B BIRNKRANT
10/23/2018

JOHN J FARLEY
10/24/2018