

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**210854Orig1s001**

*Trade Name:* XOFLUZA® 20 mg and 40 mg tablets

*Generic or Proper Name:* baloxavir marboxil

*Sponsor:* Genentech, Incorporated

*Approval Date:* October 16, 2019

*Indication:* For the treatment of acute uncomplicated influenza in patients 12 years of age or older, who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 210854Orig1s001

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*APPLICATION NUMBER:*

**210854Orig1s001**

**APPROVAL LETTER**



NDA 210854/S-01

## SUPPLEMENT APPROVAL

Genentech, Incorporated  
Attention: Roberto Barrozo, Ph.D.  
Associate Regulatory Program Director  
1 DNA Way  
South San Francisco, CA 94080

Dear Dr. Barrozo:

Please refer to your supplemental new drug application (sNDA) dated January 4, 2019 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XOFLUZA® (baloxavir marboxil), 20 mg and 40 mg tablets.

This supplemental application provides for the following updates to the content of labeling and the carton and container labeling:

- Revise INDICATIONS AND USAGE, ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS, and CLINICAL STUDIES sections with data to support the use of XOFLUZA for the treatment of acute uncomplicated influenza in patients 12 years of age or older, who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications;
- Revise the DOSAGE AND ADMINISTRATION, HOW SUPPLIED/STORAGE AND HANDLING, PATIENT COUNSELING INFORMATION sections of the labeling, and the carton and container labeling with revised dosage instructions to prevent medication errors;
- Add Hypersensitivity subsection to the WARNINGS and PRECAUTIONS section;
- Add Postmarketing Experience subsection to the ADVERSE REACTIONS section and update PATIENT COUNSELING INFORMATION to reflect serious postmarketing adverse events; and
- Make corresponding changes to the Patient Information.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup> The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 210854/S-001.**” Approval of this submission by FDA is not required before the labeling is used.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## **FULFILLMENT OF POSTMARKETING REQUIREMENTS/COMMITMENTS**

Your submission reported the final report for the following postmarketing commitment listed in the October 24, 2018 approval.

3503-7      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.

Study/Trial Completion:	04/2018
Final Report Submission:	02/2019

We have reviewed your submission and conclude that the above postmarketing commitment was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the October 24, 2018 approval that are still open.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>3</sup>

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at [FDA.gov](http://FDA.gov).<sup>4</sup> Information and Instructions for completing the form can be found at [FDA.gov](http://FDA.gov).<sup>5</sup> For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see [FDA.gov](http://FDA.gov).<sup>6</sup>

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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<sup>3</sup> When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>6</sup> <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

If you have any questions, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at (301) 796-0807.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, MD  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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**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.**  
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/s/  
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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**210854Orig1s001**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOFLUZA safely and effectively. See full prescribing information for XOFLUZA.

XOFLUZA® (baloxavir marboxil) tablets, for oral use

Initial U.S. Approval: 2018

### RECENT MAJOR CHANGES

Indications and Usage (1)	10/2019
Dosage and Administration (2)	10/2019
Contraindications (4)	10/2019
Warnings and Precautions (5.1)	10/2019

### INDICATIONS AND USAGE

XOFLUZA® is a polymerase acidic (PA) endonuclease inhibitor 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 and who are:

- otherwise healthy, or
- at high risk of developing influenza-related complications<sup>1</sup>. (1)

**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. (1)

### DOSAGE AND ADMINISTRATION

Take a single dose of XOFLUZA orally within 48 hours of symptom onset with or without food. Avoid 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). The dose of XOFLUZA depends on weight. (2)

Patient Body Weight (kg)	Recommended Single Oral Dose
40 to less than 80	Two 20 mg tablets taken at the same time for a total single dose of 40 mg (blister card contains two 20 mg tablets)
At least 80	Two 40 mg tablets taken at the same time for a total single dose of 80 mg

(blister card contains two 40 mg tablets)

### DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg and 40 mg (3)

### CONTRAINDICATIONS

XOFLUZA is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. (4)

### WARNINGS AND PRECAUTIONS

Hypersensitivity such as anaphylaxis, angioedema, urticaria, and erythema multiforme: Initiate appropriate treatment if an allergic-like reaction occurs or is suspected. (5.1)

Risk of Bacterial Infection: Serious bacterial infections may begin with influenza-like symptoms, may coexist with, or occur as a complication of influenza. XOFLUZA has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate. (5.2)

### ADVERSE REACTIONS

Adverse events reported in at least 1% of adult and adolescent subjects treated with XOFLUZA included diarrhea (3%), bronchitis (3%), nausea (2%), sinusitis (2%) and headache (1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Avoid co-administration of XOFLUZA with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc). (7.1)
- Live attenuated influenza vaccines may be affected by antivirals. (7.2)

### USE IN SPECIFIC POPULATIONS

- Safety and efficacy in patients less than 12 years of age or weighing less than 40 kg have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2019

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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### 2 DOSAGE AND ADMINISTRATION

### 3 DOSAGE FORMS AND STRENGTHS

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## FULL PRESCRIBING INFORMATION

### 1 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 and who are:

- otherwise healthy, or
- at high risk of developing influenza-related complications<sup>1</sup> [*see Clinical Studies (14.2)*].

#### 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)*].

### 2 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 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 Single Oral Dose
40 kg to less than 80 kg	Two 20 mg tablets taken at the same time for a total single dose of 40 mg (blister card contains two 20 mg tablets)
At least 80 kg	Two 40 mg tablets taken at the same time for a total single dose of 80 mg (blister card contains two 40 mg tablets)

### 3 DOSAGE FORMS AND STRENGTHS

XOFLUZA 20 mg Tablets are white to light yellow, oblong shaped film-coated tablets debossed with “Ⓢ772” on one side and “20” on the other side.

XOFLUZA 40 mg Tablets are white to light yellow, oblong shaped film-coated tablets debossed with “BXM40” on one side.

## 4 CONTRAINDICATIONS

XOFLUZA is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. Serious allergic reactions have included anaphylaxis, angioedema, urticaria and erythema multiforme [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Cases of anaphylaxis, urticaria, angioedema, and erythema multiforme have been reported in post-marketing experience with XOFLUZA. Appropriate treatment should be instituted if an allergic-like reaction occurs or is suspected. The use of XOFLUZA is contraindicated in patients with known hypersensitivity to XOFLUZA [see *Contraindications (4) and Adverse Reactions (6.2)*].

### 5.2 Risk of Bacterial Infections

There is no evidence of efficacy of XOFLUZA in any illness caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms, may coexist with, or occur as a complication of influenza. XOFLUZA has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of XOFLUZA is based on data from 3 placebo-controlled trials in which a total of 1,640 subjects received XOFLUZA: 1,334 subjects (81%) were 18 to 64 years of age, 209 subjects (13%) were adults 65 years of age or older and 97 subjects (6%) were adolescents 12 to 17 years of age. These trials included otherwise healthy adults and adolescents (N=910) and subjects at high risk of developing complications associated with influenza (N=730). Of these, 1,440 subjects received XOFLUZA at the recommended dose [see *Clinical Studies (14)*].

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, 2 and 3.

**Table 2 Incidence of Adverse Events Occurring in At Least 1% of Subjects Receiving XOFLUZA in the Acute Uncomplicated Influenza Trials 1, 2, and 3**

Adverse Event	XOFLUZA (N = 1,440)	Placebo (N = 1,136)
Diarrhea	3%	4%
Bronchitis	3%	4%
Nausea	2%	3%
Sinusitis	2%	3%
Headache	1%	1%

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of XOFLUZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to XOFLUZA exposure.

*Body as a Whole:* Swelling of the face, eyelids or tongue, dysphonia, angioedema, anaphylactic reactions, anaphylactic shock, anaphylactoid reactions

*Skin and Subcutaneous Tissue Disorders:* Rash, urticaria, erythema multiforme

*Gastrointestinal disorders:* Vomiting, bloody diarrhea, melena, colitis

*Psychiatric:* Delirium, abnormal behavior, and hallucinations

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on XOFLUZA

Co-administration with polyvalent cation-containing products may decrease plasma concentrations of baloxavir which may reduce XOFLUZA efficacy. Avoid co-administration of XOFLUZA with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).

### 7.2 Vaccines

The concurrent use of XOFLUZA with intranasal live attenuated influenza vaccine (LAIV) has not been evaluated. Concurrent administration of antiviral drugs may inhibit viral replication of LAIV and thereby decrease the effectiveness of LAIV vaccination. Interactions between inactivated influenza vaccines and XOFLUZA have not been evaluated.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no available data on XOFLUZA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with influenza virus infection in pregnancy (*see Clinical Considerations*). In animal reproduction studies, no adverse developmental effects were observed in rats or rabbits with oral administration of baloxavir marboxil at exposures approximately 5 (rats) and 7 (rabbits) times the systemic baloxavir exposure at the maximum recommended human dose (MRHD) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo/fetal risk*

Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal outcomes including maternal death, stillbirth, birth defects, preterm delivery, low birth weight and small for gestational age.

## Data

### *Animal Data*

Baloxavir marboxil was administered orally to pregnant rats (20, 200, or 1,000 mg/kg/day from gestation day 6 to 17) and rabbits (30, 100, or 1,000 mg/kg/day from gestation day 7 to 19). No adverse embryo-fetal effects were observed in rats up to the highest dose of baloxavir marboxil (1,000 mg/kg/day), resulting in systemic baloxavir exposure (AUC) of approximately 5 times the exposure at the MRHD. In rabbits, fetal skeletal variations occurred at a maternally toxic dose (1,000 mg/kg/day) resulting in 2 abortions out of 19 pregnancies. No adverse maternal or embryo-fetal effects were observed in rabbits at the middle dose (100 mg/kg/day) resulting in systemic baloxavir exposure (AUC) approximately 7 times the exposure at the MRHD.

In the prenatal and postnatal development study in rats, baloxavir marboxil was administered orally at 20, 200, or 1,000 mg/kg/day from gestation day 6 to postpartum/lactation day 20. No significant effects were observed in the offspring at maternal systemic baloxavir exposure (AUC) approximately 5 times the exposure at the MRHD.

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of baloxavir marboxil in human milk, the effects on the breastfed infant, or the effects on milk production. Baloxavir and its related metabolites were present in the milk of lactating rats (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XOFLUZA and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

### Data

In a lactation study, baloxavir and its related metabolites were excreted in the milk of lactating rats administered baloxavir marboxil (1 mg/kg) on postpartum/lactation day 11, with peak milk concentration approximately 5 times that of maternal plasma concentrations occurring 2 hours post-dose. No effects of baloxavir marboxil on growth and postnatal development were observed in nursing pups at the highest oral dose tested in rats. Maternal systemic exposure was approximately 5 times the baloxavir exposure in humans at the MRHD.

## **8.4 Pediatric Use**

The safety and effectiveness of XOFLUZA for the treatment of acute uncomplicated influenza have been established in pediatric patients 12 years of age and older weighing at least 40 kg [*see Adverse Reactions (6.1) and Clinical Studies (14.1)*]. The safety and effectiveness of XOFLUZA have not been established in pediatric patients less than 12 years of age.

### Treatment of Acute Uncomplicated Influenza in Otherwise Healthy Pediatric Patients

The safety and effectiveness of XOFLUZA in otherwise healthy pediatric patients 12 years of age and older weighing at least 40 kg is supported by one randomized, double-blind, controlled trial (Trial 2) [*see Clinical Studies (14.1)*]. In this phase 3 trial, 117 adolescents 12-17 years old were randomized and received either XOFLUZA (N=76) or placebo (N=41). The median time to alleviation of symptoms in influenza-infected adolescent subjects aged 12 to 17 years was 54 hours and 93 hours for subjects who received XOFLUZA (N=63) or placebo (N=27), respectively, and was comparable to that observed in the overall trial population [*see Clinical Studies (14.1)*]. Adverse events reported in adolescents were similar to those reported in adults [*see Adverse Reactions (6.1)*].

## Treatment of Acute Uncomplicated Influenza in Pediatric Patients at High Risk for Influenza Complications

The safety and effectiveness of XOFLUZA in pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk of developing influenza-related complications is supported by extrapolation from a clinical trial in otherwise healthy adults and adolescents with acute uncomplicated influenza (Trial 2), and from one randomized, double-blind, phase 3 controlled trial in patients at high risk for influenza complications (Trial 3) in which 38 adolescents aged 12 to 17 years were randomized and received either XOFLUZA (N=21) or placebo (N=17). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years who were infected with influenza was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively) [see *Clinical Studies (14.2)*]. Adverse events reported in adolescents were similar to those reported in adults [see *Adverse Reactions (6.1)*].

### **8.5 Geriatric Use**

The safety and effectiveness of XOFLUZA in subjects 65 years of age and older has been established and is supported by one randomized, double-blind, controlled trial [see *Clinical Studies (14.2)*]. In Trial 3, of 730 XOFLUZA-treated subjects at high risk of influenza-related complications, 209 (29%) subjects were 65 years of age and older. The median time to improvement of influenza symptoms in subjects 65 years of age and older was 70 hours in subjects who received XOFLUZA (N=112) and 88 hours in those who received placebo (N=102). The safety profile observed for this population was similar to that reported in the overall trial population except for nausea, which was reported in 6% of elderly subjects compared to 1% of subjects from 18 to 64 years of age.

## **10 OVERDOSAGE**

Treatment of an overdose of XOFLUZA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA.

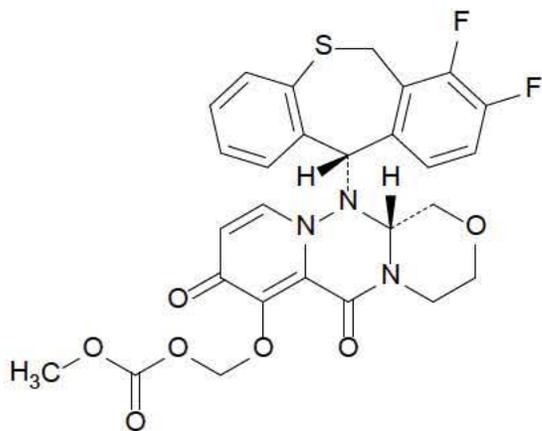
Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding [see *Clinical Pharmacology (12.3)*].

## **11 DESCRIPTION**

XOFLUZA (baloxavir marboxil) is an antiviral PA endonuclease inhibitor. XOFLUZA is supplied as white to light yellow film-coated tablets for oral administration.

The active component of XOFLUZA is baloxavir marboxil. Baloxavir marboxil has a molecular weight of 571.55 and a partition coefficient (log P) of 2.26. It is freely soluble in dimethylsulfoxide, soluble in acetonitrile, slightly soluble in methanol and ethanol and practically insoluble in water.

The chemical name of baloxavir marboxil is ((12aR)-12-[(11S)-7,8-Difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate. The empirical formula of baloxavir marboxil is C<sub>27</sub>H<sub>23</sub>F<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S and the chemical structure is shown below.



The inactive ingredients of XOFLUZA are: croscarmellose sodium, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, sodium stearyl fumarate, talc, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Baloxavir marboxil is an antiviral drug with activity against influenza virus [see *Microbiology (12.4)*].

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

At twice the expected exposure from recommended dosing, XOFLUZA did not prolong the QTc interval.

#### Exposure-Response Relationships

When XOFLUZA is dosed by weight, as recommended (40 mg in patients weighing 40-80 kg; and 80 mg in patients weighing at least 80 kg), no difference in baloxavir exposure-response (time to alleviation of influenza symptoms in the Otherwise Healthy population or time to improvement of influenza symptoms in the High Risk population) relationship has been observed.

### 12.3 Pharmacokinetics

Baloxavir marboxil is a prodrug that is almost completely converted to its active metabolite, baloxavir, following oral administration.

In Trial 2, at the recommended dose of 40 mg for subjects weighing less than 80 kg, the mean (CV%) values of baloxavir  $C_{max}$  and  $AUC_{0-inf}$  were 96.4 ng/mL (45.9%) and 6160 ng·hr/mL (39.2%), respectively. At the recommended dose of 80 mg for subjects weighing 80 kg and more, the mean (CV%) values of baloxavir  $C_{max}$  and  $AUC_{0-inf}$  were 107 ng/mL (47.2%) and 8009 ng·hr/mL (42.4%), respectively. Refer to Table 3 for pharmacokinetic parameters of baloxavir in healthy subjects. The pharmacokinetic profile of XOFLUZA was similar for adults and adolescents who were otherwise healthy and those at high risk of developing influenza-related complications.

**Table 3 Pharmacokinetic Parameters of Plasma Baloxavir**

<b>Absorption</b>	
T <sub>max</sub> (hr) <sup>a</sup>	4
Effect of food (relative to fasting) <sup>b</sup>	C <sub>max</sub> : ↓48%, AUC <sub>0-inf</sub> : ↓36%
<b>Distribution</b>	
% Bound to human serum proteins <sup>c</sup>	92.9 - 93.9
Ratio of blood cell to blood	48.5% - 54.4%
Volume of distribution (V/F, L) <sup>d</sup>	1180 (20.8%)
<b>Elimination</b>	
Major route of elimination	Metabolism
Clearance (CL/F, L/hr) <sup>d</sup>	10.3 (22.5%)
t <sub>1/2</sub> (hr) <sup>d, e</sup>	79.1 (22.4%)
<b>Metabolism</b>	
Metabolic pathways <sup>f</sup>	UGT1A3, CYP3A4
<b>Excretion</b>	
% of dose excreted in urine <sup>g</sup>	14.7 (Total radioactivity), 3.3 (Baloxavir)
% of dose excreted in feces <sup>g</sup>	80.1 (Total radioactivity)

<sup>a</sup> Median<sup>b</sup> Meal: approximately 400 to 500 kcal including 150 kcal from fat<sup>c</sup> *in vitro*<sup>d</sup> Geometric mean (geometric CV%)<sup>e</sup> Apparent terminal elimination half-life<sup>f</sup> Baloxavir is primarily metabolized by UGT1A3 with minor contribution from CYP3A4<sup>g</sup> Ratio of radioactivity to radio-labeled [<sup>14</sup>C]-baloxavir marboxil dose in mass balance study

### Specific Populations

There were no clinically significant differences in the pharmacokinetics of baloxavir based on age (adolescents as compared to adults), or sex.

#### *Patients with Renal Impairment*

A population pharmacokinetic analysis did not identify a clinically meaningful effect of renal function on the pharmacokinetics of baloxavir in patients with creatinine clearance (CrCl) 50 mL/min and above. The effects of severe renal impairment on the pharmacokinetics of baloxavir marboxil or its active metabolite, baloxavir, have not been evaluated.

#### *Patients with Hepatic Impairment*

In a clinical study comparing pharmacokinetics of baloxavir in subjects with moderate hepatic impairment (Child-Pugh class B) to subjects with normal hepatic function, no clinically meaningful differences in the pharmacokinetics of baloxavir were observed.

The pharmacokinetics in patients with severe hepatic impairment have not been evaluated.

#### *Body Weight*

Body weight had a significant effect on the pharmacokinetics of baloxavir (as body weight increases, baloxavir exposure decreases). When dosed with the recommended weight-based dosing, no clinically significant difference in exposure was observed between body weight groups.

#### *Race/Ethnicity*

Based on a population pharmacokinetic analysis, baloxavir exposure is approximately 35% lower in non-Asians as compared to Asians; this difference is not considered clinically significant when the recommended dose was administered.

### Drug Interaction Studies

#### *Clinical Studies*

No clinically significant changes in the pharmacokinetics of baloxavir marboxil and its active metabolite, baloxavir, were observed when co-administered with itraconazole (combined strong CYP3A and P-gp inhibitor), probenecid (UGT inhibitor), or oseltamivir.

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.

#### *In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically*

*Cytochrome P450 (CYP) Enzymes:* 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.

*Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) Enzymes:* Baloxavir marboxil and its active metabolite, baloxavir, did not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.

*Transporter Systems:* 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.

*Potential for Interactions with Polyvalent Cations:* Baloxavir may form a chelate with polyvalent cations such as calcium, aluminum, or magnesium in food or medications. A significant decrease in baloxavir exposure was observed when XOFLUZA was co-administered with calcium, aluminum, magnesium, or iron in monkeys. No study has been conducted in humans.

## **12.4 Microbiology**

### Mechanism of Action

Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication. The 50% inhibitory concentration (IC<sub>50</sub>) values 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 in a PA endonuclease assay. Viruses with reduced susceptibility to baloxavir have amino acid substitutions in the PA protein.

### Antiviral Activity

The antiviral activity of baloxavir against laboratory strains and clinical isolates of influenza A and B viruses was determined in an MDCK cell-based plaque reduction assay. The median 50% effective concentration (EC<sub>50</sub>) values of baloxavir were 0.73 nM (n=31; range: 0.20-1.85 nM) for subtype A/H1N1 strains, 0.83 nM (n=33; range: 0.35-2.63 nM) for subtype A/H3N2 strains, and 5.97 nM (n=30; range: 2.67-14.23 nM) for type B strains. In an MDCK cell-based virus titer reduction assay, the 90% effective concentration (EC<sub>90</sub>) values of baloxavir against avian subtypes A/H5N1 and A/H7N9 were in the range of 0.80 to 3.16 nM. The relationship between antiviral activity in cell culture and clinical response to treatment in humans has not been established.

## Resistance

Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir were selected by serial passage of virus in cell culture in the presence of increasing concentrations of baloxavir. Reduced susceptibility of influenza A virus to baloxavir was conferred by amino acid substitutions I38T (A/H1N1 and A/H3N2) and E199G (A/H3N2) in the PA protein of the viral RNA polymerase complex.

Clinical studies: Influenza A and B viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were observed in clinical studies (Table 4). The overall frequencies of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir in Trials 1, 2, and 3 [see *Clinical Studies (14)*] were 2.7% (5/182), 11% (39/370), and 5.5% (16/290), respectively.

**Table 4 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/N/T	E23G/K, A37T, I38M/T, E199G	I38T

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. Strains containing substitutions known to be associated with reduced susceptibility to baloxavir were identified in approximately 0.05% of PA sequences in the National Center for Biotechnology Information/GenBank database (queried August 2018).

Prescribers should consider currently available surveillance information on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use XOFLUZA.

## Cross-Resistance

Cross-resistance between baloxavir and neuraminidase (NA) inhibitors, or between baloxavir and M2 proton pump inhibitors (adamantanes), is not expected, because these drugs target different viral proteins. Baloxavir is active against NA inhibitor-resistant strains, including A/H1N1 and A/H5N1 viruses with the NA substitution H275Y (A/H1N1 numbering), A/H3N2 virus with the NA substitutions E119V and R292K, A/H7N9 virus with the NA substitution R292K (A/H3N2 numbering), and type B virus with the NA substitutions R152K and D198E (A/H3N2 numbering). The NA inhibitor oseltamivir is active against viruses with reduced susceptibility to baloxavir, including A/H1N1 virus with PA substitutions E23K or I38F/T, A/H3N2 virus with PA substitutions E23G/K, A37T, I38M/T, or E199G, and type B virus with the PA substitution I38T. Influenza virus may carry amino acid substitutions in PA that reduce susceptibility to baloxavir and at the same time carry resistance-associated substitutions for NA inhibitors and M2 proton pump inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

## Immune Response

Interaction studies with influenza vaccines and baloxavir marboxil have not been conducted.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Carcinogenicity studies have not been performed with baloxavir marboxil.

## Mutagenesis

Baloxavir marboxil and the active metabolite, baloxavir, were not mutagenic in *in vitro* and in *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, micronucleus tests with cultured mammalian cells, and in the rodent micronucleus assay.

## Impairment of Fertility

In a fertility and early embryonic development study in rats, doses of baloxavir marboxil at 20, 200, or 1,000 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 7 of pregnancy. Males were dosed for 4 weeks before mating and throughout mating. There were no effects on fertility, mating performance, or early embryonic development at any dose level, resulting in systemic drug exposure (AUC) approximately 5 times the MRHD.

## **14 CLINICAL STUDIES**

### **14.1 Treatment of Acute Uncomplicated Influenza – Otherwise Healthy Patients**

Two randomized controlled double-blinded clinical trials conducted in two different influenza seasons evaluated efficacy and safety of XOFLUZA in otherwise healthy subjects with acute uncomplicated influenza.

In Trial 1, a placebo-controlled phase 2 dose-finding trial, a single oral dose of XOFLUZA was compared with placebo in 400 adult subjects 20 to 64 years of age in Japan. All subjects in Trial 1 were Asian, the majority of subjects were male (62%), and the mean age was 38 years. In this trial, among subjects who received XOFLUZA and had influenza virus typed, influenza A/H1N1 was the predominant strain (63%), followed by influenza B (25%), and influenza A/H3N2 (12%).

In Trial 2 (NCT02954354), a phase 3 active- and placebo-controlled trial, XOFLUZA was studied in 1,436 adults and adolescents with signs and symptoms of influenza in the U.S. and Japan. Subjects were 12 to 64 years of age and weighed at least 40 kg. Adults ages 20 to 64 years received weight-based XOFLUZA (subjects who weighed 40 to less than 80 kg received 40 mg and subjects who weighed 80 kg and above received 80 mg) or placebo as a single oral dose on Day 1 or oseltamivir twice a day for 5 days. Subjects in the XOFLUZA and placebo arms received a placebo for the duration of oseltamivir dosing after XOFLUZA or placebo dosing in that arm. Adolescent subjects 12 to less than 20 years of age received weight-based XOFLUZA or placebo as a single oral dose.

Seventy-eight percent of subjects in Trial 2 were Asian, 17% were White, and 4% were Black or African American. The mean age was 34 years, and 11% of subjects were less than 20 years of age; 54% of subjects were male and 46% female. In Trial 2, 1,062 of 1,436 enrolled subjects had influenza confirmed by RT-PCR and were included in the efficacy analysis (XOFLUZA N=455, placebo N=230, or oseltamivir N=377). Among subjects who received XOFLUZA and had influenza virus typed, influenza A/H3N2 was the predominant strain (90%), followed by influenza B (9%), and influenza A/H1N1 (2%).

In both Trials 1 and 2, eligible subjects had an axillary temperature of at least 38°C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptom onset. Subjects participating in the trial were required to self-assess their influenza symptoms as “none”, “mild”, “moderate” or “severe” twice daily. The primary efficacy population was defined as those with a positive rapid influenza diagnostic test (Trial 1) or positive influenza RT-PCR (Trial 2) at trial entry.

The primary endpoint of both trials, time to alleviation of symptoms, was defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the subject as none or mild for a duration of at least 21.5 hours.

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 Otherwise Healthy Adults with Acute Uncomplicated Influenza in Trial 1 (Median Hours)**

	<b>XOFLUZA 40 mg (95% CI<sup>a</sup>) N = 100</b>	<b>Placebo (95% CI<sup>a</sup>) N = 100</b>
<b>Adults (20 to 64 Years of Age)</b>	50 hours <sup>b</sup> (45, 64)	78 hours (68, 89)

<sup>a</sup>CI: Confidence interval

<sup>b</sup>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 using the Bonferroni method). 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 Otherwise Healthy Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 2 (Median Hours)**

	<b>XOFLUZA 40 mg or 80 mg (95% CI<sup>a</sup>) N = 455</b>	<b>Placebo (95% CI<sup>a</sup>) N = 230</b>
<b>Subjects (≥ 12 Years of Age)</b>	54 hours <sup>b</sup> (50, 59)	80 hours (73, 87)

<sup>a</sup>CI: Confidence interval

<sup>b</sup>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 (age ≥ 20) who received XOFLUZA (54 hours) and those who received oseltamivir (54 hours). For adolescent subjects (12 to 17 years of age) in Trial 2, the median time to alleviation of symptoms for subjects infected with influenza and 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).

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.

## 14.2 Treatment of Acute Uncomplicated Influenza – High Risk Patients

Trial 3 (NCT02949011) was a randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of a single oral dose of XOFLUZA compared with placebo or oseltamivir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza-related complications.

A total of 2,182 subjects with signs and symptoms of influenza were randomized to receive a single oral dose of 40 mg or 80 mg of XOFLUZA according to body weight (subjects who weighed 40 to less than 80 kg received

40 mg and subjects who weighed 80 kg and above received 80 mg) (N=729), oseltamivir 75 mg twice daily for 5 days (N=725), or placebo (N=728). Twenty-eight percent of subjects were Asian, 59% were White, and 10% were Black or African American. The mean age was 52 years, and 3% of subjects were less than 18 years of age; 43% of subjects were male and 57% female.

High risk factors were based on the Centers for Disease Control definition<sup>1</sup> of health factors known to increase the risk of developing serious complications from influenza. The majority of subjects had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity, or were 65 years of age or older.

In Trial 3, 1,158 of the 2,182 enrolled subjects had influenza confirmed by RT-PCR and were included in the efficacy analysis (XOFLUZA N=385, placebo N=385, or oseltamivir N=388). Among subjects in whom only one type/subtype of influenza virus was identified, 50% were infected with subtype A/H3N2, 43% were infected with type B, and 7% were infected with subtype A/H1N1.

Eligible subjects had an axillary temperature of at least 38°C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptom onset. Subjects participating in the trial were required to self-assess their influenza symptoms as “none”, “mild”, “moderate” or “severe” twice daily. A total of 215 subjects (19%) had pre-existing symptoms (cough, muscle or joint pain, or fatigue) associated with their underlying high-risk condition that were worsened due to influenza infection. The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). This endpoint included alleviation of new symptoms and improvement of any pre-existing symptoms that had worsened due to influenza. A statistically significant improvement in the primary endpoint was observed for XOFLUZA when compared with placebo, see Table 7.

**Table 7 Time to Improvement of Symptoms After Single Dose in High Risk Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 3 (Median Hours)**

<b>XOFLUZA 40/80 mg (95% CI<sup>a</sup>) N=385</b>	<b>Placebo (95% CI<sup>a</sup>) N=385</b>
73 <sup>b</sup> (67, 85)	102 <sup>b</sup> (93, 113)

<sup>a</sup>CI: Confidence Interval

<sup>b</sup>XOFLUZA treatment resulted in a significant reduction in Time to Improvement of Influenza Symptoms compared to placebo using Peto-Prentice’s generalized Wilcoxon test (p-value: <0.001).

There was no statistically significant difference in the median time to improvement of influenza symptoms in the subjects who received XOFLUZA (73 hours) and those who received oseltamivir (81 hours). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years infected with influenza virus was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively).

For subjects infected with type B virus, the median time to improvement of influenza symptoms was 75 hours in the XOFLUZA group (95% CI of 67, 90) compared to 101 hours in the placebo group (95% CI of 83, 116).

## 15 REFERENCES

1. “People at High Risk For Flu Complications.” CDC. <https://www.cdc.gov/flu/highrisk/index.htm>.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

XOFLUZA Tablets:

- 20 mg white to light yellow, oblong shaped film-coated tablets debossed with “Ⓢ772” on one side and “20” on the other side available as:
  - 2 x 20 mg tablets per blister card in secondary packaging: NDC 50242-828-02
- 40 mg white to light yellow, oblong shaped film-coated tablets debossed with “BXM40” on one side available as:
  - 2 x 40 mg tablets per blister card in secondary packaging: NDC 50242-860-02

Store XOFLUZA in its blister package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Important Dosing Information

Instruct patients to begin treatment with XOFLUZA as soon as possible at the first appearance of influenza symptoms, within 48 hours of onset of symptoms. XOFLUZA can be taken with or without food, but advise patients not to take with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) [see *Dosage and Administration (2) and Drug Interactions (7.1)*].

Advise patients to follow the healthcare provider’s dosing recommendation for a single, one-time dose of XOFLUZA. XOFLUZA is dosed based on weight and is available in blister cards containing two tablets of 20 mg to be taken together as a single 40 mg dose and blister cards containing two tablets of 40 mg to be taken together as a single 80 mg dose [see *How Supplied/Storage and Handling (16)*].

### Hypersensitivity

Advise patients and/or caregivers of the risk of severe allergic reactions such as anaphylaxis, angioedema, urticaria and erythema multiforme. Instruct patients and/or caregivers to seek immediate medical attention if an allergic-like reaction occurs or is suspected [see *Contraindications (4), and Warnings and Precautions (5.1)*].

### Influenza Vaccines

Because of the potential for antivirals to decrease the effectiveness of live attenuated influenza vaccine, advise patients to consult their healthcare provider prior to receiving a live attenuated influenza vaccine after taking XOFLUZA [see *Drug Interactions (7.2)*].

Distributed by:

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South San Francisco, CA 94080-4990

Manufactured by:  
**Shionogi Pharma Co., Ltd.**  
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Osaka 566-0022, Japan

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**PATIENT INFORMATION**  
**XOFLUZA®** (zoh-FLEW-zuh)  
(baloxavir marboxil)  
tablets

**What is XOFLUZA?**

XOFLUZA is a prescription medicine used to treat the flu (influenza) in people 12 years of age and older who have had flu symptoms for no more than 48 hours.

It is not known if XOFLUZA is safe and effective in children less than 12 years of age or weighing less than 88 pounds (40 kg).

**Do not take XOFLUZA if you** are allergic to baloxavir marboxil or any of the ingredients in XOFLUZA. See the end of this leaflet for a complete list of ingredients in XOFLUZA.

**Before you take XOFLUZA, tell your healthcare provider about all of your medical conditions, including if you:**

- are pregnant or plan to become pregnant. It is not known if XOFLUZA can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XOFLUZA passes into your breast milk.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**Talk to your healthcare provider before you receive a live flu vaccine after taking XOFLUZA.**

**How should I take XOFLUZA?**

- Take XOFLUZA exactly as your healthcare provider tells you to.
- Your healthcare provider will prescribe 2 tablets of XOFLUZA you will take at the same time as a single dose.
- Take XOFLUZA with or without food.
- Do not take XOFLUZA with dairy products, calcium-fortified beverages, laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium.
- If you take too much XOFLUZA, go to the nearest emergency room right away.

**What are the possible side effects of XOFLUZA?**

**XOFLUZA may cause serious side effects, including:**

- **Allergic reactions.** Get emergency medical help right away if you develop any of these signs and symptoms of an allergic reaction:
  - trouble breathing
  - swelling of your face, throat or mouth
  - skin rash, hives or blisters
  - dizziness or lightheadedness

**The most common side effects of XOFLUZA in adults and adolescents include:**

- diarrhea
- headache
- bronchitis
- nausea
- sinusitis

XOFLUZA is not effective in treating infections other than influenza. Other kinds of infections can appear like flu or occur along with flu and may need different kinds of treatment. Tell your healthcare provider if you feel worse or develop new symptoms during or after treatment with XOFLUZA or if your flu symptoms do not start to get better.

These are not all the possible side effects of XOFLUZA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store XOFLUZA?**

- Store XOFLUZA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store XOFLUZA in the blister package that it comes in.

**Keep XOFLUZA and all medicines out of the reach of children.**

**General information about the safe and effective use of XOFLUZA.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XOFLUZA for a condition for which it was not prescribed. Do not give XOFLUZA to other people, even if they have the same symptoms that you have. It may harm them. You can ask for information about XOFLUZA that is written for health professionals.

**What are the ingredients in XOFLUZA?**

**Active ingredient:** baloxavir marboxil

**Inactive ingredients:** croscarmellose sodium, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, sodium stearyl fumarate, talc, and titanium dioxide.

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Manufactured by: **Shionogi Pharma Co., Ltd.** 2-5-1 Mishima, Settsu, Osaka 566-0022, Japan

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For more information, go to [www.XOFLUZA.com](http://www.XOFLUZA.com) or call 1-855-XOFLUZA (1-855-963-5892).

**Xofluza®**  
(baloxavir marboxil) tablets  
20 mg per tablet

NDC 50242-828-02

**Contains 40 mg total dose (2 x 20 mg tablets)**

**Usual dosage:**  
Take both tablets in this package  
as a single, one-time dose

LIFT HERE  
TO OPEN

**R<sub>x</sub> only**  
**Genentech**

**Xofluza®** (baloxavir marboxil) 20 mg per tablet

Each tablet for oral administration contains 20 mg baloxavir marboxil.

**Usual dosage:** Take both tablets in this package by mouth as a single, one-time dose.  
See package insert for full prescribing information.

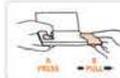
**Keep out of reach of children.**

Store in blister package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)  
[see USP Controlled Room Temperature].

**A**  
PRESS  
&  
HOLD  
HERE

PULL OUT HERE

**B**



**OPENING INSTRUCTIONS**

- A. Press and hold down tip of the thumb-shaped button on the left.
- B. While holding down the button, pull out the medication cart.

**Xofluza®** (baloxavir marboxil) tablets  
20 mg per tablet

**Genentech**



Store in blister package at 20°C to 25°C  
(68°F to 77°F); excursions permitted to  
15°C to 30°C (59°F to 86°F)  
[see USP Controlled Room Temperature].



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GTIN 00350242828024

Xofluza® (baloxavir marboxil) tablets

**Genentech**

**Xofluza®** (baloxavir marboxil) tablets  
20 mg per tablet



**Xofluza®**  
(baloxavir marboxil) tablets  
40 mg per tablet

NDC 50242-860-02

**Contains 80 mg total dose (2 x 40 mg tablets)**

**Usual dosage:**  
Take both tablets in this package  
as a single, one-time dose

LIFT HERE  
TO OPEN

**R<sub>x</sub> only**  
**Genentech**

**Xofluza® (baloxavir marboxil) 40 mg per tablet**

Each tablet for oral administration contains 40 mg baloxavir marboxil.

**Usual dosage:** Take both tablets in this package by mouth as a single, one-time dose.  
See package insert for full prescribing information.

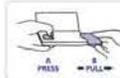
**Keep out of reach of children.**

Store in blister package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)  
[see USP Controlled Room Temperature].

**A**  
PRESS  
&  
HOLD  
HERE

PULL OUT HERE

**B**



**OPENING INSTRUCTIONS**

- A. Press and hold down tip of the thumb-shaped button on the left.
- B. While holding down the button, pull out the medication cart.



TX201404  
U2  
EN

**Xofluza® (baloxavir marboxil) tablets**  
40 mg per tablet

**Genentech**



Store in blister package at 20°C to 25°C  
(68°F to 77°F); excursions permitted to  
15°C to 30°C (59°F to 86°F)  
[see USP Controlled Room Temperature].



Made in Japan  
Distributed by: **Genentech USA, Inc.**  
A Member of the Roche Group  
South San Francisco, CA 94080-4990  
Manufactured by: **Shionogi Pharma Co., Ltd.**  
2-5-1 Mishima, Settsu, Osaka 566-0022, Japan

GTIN 00350242860024

Xofluza® (baloxavir marboxil) tablets

**Genentech**

**Xofluza® (baloxavir marboxil) tablets**  
40 mg per tablet



NDC 50242-828-02

**Xofluza®** (baloxavir marboxil) tablets  
20 mg per tablet

Each tablet contains 20 mg baloxavir marboxil.  
Take both tablets in this package as a single, one-time dose.  
**Keep out of reach of children.**

Take both tablets in this package as a single, one-time dose.

See package insert for full prescribing information.

**Xofluza®** (baloxavir marboxil) tablets  
20 mg per tablet

Contains 40 mg total dose (2 x 20 mg tablets).

**Xofluza®**  
(baloxavir marboxil) tablets  
20 mg per tablet

NDC 50242-828-02

TX202407

**Contains 40 mg total dose (2 x 20 mg tablets)**

Take both tablets as a single, one-time dose

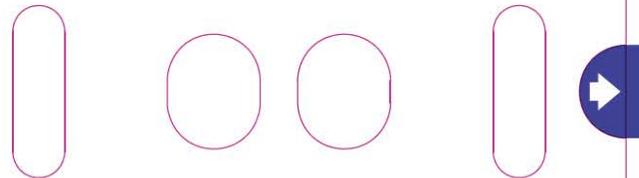
**Genentech** TX202407

NDC 50242-860-02

**Xofluza®** (baloxavir marboxil) tablets  
40 mg per tablet

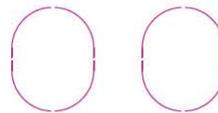
Each tablet contains 40 mg baloxavir marboxil.  
Take both tablets in this package as a single, one-time dose.  
**Keep out of reach of children.**

Take both tablets in this package as a single, one-time dose.



See package insert for full prescribing information.

**Xofluza®** (baloxavir marboxil) tablets  
40 mg per tablet



Contains 80 mg total dose (2 x 40 mg tablets).

**Xofluza®**  
(baloxavir marboxil) tablets  
40 mg per tablet

NDC 50242-860-02

TX202409

**Contains 80 mg total dose (2 x 40 mg tablets)**

Take both tablets as a single, one-time dose

**Genentech** TX202409

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**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.**  
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/s/  
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10/16/2019 04:30:16 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**CLINICAL REVIEW(S)**

sNDA 210,854/S-001: Baloxavir marboxil  
Melisse Baylor, M.D.

### Clinical and Cross-Discipline Team Leader Review

<b>Date</b>	September 30, 2019
<b>From</b>	Melisse Baylor, M.D.
<b>Subject</b>	Clinical Review

<b>Supplemental NDA #</b>	210854 / Supplement 001
<b>Applicant</b>	Genentech, Incorporated
<b>Date of Submission</b>	January 4, 2019
<b>PDUFA Goal Date</b>	November 4, 2019
<b>Proprietary Name/ Established (USAN) names</b>	Xofluza® / baloxavir marboxil
<b>Dosage forms / Strength</b>	Oral tablets: 20 mg and 40 mg
<b>Proposed indication(s)</b>	Indicated for treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and who: <ul style="list-style-type: none"><li>• are otherwise healthy, or</li><li>• at high risk of developing influenza-related complications</li></ul>
<b>Recommendation on Regulatory Action</b>	Approval

#### 1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of baloxavir marboxil use in the treatment of acute, uncomplicated influenza in patients with health factors that place them at high risk of influenza complications. The data support extension of the baloxavir marboxil indication to include a new population of patients 12 years of age and older who are at an increased risk of complications from influenza.

#### 2. Background

This supplemental NDA contains the results of a single trial, 1602T0832 (T032), a safety and efficacy trial of baloxavir marboxil in subjects who have acute, uncomplicated influenza and who have health factors placing them at high risk of influenza complications. Safety and efficacy from the Phase 3, randomized, placebo- and active-controlled trial T0832 support approval of baloxavir marboxil for the treatment of acute, uncomplicated influenza in patients 12 years of age and older at risk of influenza complications.

##### 2.1 Baloxavir marboxil

Baloxavir marboxil (Xofluza®), a polymerase acidic endonuclease inhibitor, was approved for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours on October 24, 2018. This approval was based on safety and efficacy from a Phase 3 trial (T0831) and from a Phase 2 dose-finding trial (T0821). Trial T0831 was a randomized, placebo- and active-controlled trial comparing

baloxavir marboxil to placebo and oseltamivir in 1,436 subjects from 12 years to 64 years of age in the U.S. and Japan. Subjects from 20 to 64 years of age were randomized to receive baloxavir marboxil, placebo, or oseltamivir while adolescent subjects from 12 to < 20 years of age were randomized to receive baloxavir marboxil or placebo. Oseltamivir was not used in subjects younger than 20 years of age because of concerns of neuropsychiatric adverse events by the Japanese regulatory authorities. In the Phase 2 trial, 400 Japanese subjects from 20 to 64 years of age were randomized to receive a single dose of baloxavir marboxil (10 mg, 20 mg, or 40 mg) or of placebo. Eligible study participants in both trials had acute, uncomplicated influenza (fever with at least one respiratory and one systemic symptom), and enrolled subjects were treated within 48 hours of symptom onset. The primary endpoint, time to alleviation of symptoms, was identical in both trials. Time to alleviation of symptoms was defined as the time when symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) were assessed by the subject as none or mild for a duration of at least 21.5 hours. In Trial T0831, the median time to alleviation of symptoms was 54 hours in the baloxavir marboxil arm compared to 80 hours in the placebo arm (p-value of < 0.001). In the Phase 2 trial, T0821, the median time to alleviation of symptoms in the baloxavir marboxil 40 mg arm was 50 hours versus 78 hours in the placebo arm; however, this difference was not statistically significant, likely due to the small sample size.

There are currently five drugs in addition to baloxavir marboxil available in the United States for the treatment of influenza: oseltamivir, peramivir, zanamivir, amantadine, and rimantadine. All of these anti-influenza antivirals are indicated for the treatment of acute, uncomplicated influenza. Baloxavir marboxil is the only FDA-approved anti-influenza drug that works by inhibition of polymerase acidic endonuclease activity resulting in inhibition of influenza virus replication. Oseltamivir, zanamivir, and peramivir are related antiviral medications classified as neuraminidase inhibitors (NAIs). Amantadine and rimantadine are adamantanes, which are thought to interact with the viral M2 ion channel protein. The use of amantadine and rimantadine is currently not recommended by the Centers for Disease Control (CDC) for antiviral treatment or chemoprophylaxis because of widespread adamantane resistance among influenza A virus strains. Because peramivir is administered intravenously and zanamivir is administered via oral inhalation, baloxavir marboxil and oseltamivir are the only two recommended influenza antiviral agents currently available as oral formulations. Oseltamivir is dosed twice daily for five days while baloxavir marboxil is administered as a single oral dose.

As stated above, all of the currently FDA-approved influenza antiviral agents are indicated for the treatment of acute, uncomplicated influenza in otherwise healthy patients. Acute, uncomplicated influenza is a self-limited febrile illness with respiratory symptoms that typically last from 3 to 7 days. According to the Centers for Disease Control, 5 to 20% of the U.S. population is infected with influenza each year. Influenza may also result in serious disease with complications that can include hospitalization and death. Certain people are at increased risk for more severe influenza or influenza complications; those at increased risk include the elderly, persons who are morbidly obese, and persons with predisposing conditions, such as asthma, heart disease, and diabetes mellitus. Complications of influenza infection include influenza virus pneumonia, myocarditis, or and rarely, central nervous system disease. Influenza infection also places patients at increased risk of secondary bacterial infections such as sepsis, pneumonia, sinusitis, and otitis media. Influenza in patients who are at risk of influenza complications results in excess morbidity and mortality in the U.S. each year.

The currently approved anti-influenza antivirals are indicated for the treatment of acute, uncomplicated influenza in otherwise healthy adults and adolescents and are not specifically approved for the treatment of acute, uncomplicated influenza in patients with health factors that

place them at an increased risk of complications due to influenza. The availability of baloxavir marboxil provides a treatment option for the patients who are at the highest risk from complications of influenza disease.

This supplement fulfills the Postmarketing Commitment 3503-7:

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.

## 2.2 Study Conduct

The Applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the Applicant, trial T0832 was conducted in conformance with Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. However, critical and major deviations of Good Clinical Practice (GCP) regulations were discovered at three trial study sites (206, 225, and 811) after site audits performed by the Applicant. As a result, a total of 107 subjects from these sites (8% of subjects in the ITTI population) were excluded from the intent-to-treat infected populations. The number of subjects excluded from each of the treatment arms (41 from the baloxavir marboxil arm, 32 from the placebo arm, and 34 from the oseltamivir arm) was similar.

The Applicant submitted a summary of audit findings from the three sites. The critical findings that resulted in censoring data from the sites included the following:

- Site 206:
  - Incomplete documentation for investigational drug product including missing packing slips, missing documentation of temperature monitoring, and missing subject accountability log
  - Noncompliance with protocol with no PK blood draws for one subject and enrollment of a subject who was not at risk of influenza complications
  - Changes to the source documentation without dating or initialing the change, including backdating virology sample entry.
- Site 811:
  - Inadequate source documentation for 8 of 9 subjects without documentation of trial eligibility
  - Inaccurate investigational drug product source documents including drug recorded as accountable when subject did not come for a visit and discrepancies in study visit dates between master and subject investigational drug logs
  - Source documents for study results were missing and there were discrepancies between source documents and electronic case report forms.
- Site 225:
  - Inadequate monitoring of trial conduct with investigator not acting on enrollment of ineligible subject, not identifying missing source documents, not notifying medical monitor of abnormal laboratory value, and not acting on abnormal drug storage temperatures
  - Lack of documentation of informed consent, training, subject compensation, and drug handling
  - Study documents were “inaccurate”.

In the opinion of this reviewer, the exclusion of subjects from these three sites was appropriate.

The Office of Scientific Investigations (OSI), Division of Clinical Compliance Evaluation was consulted and inspected two additional clinical sites. After discussion with reviewers from OSI and Biostatistics, one site enrolling a large number of subjects (site 205) and a second site (site 128) with a high number of adverse events and screen failures were selected for inspection. On inspection of the two study sites, no significant deficiencies were noted at either site, and the data appeared reliable. The OSI reviewer noted that one of the trial sites (site 225) with substantial GCP violations reported by the Applicant had recently been inspected by FDA, and FDA investigators had observed substantial GCP violations at that site. OSI had documented regulatory violations sufficient to justify the sponsor's decision to censor the data from that site.

### 2.3 Financial Disclosure

The Applicant submitted financial information pertinent to the application. The trial included in this sNDA was conducted by Shionogi, Incorporated under U.S. IND 126,653; the IND was transferred to Genentech, Incorporated in May 2018. Genentech, Incorporated is the sNDA Applicant. There were a total of 2,352 investigators: 566 principal investigators and 1,786 sub-investigators; none were employees of Shionogi, Incorporated or Genentech, Incorporated. None of the investigators received compensation where the value could have influenced the outcome of the study, none received payments greater than \$25,000, none held proprietary interest in the study drug, and none held significant equity interest in Shionogi, Incorporated or Genentech, Incorporated. Therefore, the conduct of this trial complied with the regulations as defined in 21 CFR 54.4(a)(3)(i), 54.2(a). Please see the Clinical Investigator Financial Disclosure Review Template in Section 16 of this review.

### 3. CMC

A new formulation was not developed for use in this trial. As a result, no new product information regarding drug substance or manufacturing was submitted. Please refer to the original review of NDA 210,854 for additional CMC information.

### 4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original review of NDA 210,854 for details.

### 5. Clinical Microbiology

The virology review of this supplement focused on resistance-associated substitutions (RAS) identified in influenza isolates from Trial T0832. The rate of emergence of substitutions that were identified in more than one subject or that reduced susceptibility to baloxavir marboxil in cell culture was 5.5%. The highest frequency of treatment-emergent resistance was observed in influenza type A/H3N2 virus (9.6%), followed by A/H1N1 (5%), and subtype B (0.7%). This is similar to the results from previous trials enrolling adult subjects.

In an analysis of subjects in trial T0831, the Phase 3 safety and efficacy trial submitted with the original NDA, treatment-emergent RAS were associated with an increase in the time to alleviation of symptoms in baloxavir marboxil arms. However, in trial T0832, submitted with this sNDA, subjects with treatment-emergent resistant virus had similar clinical responses to treatment compared to those without treatment-emergent resistance.

In the package insert, Section 12.4, **Microbiology**, the Resistance section was revised to include the percentage of subjects in trial T0832 with the rate of treatment-emergent resistance and to add the A/H1N1 amino acid substitution at I138N to the table of treatment-emergent

resistance mutations identified in clinical trials.

Please see Dr. Ince's review of this NDA supplement for additional details.

## 6. Clinical Pharmacology / Biopharmaceutics

Please refer to the USPI and reviews from the original NDA for details of adult pharmacokinetics (PK). Please see Dr. Hassan's Clinical Pharmacology review of this application for additional information regarding the pharmacokinetics (PK) results summarized below.

Pharmacokinetic samples for baloxavir marboxil plasma concentration were obtained from 664 subjects in T0832. Baloxavir  $C_{24}$  and  $C_{96}$  values obtained from this trial were similar to those observed in the Phase 3 trial, T0831.  $C_{24}$  values were also compared by region, body weight, food conditions, age, and race. As previously observed in T0831,  $C_{24}$  values were substantially higher in Asian subjects compared to non-Asian subjects. As a result, the  $C_{24}$  values were higher in Asia than in North America/Europe and the Southern Hemisphere. As discussed in the analysis of efficacy by subgroups, the median time to improvement of symptoms was significantly shorter in the baloxavir arm compared to the placebo arm for both subjects from Asia and those from North American and Europe. There were too few subjects from the Southern Hemisphere to determine efficacy in that subgroup. Baloxavir  $C_{24}$  values were 45% higher for subjects with body weight  $\geq 80$  kg than in subjects weighing  $< 80$  kg. Efficacy was demonstrated for both subjects weighing  $< 80$  kg and those weighing  $\geq 80$  kg in Trial T0832. The  $C_{24}$  values were similar in adolescents, adults 18 to 64 years of age, and adults 65 years of age and older.  $C_{24}$  values were also similar regardless of time since food intake.

Overall, few revisions were made to Section 12. 3, **Pharmacokinetics**, of the baloxavir marboxil package insert. A sentence stating that the pharmacokinetic profile of baloxavir marboxil was similar in adults and adolescents was added.

## 7. Clinical / Statistical – Efficacy

The safety and efficacy of baloxavir marboxil in patients who have acute uncomplicated influenza and who have a health factor that places them at high risk of influenza complications was supported by the results of a single study, Trial T0832. Trial T0832 was a Phase 3, randomized, controlled, safety and efficacy trial of baloxavir marboxil in subjects 12 years of age and older conducted in North American, Asia, and South America.

### Overview of Trial Design

#### Study Objectives:

The primary objective of the study was to evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo by measuring the time to improvement of symptoms in subjects who had acute, uncomplicated influenza virus infection and who had an increased risk of complications associated with influenza infection.

*Reviewer comment:* This trial was conducted in subjects with health factors that place them at increased risk of complications associated with influenza. The definition of increased risk is based on criteria<sup>1</sup> defined by the Centers for Disease Control (CDC) and discussed in the Inclusion Criteria section of this review.

The trial enrolled subjects with chronic illnesses who may have preexisting symptoms (cough, muscle pain, or fatigue) that are consistent with symptoms of influenza, for example, chronic cough in a subject with asthma. Therefore, the primary endpoint was

time to improvement of symptoms and not time to alleviation of symptoms. Please see the Endpoints section of this review for a full explanation of this endpoint.

Secondary efficacy objectives included evaluation of the efficacy of baloxavir marboxil compared with oseltamivir.

### Study Design

Trial 1601T0832 was a randomized, double-blind, active- (oseltamivir) and placebo-controlled, safety and efficacy trial of baloxavir marboxil in adults and adolescents 12 years of age and older who were at high risk of influenza complications and who had acute, uncomplicated influenza.

*Reviewer comment:* The CDC and the Clinical Practice Guidelines from the Infectious Diseases Society of America recommend antiviral treatment for all patients who are at high risk of complications from influenza; however, the trial was allowed to include a placebo arm because of the lack of scientific evidence (from high quality prospective, randomized controlled trials) for efficacy for any approved anti-influenza drug in this population. In addition, the risks associated with placebo use were addressed in the informed consent form.

Eligible patients were those with a clinical diagnosis of influenza, defined as having 1) fever (temperature  $\geq 38^{\circ}$  C), 2) at least one general systemic symptom of moderate or greater severity (headache, feverishness/chills, muscle or joint pain, or fatigue), and 3) at least one respiratory symptom of moderate or greater severity (cough, sore throat, or nasal congestion). Patients then had a nasopharyngeal sample obtained. Patients at some sites had a rapid influenza diagnosis test (RIDT) performed prior to enrollment in the trial, while patients at other sites were enrolled based only on influenza-like symptoms. All study subjects had a nasopharyngeal sample sent to a central laboratory for influenza RT-PCR, which was the official assessment for influenza infection.

After informed consent was obtained for all subjects and assent was obtained from adolescent subjects, the first dose of study drug was administered at the study site. Study subjects were stratified by four factors: baseline symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsening symptoms (yes or no), region (Asia, North America/Europe, or Southern Hemisphere), and weight ( $< 80$  kg or  $\geq 80$  kg). All subjects were randomized in a 1:1:1 ratio to receive baloxavir marboxil, oseltamivir, or placebo

*Reviewer comment:* The baseline symptom score was calculated by assigning a number to each influenza symptom. The number assigned increased as severity increased from mild to moderate to severe. The numbers for each symptom were then added together to determine the total symptom score. The use of aggregate scores of different symptoms as a clinical endpoint is discouraged in the FDA Guidance for Industry, "Influenza: Developing Drugs for Treatment and Prophylaxis." However, in this protocol, the symptom score was used at baseline for stratification and not as an endpoint and therefore was acceptable.

Each subject recorded his/her signs and symptoms of influenza on a paper questionnaire on Day 1 prior to treatment. If patients had a pre-existing symptom that was also a symptom of influenza, such as a chronic cough with COPD, that symptom was documented at baseline as stable or worsened with influenza. Subjects then received and were trained in the use of an electronic Diary (eDiary) to record signs and symptoms of influenza. Subjects self-assessed 7

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

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

The presence of influenza-related complications (hospitalization, death, sinusitis, bronchitis, otitis media, radiologically-confirmed pneumonia) was documented as an adverse event at each study visit. The criteria for diagnoses of each of these complications were not provided in the protocol but were included in a separate electronic CRF, which was not included with the submission.

*Reviewer comment:* During FDA review of the protocol, the sponsor was informed that while this endpoint (i.e. influenza-related complications) is of interest, the definitions for each complication should be consistent with FDA guidance for diagnosis of each complication (e.g., community acquired pneumonia, otitis media, and sinusitis) for the analysis to be meaningful. The analysis may also have been valid if an adjudication committee had been used. While the protocol did not include definitions for each of the complications, it did state that the incidence of complications would be defined as the percentage of subjects with an influenza-related complication reported as an adverse event.

Nasopharyngeal swabs for influenza were collected at study visits until Day 9; nasopharyngeal swabs were collected on Days 15 and 22 from subjects if they still had symptoms of influenza.

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

*Study Drug:*

Baloxavir marboxil was administered as a 20 mg tablet. Subjects also received a placebo for oseltamivir starting on Day 1 and continuing for a total of 5 days. Subjects in the oseltamivir arm received a placebo for baloxavir marboxil on Day 1 and also received the 75 mg capsule manufactured by Roche as Tamiflu®, which was administered twice daily for a total of 5 days. Subjects in the placebo arm received a placebo matching baloxavir marboxil on Day 1 and a placebo matching the 75 mg oseltamivir capsule starting on Day 1 and continuing for a total of 5 days. Oseltamivir and oseltamivir placebo were administered twice daily.

Subjects were instructed to take the study drug without regard to food. The initial dose of study drug was administered at the study site.

### Study Population:

#### Inclusion criteria:

The trial enrolled males and females  $\geq 12$  years of age at high risk of influenza complications and with a diagnosis of influenza. Influenza was diagnosed clinically in subjects having all three of the following:

- Fever  $\geq 38^{\circ}$  C (axillary) in the predose examination or more than 4 hours after dosing of antipyretics, if they were taken;
- At least one of the following general systemic symptoms (excluding those that were chronic and existed in the 30 days prior to influenza symptom onset) with a severity of moderate or greater:
  - Headache,
  - Feverishness or chills,
  - Muscle or joint pain, or
  - Fatigue
- At least one of the following respiratory symptoms (excluding those that were chronic and existed in the 30 days prior to influenza symptom onset) with a severity of moderate or greater:
  - Cough,
  - Sore throat, or
  - Nasal congestion.

If a subject had one of the seven influenza symptoms (i.e., a systemic or respiratory symptom) prior to developing influenza, such as cough due to asthma, and that pre-existing symptom was worse than usual, (cough that is usually mild becomes moderate with influenza), the symptom would be counted as an influenza respiratory symptom for the diagnosis of clinical influenza. If a subject had a pre-existing symptom that had not changed with the onset of influenza, that symptom could not be included as one of the symptoms for the diagnosis of influenza. For example, if a subject with cough due to underlying COPD developed symptoms of influenza, but their cough was unchanged from the usual intensity, the subject had to have another respiratory symptom (either sore throat or nasal congestion) to be included as having influenza.

The time interval between the onset of symptoms and the predose examination must have been  $\leq 48$  hours. The onset of symptoms as defined as the time either of the first increase in body temperature (increase of at least  $1^{\circ}$  C from normal body temperature) or time when the patient experienced at least one general or respiratory symptom.

Patients were considered to be at high risk of influenza complications due to the presence of at least one of the following health factors:

- Asthma or chronic lung disease [such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis];
- Endocrine disorders (including diabetes mellitus);
- Residents of long-term care facilities (e.g., nursing homes);
- Compromised immune system (including patients receiving corticosteroids not exceeding 20 mg of prednisone or the equivalent and HIV-infected patients who are receiving treatment and who have a CD4 count  $> 350$  cells/mm<sup>3</sup> within the last 6 months);
- Neurological and neurodevelopmental disorders [including disorders of the brain, spinal cord, peripheral nerve, and muscle, e.g., cerebral palsy, epilepsy (seizure disorders), stroke, muscular dystrophy, or spinal cord injury];

- Heart disease (such as congenital heart disease, congestive heart failure, or coronary artery disease), excluding hypertension without any other heart-related symptoms;
- Adults  $\geq 65$  years of age;
- Native Americans and Alaskan Natives;
- Blood disorders (such as sickle cell disease);
- Metabolic disorders (such as inherited metabolic diseases and mitochondrial disorders);
- Morbid obesity (body mass index  $\geq 40$ ); and
- Women within 2 weeks post-partum and not breastfeeding.

These criteria were based on the definition of high risk by CDC criteria.<sup>1</sup> Some patients included in the CDC criteria for health factors associated with an increased risk of influenza complications were not allowed to participate in the trial due to 1) a possible increase in risk associated with study drugs (patients with liver disease, patients severely immunocompromised due to an underlying condition or medication, and breastfeeding women), 2) possible increase in risk due to study procedures (chronic aspirin therapy), or 3) difficulties in obtaining consent (some neurologic and neurodevelopmental conditions).

*Exclusion criteria:*

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

- Severe influenza virus infection requiring inpatient treatment;
- Concurrent infection(s) requiring systemic antimicrobial and/or antiviral therapy at the predose examination;
- Receipt of peramivir, laninamivir (not approved in U.S.), oseltamivir, zanamivir, rimantidine, umifenovir (not approved in the U.S.), or amantadine within 30 days prior to the predose examination;
- Receipt of an investigational monoclonal antibody for a viral disease within the previous year;
- Creatinine clearance  $\leq 60$  mL/min ( $\leq 30$  mL/min in Japan); and
- Weight  $< 40$  kg.
- Women who were pregnant or breast feeding

Patients were also excluded for any of the following health factors that increased their risk of complications due to influenza:

- Cancer within the last 5 years (except for non-melanoma skin cancer);
- Untreated HIV infection, HIV infection with an unknown CD4 count, or HIV infection with a CD4 count  $< 350$  cells/mm<sup>3</sup> in the last 6 months;
- Immunosuppression following organ or bone marrow transplant;
- Receipt of chronic systemic corticosteroids exceeding 20 mg of prednisone daily or equivalent dose

*Prohibited concomitant therapy:*

The use of the following drugs or drugs with equivalent efficacy was prohibited from Day 1 to Day 22:

- Systemic antiviral drugs;
- Antimicrobial drugs except for those used to treat complications of influenza that are suspected to be bacterial infections after Day 1;
- Antifungal drugs except for dermal preparations;
- Antipyretics/analgesics except for acetaminophen;
- Antitussives/expectorants;

- Combination cold remedies;
- Antihistamines except for dermal preparations;
- Herbal medicines or complementary therapies used for the treatment of influenza.

Safety Monitoring:

Subjects were seen at the study site on Days 1, 2, 3, 5, 9, 15, and 22. Study visits on Days 4 and 6 were optional.

Medical history, a full physical examination, and vital signs (blood pressure, heart rate, respiratory rate, and body temperature) were obtained on Day 1. A full physical examination was repeated on Day 22. Symptom-directed physical examinations were conducted on all other study visits. Vital signs (blood pressure heart rate, and respiratory rate but not temperature) were obtained at all visits after Day 1. However, subjects measured and recorded their own temperature in their eDiaries daily from Day 1 to Day 14. A 12-lead ECG was obtained on Days 1, 2, and 22. Clinical laboratory tests measured on Days 1, 5, 15, and 22 included a complete blood count with differential and platelets; chemistry tests (ALT, AST, LDH, GGT, alkaline phosphatase, direct, indirect and total bilirubin, total protein, albumin, BUN, creatinine, electrolytes, and C-reactive protein); and dipstick urinalysis. In addition, serology for HIV, HB<sub>s</sub> antigen, and HCV antibody were collected at Day 1. Urine pregnancy tests were performed for women of child bearing potential on Day 1 (predose), Day 5 and Day 22.

Information on adverse events was collected at each study visit. Adverse events were classified by system organ class and preferred term using the MedDRA dictionary. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Abnormal laboratory test results were defined as those with a value outside the reference range. Laboratory test results were reported as an adverse event if they were considered as clinically significant by the investigator. Criteria for considering a laboratory test as clinically significant were an abnormal laboratory test that led to a SAE, that led to a change in study drug dosing or premature study discontinuation, that required treatment, that required additional diagnostic testing or medical intervention, or that met the criteria for abnormal liver function tests. The trial criteria for abnormal liver function tests were based on the FDA Guidance, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation." Criteria for abnormal liver function tests included the following parameters:

- AST or ALT > 5 times the ULN,
- AST or ALT > 3 times the ULN with the total bilirubin > 2 times the ULN or the PT-INR > 1.5, or
- AST or ALT > 3 times the ULN with signs or symptoms compatible with hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia [ $> 5\%$ ]).

*Amino Acid Substitutions:*

The gene for polymerase acidic protein (PA) was sequenced to evaluate the incidence and characteristics of treatment-emergent amino acid substitutions that may confer resistance to baloxavir marboxil in subjects with evaluable virus. PA gene sequencing was performed for all subjects who received baloxavir marboxil and in 100 subjects who received placebo.

Study Endpoints:

The primary efficacy endpoint was the time to improvement of symptoms. Time to improvement of symptoms was defined as the time between the initiation of the study treatment and the

alleviation **or** improvement of seven influenza symptoms: cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue. Influenza symptoms at baseline included either new symptoms, (i.e., due to influenza only and not preexisting symptoms), or preexisting symptoms (due to the underlying health factor that placed the subject at increased risk of influenza complications) which may have been exacerbated by influenza infection or unchanged. Preexisting symptoms that overlapped with underlying diseases and influenza included cough, muscle or joint pain, and fatigue.

The primary endpoint was assessed differently for subjects based on the presence of pre-existing symptoms that overlapped with influenza and whether the pre-existing symptom had worsened with the influenza illness. In subjects **without pre-existing symptoms that overlapped with influenza**, the primary endpoint was the time to alleviation of symptoms, the same primary endpoint used in the Phase 3 trial conducted in otherwise healthy subjects. In this population, in order to reach the primary endpoint, all influenza symptoms must have been alleviated, i.e., assessed by the subject as 0 (none) or 1 (mild) in the eDiary for a duration of at least 21.5 hours (24 hours – 10%). In subjects **with pre-existing symptoms that overlapped with influenza but that had not worsened** with the influenza illness, subjects had to meet the following criteria to fulfill the primary endpoint:

- Influenza symptoms that were new and not pre-existing had to be alleviated [assessed by the subject as 0 (none) or 1 (mild) in the eDiary for a duration of at least 21.5 hours (24 hours – 10%)]
- The pre-existing symptom must have remained stable. It did not need to resolve, but it could not worsen. For example, if the subject had a mild cough due to COPD, and that cough had not gotten worse with influenza, the cough had to remain mild for the subject to meet the primary endpoint.

In subjects with pre-existing symptoms which overlapped with influenza and that **had worsened** with influenza, subjects had to meet the following criteria to reach the primary endpoint of time to improvement of symptoms:

- Influenza symptoms that were new and not pre-existing had to be alleviated [assessed by the subject as alleviated as 0 (none) or 1 (mild) in the eDiary for a duration of at least 21.5 hours (24 hours – 10%)]
- The pre-existing and worsened symptom had to decrease in intensity to be counted as improved. For example, if the subject had a cough due to COPD, and that cough was mild before influenza and increased to severe with influenza, the cough had to improve to moderate or mild for the subject to meet the primary endpoint.

*Reviewer comment:* The endpoint, time to improvement of symptoms, was discussed and agreed upon with the Applicant prior to study initiation. Although the endpoint had not been tested previously, it is based on a modification of the typical endpoint, time to alleviation of symptoms, which is used as the clinical endpoint in trials of drugs to treat acute, uncomplicated influenza, and therefore, time to improvement of symptoms was considered a reasonable primary endpoint for this trial.

Select Secondary efficacy endpoints included:

- Time to improvement of symptoms in the baloxavir marboxil arm compared to the oseltamivir arm;
- Requirement for systemic antibiotics for infections secondary to influenza infection;
- Incidence of influenza-related complications (hospitalization, death, sinusitis, otitis media, bronchitis, and radiologically confirmed pneumonia) after the initiation of study treatment.

**Statistical Analysis:**

Subjects were randomized in a 1:1:1 ratio to receive baloxavir marboxil, oseltamivir, or placebo. Randomization were stratified by baseline symptom score ( $\leq 14$  or  $\geq 15$ ), preexisting and worsening symptoms (yes or no), region (Asia, North America/Europe, or Southern Hemisphere), and weight ( $< 80$  kg or  $\geq 80$  kg). An interactive response technology (IRT) was used for random assignment of subjects. Information was obtained on current smoking status and whether the subject had received an influenza vaccine in the previous 6 months. This information was used for subgroup analyses; but subjects were not be stratified by either smoking status or previous vaccination, and the study was not powered for either analysis.

The trial was conducted in a double-blind, double-dummy fashion by using two different placebos, one matching baloxavir marboxil and one matching oseltamivir. All study subjects, investigators, study personnel, and data analysts were blinded to treatment assignment until database lock.

The analysis populations for this trial were as follows:

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

**Disposition**

The study was conducted at 551 study sites: 242 sites in the United States, 142 sites in Japan, 98 sites in Europe, 48 sites in Asian Pacific countries (Australia, New Zealand, Philippines, and South Korea), and 21 sites in South Africa. The first subject was enrolled on January 11, 2017 and the last subject completed the trial on April 20, 2018.

A total of 2184 subjects were enrolled and randomized in the trial; however, there were 2182 unique subjects, because two subjects were assigned two different patient identification numbers and randomized twice. Both subjects were rescreened and were only treated with study drug one time. Of the 2182 subjects, 730 were randomized to receive baloxavir marboxil, 729 to receive placebo, and 725 to receive oseltamivir. The majority of trial subjects (2075 or 95%) completed the trial: 96% in the baloxavir marboxil arm, 95% in the placebo arm, and 94% in the oseltamivir arm. The number of subjects prematurely discontinuing the trial and the reasons for premature discontinuation are shown in the following table.

**Table 1: Subject Disposition and Reason for Premature Discontinuation**

	<b>Placebo</b>	<b>Baloxavir</b>	<b>Oseltamivir</b>
<b>Randomized</b>	729	730	725
<b>Completed trial</b>	695 (95%)	697 (95%)	683 (94%)
<b>Prematurely discontinued trial</b>	34 (5%)	33 (5%)	42 (6%)
<b>Reason for premature discontinuation</b>			
Consent withdrawn	13	13	21
Lost to follow-up	5	7	5
Adverse event	7	6	3
Lack of efficacy	2	0	0
Protocol deviation	3	5	3
Failure to meet entry criteria	0	0	3
Death	0	0	1
Other	4	2	6

Source: Clinical Study Report T0832, Table 10-1, page 99.

As shown in the table above, the majority of subjects finished the trial, and the percentage of subjects who finished the trial was similar in the three study arms. The most common reasons for premature discontinuation were withdrawn consent and loss to follow-up. The proportions of subjects who discontinued due to withdrawn consent and loss to follow-up were similar between the three trial arms. Twelve subjects discontinued the study for “other” reasons. Two subjects who discontinued due to “other” reasons were the two subjects who were rescreened. Three subjects were discontinued due to an abnormal creatinine clearance, three for noncompliance, and two for testing positive for hepatitis C antibody at baseline. One subject was discontinued for an abnormal laboratory value that was not specified, and for one “early termination.” The reasons for premature discontinuation in the “other” category were varied, and no single reason was observed in a high percentage of subjects. Lack of efficacy as a reason for premature study discontinuation was only observed in the placebo arm and was reported in two subjects. Discontinuations due to AEs will be discussed in the discussion of Trial 1601T031 safety. Overall, the numbers of subjects who discontinued prematurely in all three treatment arms were small, and the reasons for premature discontinuation were similar between the arms.

### **Protocol Violations/Deviations**

The number of subjects in the safety population, intent-to-treat infected population (ITTI), and per protocol (PP) population is shown in the following table. Subjects may have been excluded for more than one reason; therefore, the number of subjects with reasons for exclusion from the ITTI population and from the PP population add up to more than the total number excluded.

**Table 2: Trial Populations and Reasons for Exclusion**

	<b>Placebo</b>	<b>Baloxavir marboxil</b>	<b>Oseltamivir</b>
<b>All Randomized</b>	<b>729</b>	<b>730</b>	<b>725</b>
Did not receive study drug	1	2	3
RT-PCR negative for influenza	337	328	323
Enrolled at GCP noncompliant sites	32	41	34
<b>Intent-to-treat infected population</b>	<b>386 (53%)</b>	<b>388 (53%)</b>	<b>389 (54%)</b>
Received prohibited medications	52	58	57
Noncompliant	32	33	48
Ineligible	16	27	24
Inadequate follow-up	4	8	3
Incorrect Treatment Allocation	1	3	5
<b>Per protocol population</b>	<b>333 (46%)</b>	<b>335 (46%)</b>	<b>332 (46%)</b>

Source: CSR, Table 11-1.

Approximately one-half of subjects (53% in the placebo and baloxavir marboxil arms and 54% in the oseltamivir arm) were included in the ITTI population. The majority of subjects excluded from the ITTI population were excluded because they were RT-PCR negative for influenza. The number and percentage of subjects excluded for a negative RT-PCR was similar in all three treatment arms: 46% in the placebo arm and 45% in the baloxavir marboxil and oseltamivir arms. Critical and major deviations from GCP were noted at three study sites (811, 226, and 206) at site audits conducted by the Applicant, as previously described in Section 2.2 above. A total of 107 subjects were excluded from the ITTI and PP populations because of the GCP noncompliance at three sites; the percentage of subjects excluded was similar in the three treatment arms (4% in the placebo arm, 5% in the baloxavir marboxil arm, and 6% in the oseltamivir arm). The PP population included the majority of subjects who were included in the ITTI population. The percentage of subjects included in the PP population was identical for each of the three treatment arms. The most common reason for exclusion from the PP population in each treatment arm was receipt of prohibited medications. The most commonly administered prohibited medication was salbutamol (albuterol) in all three treatment arms. Although the number of subjects excluded for noncompliance was lower in the placebo and baloxavir marboxil arms compared to the oseltamivir arm and the number of subjects excluded because they were enrolled despite being ineligible for the trial was slightly lower in the placebo arm, the overall percentages of subjects excluded for these reasons were small (5% for noncompliance and 3% ineligible).

The study appears to have been adequately conducted. Almost all subjects with influenza were included in the ITTI population, the primary population for analysis of efficacy. The exclusion of subjects from three sites for GCP violations is concerning; however, this represented only 5% of the study population and the percentage excluded was similar between the three treatment arms. An additional 7% to 8% of subjects were excluded from the Per Protocol population, which was a secondary population for analysis of efficacy. In the overall population, the percentages of subjects excluded from the ITTI and from the PP populations and the reasons for exclusion from the populations were similar between the three treatment arms.

## Demographics and Baseline Characteristics

Demographic and baseline characteristics for the ITTI population are shown in the following table.

**Table 3: Demographic Characteristics of the Intent-to-Treat Infected Population**

Demographic Parameters	Placebo (N=386) n (%)	Baloxavir (N=388) n (%)	Oseltamivir (N=389) n (%)
<b>Sex</b>			
Male	180 (47%)	193 (50%)	191 (49%)
Female	206 (53%)	195 (50%)	198 (51%)
<b>Age</b>			
Mean years (SD)	51.9 (16.7)	52.3 (16.8)	51.1 (17.0)
Median (years)	53	55	53
Min, max (years)	12, 86	12, 84	12, 89
<b>Age Group</b>			
≥ 12 - ≤ 19 years	17 (4%)	19 (5%)	22 (6%)
≥ 20 - ≤ 29 years	22 (6%)	29 (8%)	27 (7%)
≥ 30 - ≤ 39 years	58 (15%)	42 (11%)	44 (11%)
≥ 40 - ≤ 49 years	55 (14%)	63 (16%)	75 (19%)
≥ 50 - ≤ 59 years	101 (26%)	83 (21%)	83 (21%)
≥ 60 - ≤ 64 years	30 (8%)	39 (10%)	35 (9%)
≥ 65 - ≤ 74 years	76 (20%)	85 (22%)	78 (20%)
≥ 75 years	27 (7%)	28 (7%)	25 (6%)
<b>Race</b>			
White	194 (50%)	178 (46%)	188 (48%)
Black or African American	30 (8%)	39 (10%)	29 (8%)
Asian	157 (41%)	167 (43%)	163 (42%)
American Indian or Alaskan Native	2 (1%)	1 (<1%)	3 (1%)
Other	3 (1%)	3 (1%)	6 (2%)
<b>Ethnicity</b>			
Hispanic or Latino	59 (15%)	62 (16%)	56 (14%)
Not Hispanic or Latino	327 (85%)	325 (83%)	331 (85%)
<b>Region</b>			
Asia	151 (39%)	159 (41%)	152 (39%)
North America/Europe	216 (56%)	212 (55%)	220 (57%)
Southern Hemisphere	19 (5%)	17 (4%)	17 (4%)
<b>Weight</b>			
< 80 kg	232 (60%)	239 (62%)	233 (60%)
≥ 80 kg	154 (40%)	149 (38%)	156 (40%)

Source: Clinical Study Report T0832, Table 11-2, pages 106-7.

Approximately one-half of the population was male and one-half female. The mean age ranged from 51 to 53 years; only 58 (5%) of subjects were younger than 20 years of age. A total of 319 (27%) subjects were 65 years of age or older, providing a sufficient number of elderly subjects for analysis of efficacy in this age group. Slightly more than one-half of subjects (56%) were enrolled in North American or Europe, and 48% of subjects were White. A large percentage of

the study population was Asian (42%). In addition, 8% of subjects were Black or African American and < 2% were Other or Native American or Alaskan Native. Fifteen percent of subjects were Hispanic or Latino. In the Phase 3 trial supporting the efficacy of baloxavir marboxil in the original NDA, only 4% of the population was Black or African American and 6% were Hispanic or Latino. DAVP encouraged the Applicant to enroll more Blacks/African Americans and persons of Hispanic or Latino ethnicity in this and future trials. A greater proportion of subjects in Trial T0832 was enrolled in the United States and the study population more closely represents the U.S. population. In addition, the Applicant is enrolling subjects in two ongoing Phase 3 trials at U.S. sites and expects to obtain additional safety and efficacy data in Blacks/African Americans and Latinos in those trials (see Table 20). Overall, the baseline characteristics of the overall population for this study were similar between the three treatment arms.

Influenza is more common in persons who smoke and often more severe; 16% of the study population were smokers (ranging from 15% to 17% in the three treatment arms).

Approximately one-fourth of subjects had received the influenza vaccine prior to study participation. The percentage of subjects (ranging from 24% to 27%) who had received influenza vaccine prior to study participation was similar between treatment groups. There are no data on the possible interaction between baloxavir marboxil and inactivated or live attenuated influenza vaccine. However, inactivated vaccine and baloxavir marboxil are unlikely to interact and the live attenuated influenza vaccine was not recommended for use during the influenza season (2017-2018) in which this study was conducted. Therefore, it is unlikely that previous influenza vaccination affected the results of this trial.

A total of 216 subjects (19%) had pre-existing symptoms that overlapped with symptoms of influenza (cough, muscle or joint pain, and/or fatigue) that worsened with their influenza infection. In this subset of subjects, the primary endpoint was assessed as time to improvement instead of time to alleviation of symptoms. See the discussion of the primary endpoint in the description of the trial protocol. The number and percentage of subjects with pre-existing symptoms are described in the following table.

**Table 4: Number and Percentage of Subjects with Pre-Existing Symptoms**

		<b>Placebo N=386</b>	<b>Baloxavir N=388</b>	<b>Oseltamivir N=389</b>
<b>No. of subjects with any pre-existing and worsened symptom</b>		76 (20%)	71 (18%)	69 (18%)
<b>Cough</b>	Pre-existing and worsened	51 (13%)	42 (11%)	49 (13%)
	Pre-existing and <b>not</b> worsened	6 (2%)	7 (2%)	8 (2%)
<b>Muscle/Joint pain</b>	Pre-existing and worsened	27 (7%)	27 (7%)	23 (6%)
	Pre-existing and <b>not</b> worsened	5 (1%)	4 (1%)	7 (2%)
<b>Fatigue</b>	Pre-existing and worsened	24 (6%)	25 (6%)	19 (5%)
	Pre-existing and <b>not</b> worsened	3 (1%)	0	2 (1%)

Source: Clinical Study Report T0832, Table 11-3, pages 109.

The majority (81%) of subjects did not have a pre-existing symptom that worsened and overlapped with influenza. The most commonly reported pre-existing symptom that overlapped with symptoms of influenza was cough. This is consistent with asthma being the most commonly reported underlying health factor placing subjects at risk of influenza complications. Pre-existing cough was reported in 14% of subjects and was worsened in 12% of subjects overall. Pre-existing muscle/joint pain and fatigue were reported in less than 10% of subjects. However, in subjects with pre-existing muscle/joint pain and fatigue, these symptoms were usually exacerbated by influenza. The proportion of subjects with pre-existing symptoms was similar across the three treatment arms.

### Disease Characteristics

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

**Table 5: Trial T0832 – Time from Influenza Symptom Onset to Treatment**

<b>Time from Influenza Onset to Treatment (Hours)</b>	<b>Placebo (N=386) n (%)</b>	<b>Baloxavir (N=388) n (%)</b>	<b>Oseltamivir (N=389) n (%)</b>
0 to ≤ 12 hours	42 (11%)	27 (7%)	37 (10%)
> 12 to ≤ 24 hours	150 (39%)	151 (39%)	119 (31%)
> 24 to ≤ 36 hours	120 (31%)	114 (29%)	144 (37%)
> 36 to ≤ 48 hours	74 (19%)	95 (25%)	92 (24%)

Source: Clinical Study Report T0832, Table 11-2, pages 106-109.

Most subjects (68%) were enrolled from 12 to 36 hours from onset of symptoms; fewer subjects were enrolled either within 12 hours of symptom onset or 36 hours or longer after symptom onset. Although the percentage of subjects in the placebo arm who were enrolled later after symptom onset (> 36 hours to ≤ 48 hours) was somewhat lower than in the baloxavir marboxil and oseltamivir arms, overall, the time from symptom onset to treatment was similar across treatment arms.

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

**Table 6: Trial T0832 – Influenza Virus Types and Subtypes Identified by RT-PCR**

<b>Influenza Virus Type or Subtype</b>	<b>Placebo (N=222) n (%)</b>	<b>Baloxavir (N=437) n (%)</b>	<b>Oseltamivir N=389 n (%)</b>
A/H1N1	17 (4%)	28 (7%)	35 (9%)
A/H3N2	185 (48%)	182 (47%)	190 (49%)
B	168 (44%)	167 (43%)	149 (38%)
Mixed infection	5 (1%)	4 (1%)	5 (1%)
Other	11 (3%)	7 (2%)	10 (3%)

Source: Clinical Study Report T0832, Table 11-2, pages 106-109.

Both influenza subtype A/H3N2 and influenza type B were the most commonly identified in the ITTI population (48% and 42% of subjects, respectively). Influenza A/H1N1 was identified in 7% of subjects. The percentages of each subtype were similar across the treatment arms.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Baloxavir marboxil was administered as a single oral dose. In this trial, the dose of baloxavir marboxil was administered by study personnel at the study site on the Day 1 visit, so compliance with baloxavir marboxil was 100%. Non-compliance with oseltamivir was defined as taking less than 80% of the prescribed doses. Five subjects (0.7%) took less than 80% of their oseltamivir. Two subjects took only 10% of their prescribed dose, one subject took 50% of his oseltamivir, and two subjects took more than 75% of their oseltamivir. Subjects who were non-compliant were included in the ITTI population but not in the PP population. Overall, compliance with study drugs was excellent.

The use of acetaminophen was allowed as a rescue medication. The proportion of subjects who used acetaminophen as a rescue medication was low and was similar in the three treatment arms (3% in the placebo arm, 3% in the baloxavir marboxil arm, and 4% in the oseltamivir arm). The use of other antipyretics, cold medications, and antivirals was prohibited and resulted in exclusion from the PP population. An analysis was conducted of concomitant medications taken during the influenza treatment period to analyze the use of these medications other than acetaminophen. The period of “during” treatment in the concomitant medication dataset was defined as the time from Day 1 to Day 6; the dataset was analyzed for medication use during this time period. The percentage of subjects who started a new medication, except for rescue medication, during treatment period was 17% in the placebo arm 17% in the baloxavir marboxil arm, and 15% in the oseltamivir arm. The most frequently used concomitant medications were adrenergic inhalers such salbutamol (albuterol), which were used in 3% of subjects in each treatment arm. All medicines that could be used for symptomatic relief of influenza, except for rescue medication, were analyzed together; this included decongestants, expectorants, cough suppressants, antipyretics and anti-inflammatory medicines. Medicines for symptomatic relief were used in 8% of subjects in the placebo arm and in the baloxavir marboxil arm and in 6% of subjects in the oseltamivir arm.

Subjects were rarely started on other antiviral drugs (NAIs) for treatment of influenza (two subjects in the placebo arm, one in the baloxavir marboxil arm, and one in the oseltamivir arm). Antibiotic use will be discussed as a secondary efficacy endpoint.

Overall, the percentage of subjects who used antipyretics and medications for the symptomatic relief of influenza was similar in the three treatment arms. The percentage of subjects using acetaminophen as a rescue medication was also similar in the three trial arms. Thus, the primary efficacy endpoint should not be affected by disproportionate use of rescue medications in this trial. Baloxavir marboxil, however, did not appear to reduce the need for concomitant medications for influenza-related symptoms.

### **Efficacy Results for the Primary Endpoint**

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

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

**Table 7: Results for Primary Efficacy Endpoint: Time to Improvement of Symptoms (Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil N=385</b>	<b>Placebo N=385</b>
Median in hours (95% CI*)	73 (67.2, 85.1)	102 (92.7, 113.1)
Difference vs. placebo in hours (95% CI*)	-29 (-42.8, -14.6)	---
p value#	< 0.0001	---

\*CI = confidence interval

#p-value was calculated using the stratified generalized Wilcoxon test.

Source: Clinical Study Report T0832, Table 11-5, page 113.

The median time to improvement of symptoms in the baloxavir marboxil arm was 73 hours compared to 102 hours in the placebo arm. The difference between the two medians was 29 hours. This difference is calculated by subtracting one median from the other median, but simple subtraction of two medians may not accurately reflect the difference between the two arms. The data from the primary analysis are continuous and not necessarily symmetrical around the median; therefore, simply subtracting median values may not be an accurate way to characterize the treatment effect. Dr. Smith analyzed the results using Hodges-Lehmann estimates to correct for any bias and determined that the median difference in time to improvement of symptoms was 21 hours. Regardless of method used to determine the difference, the time to improvement of symptoms between the baloxavir marboxil and placebo arm was statistically significant. The primary endpoint was met, and the efficacy of baloxavir marboxil in the treatment of uncomplicated influenza in subjects at high risk for influenza complications was demonstrated.

A sensitivity analysis of the primary endpoint was performed using the per protocol population. In this analysis, the median time to improvement of symptoms in the baloxavir marboxil arm was 75 hours (95% CI of 67.9, 86.2). The median time to improvement of symptoms in the placebo arm was 99 hours (95% CI of 87.6, 106.1). The time to improvement of symptoms in the baloxavir marboxil arm was 24 hours shorter (95% CI of -35.0, -7.6) than in the placebo arm ( $p < 0.0001$ ) when subtracting one median from the other. Efficacy was also demonstrated in this analysis of the primary endpoint.

Subjects from the study sites that were excluded due to violations of GCP were excluded from the analysis of the primary endpoint. A sensitivity analysis was conducted including subjects from these sites. In the analysis of the primary endpoint including subjects from sites with GCP violations, the median time to improvement of symptoms was 73 hours (95% CI of 67.1, 85.1) in the baloxavir marboxil arm and 102 hours (95% CI of 92.7, 113.2) in the placebo arm. These results are almost identical to those in which subjects from these sites were excluded.

### **Efficacy Results for Subgroups of the Primary Endpoint**

#### *Time to improvement of symptoms by influenza subtype*

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

**Table 8: Time to Improvement of Symptoms by Influenza Virus Type and Subtype (Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>Influenza A/H1N1</b>	<b>N=28</b>	<b>N=17</b>
Median in hours (95% CI*)	67 (58.3, 101.4)	192 (61.3, --)
Difference vs. placebo in hours	-125	---
P-value#	0.1079	
<b>Influenza A/H3N2</b>	<b>N=180</b>	<b>N=185</b>
Median in hours (95% CI*)	75 (62.4, 91.6)	100 (88.4, 113.4)
Difference vs. placebo in hours	-25	---
P-value#	<0.0141	---
<b>Influenza B</b>	<b>N=166</b>	<b>N=167</b>
Median in hours (95% CI*)	75 (67.4, 90.2)	100.6 (82.8, 115.8)
Difference vs. placebo in hours	-26	---
p-value#	0.0138	---

\*CI = confidence interval

#p-value was calculated using the stratified Generalized Wilcoxon test.

Source: Clinical Study Report T0832, Table 11-8, page 119-120.

Most subjects were infected with either influenza A/H3N2 or influenza B, and the results for both strains support for the efficacy of baloxavir marboxil and align with the primary analysis in ITTI population. There were two few subjects with A/H1N1 to reach any definitive conclusions about the efficacy of baloxavir marboxil against A/H1N1 from these data.

#### *Time to improvement of symptoms by age*

The median time to improvement of symptoms in adults from 18 to < 65 years of age and who received baloxavir marboxil was 74 hours (95% CI of 64.6, 88.2); the median time to improvement of symptoms in adults 18 to < 65 years old who received placebo was 106 hours (95% CI of 96.3, 116.2). Time to improvement of symptoms was 32 hours shorter in adults (18 to < 65 years of age) who received baloxavir marboxil compared to in those who received placebo. The median time to improvement of influenza symptoms in subjects 65 years of age and older was 70 hours in subjects who received baloxavir marboxil (N=112) and 88 hours in those who received placebo (N=102) for a difference of 18 hours. Efficacy was demonstrated in both adults 18 to 64 years of age and those 65 years of age and older in this trial.

The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years infected with influenza virus was similar for subjects who received baloxavir marboxil (188 hours) or placebo (191 hours). Although the time to improvement of influenza symptoms was shorter in the baloxavir marboxil arm than the placebo arm, there were too few adolescents in the in this subgroup (13 subjects in the baloxavir marboxil arm and 12 in the placebo arm) to accurately analyze the median time to improvement of influenza symptoms in this age group. Despite the inconclusive results in the adolescent subgroup in this trial, baloxavir marboxil can be approved for use in adolescents with acute, uncomplicated influenza who are at high risk of influenza complications based on extrapolation of efficacy from Trial T0831. Extrapolation is appropriate because influenza disease is similar in adults and adolescents, the same baloxavir marboxil dose is used in adults and adolescents, there are

similar baloxavir exposures in adults and adolescents, and efficacy has been demonstrated in both adults and adolescents in Trial T0831.

*Time to improvement of symptoms by geographic area*

The primary endpoint was analyzed by region. The trial was conducted in three regions, Asia, North America/Europe, and the Southern Hemisphere. However, only 53 subjects were enrolled in the Southern Hemisphere. The median time to improvement of symptoms by geographic region is shown in the following table.

**Table 9: Time to Improvement of Symptoms by Geographic Region (Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>North America/Europe</b>	<b>N=209</b>	<b>N=216</b>
Median in hours (95% CI*)	92 (77.0, 103.2)	116 (101.4, 141.3)
Difference vs. placebo in hours	-24	---
P value	0.0013	
<b>Asia</b>	<b>N=159</b>	<b>N=150</b>
Median in hours (95% CI*)	64 (53.1, 68.6)	80 (67.4, 92.7)
Difference vs. placebo in hours	-16	---
P value	0.0234	---
<b>Southern Hemisphere</b>	<b>N=17</b>	<b>N=19</b>
Median in hours (95% CI*)	104 (31.1, 292.7)	138 (56.4, 293.7)
Difference vs. placebo in hours	-34	---
P value	0.3104	---

\*CI = confidence interval

Source: Clinical Study Report T0832, Table 11-41, page 177-178.

The median time to improvement of symptoms was shorter in the baloxavir marboxil than placebo arms for subjects in both Asia and North America/Europe; and both comparisons reached statistical significance. However, the median times to improvement of symptoms differed by region. In Asia, the median times to improvement of symptoms were shorter in both the baloxavir marboxil and the placebo arms compared to the median times in the US and Canada. The median time to improvement of symptoms in the baloxavir marboxil arm in the US and Canada was actually longer than in the placebo arm in Japan. It is unclear why there were differences in the times to improvement of symptoms for both the baloxavir marboxil and placebo arms between Asia and the North America/Europe, but this difference was also observed in the Phase 3 trial in otherwise healthy subjects (Trial T0831). It is possible that the differences were due to influenza strains or to cultural differences in reporting symptoms. Although the median time to improvement of symptoms was shorter in the baloxavir arm than the placebo arm in Southern Hemisphere subjects, the difference was not statistically significant. However, this may be due to the relatively small sample size in that subgroup.

*Time to improvement of symptoms by weight and dose*

The primary endpoint was analyzed by baseline weight; because dose was based on weight, the analysis for dose and weight are the same. The majority of subjects (N=702 or 60%) weighed < 80 kg and received the 40 mg dose of baloxavir marboxil. The remaining 40% of subjects weighed 80 kg or more and received the 80 mg dose of baloxavir marboxil.

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**Table 10: Time to Improvement of Symptoms by Weight  
(Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>&lt; 80 kg</b>	<b>N=238</b>	<b>N=231</b>
Median in hours (95% CI*)	77 (68.4, 90.3)	94 (80.5, 106.1)
Difference vs. placebo in hours	-17	---
p- value	0.0348	
<b>≥ 80 kg</b>	<b>N=147</b>	<b>N=154</b>
Median in hours (95% CI*)	68 (62.4, 85.1)	118 (99.1, 140.5)
Difference vs. placebo in hours	-49	---
p- value	0.0013	---

\*CI = confidence interval

Source: Clinical Study Report T0832, Table 11-45, page 187.

The median time to improvement of symptoms was shorter in the baloxavir marboxil than the placebo arm in both subgroups. However, the difference between the median times for the baloxavir marboxil and placebo arm was considerably greater in the subgroup of subjects weighing 80 kg or more (49 hours) compared to those weighing less than 80 kg (17 hours). The reason for the difference in results for the two weight and dose groups is largely due to the longer median time to improvement of symptoms in the placebo group for subjects weighing ≥ 80 kg (118 hours) compared to the time to improvement in the placebo group for subjects < 80 kg (94 hours). However, whether the longer time to improvement in the placebo group for subjects weighing ≥ 80 kg was due only to weight or to some other factor is not clear.

*Time to improvement of symptoms by influenza vaccine status*

Twenty-five percent of the trial population were vaccinated against influenza prior to the influenza season of study. The time to improvement of symptoms was analyzed for subjects who had received an influenza vaccination compared to those who had not, and the results are shown in the following table.

**Table 11: Median Time to Improvement of Symptoms by Influenza Vaccine Status  
(Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>Received Influenza Vaccine</b>	<b>N=91</b>	<b>N=99</b>
Median in hours (95% CI*)	65 (52.6, 85.1)	93 (76.1, 110.6)
Difference vs. placebo in hours	-27	---
P value	0.1042	
<b>Did NOT receive Influenza Vaccine</b>	<b>N=294</b>	<b>N=286</b>
Median in hours (95% CI*)	77 (68.4, 90.2)	103 (93.2, 94.8)
Difference vs. placebo in hours	-26	---
P value	0.0003	---

\*CI = confidence interval

Source: Clinical Study Report T0832, Table 11-7, page 117.

The median time to improvement of symptoms was shorter for the baloxavir arm than in the placebo group whether or not subjects had received an influenza vaccine. In both subgroups, the difference in time to improvement of symptoms between baloxavir and placebo arms was similar (i.e. 26 to 27 hours shorter in the baloxavir arm). These results, however, only reached

statistical significance for the subgroup of subjects who had not been vaccinated, possibly because of the smaller sample size for the subgroup of subjects who had been vaccinated.

*Time to improvement of symptoms by time since onset of influenza symptoms*

The primary endpoint was analyzed by time from onset of influenza symptoms to time of treatment. The trial enrolled patients who had symptoms of influenza for 48 hours or less. This analysis compared the median time to alleviation of symptoms for subjects with symptom onset to treatment for four time periods as shown in the following table.

**Table 12: Time to Improvement of Symptoms by Time from Influenza Symptom Onset to Treatment  
(Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>≥ 0 to ≤ 12 hours</b>	<b>N=27</b>	<b>N=42</b>
Median in hours (95% CI*)	62 (37.2, 89.9)	110 (50.6, 141.8)
Difference vs. placebo in hours	-48	---
P value	0.0167	
<b>&gt;12 to ≤ 24 hours</b>	<b>N=150</b>	<b>N=150</b>
Median in hours (95% CI*)	70 (64.4, 83.0)	99 (78.2, 110.6)
Difference vs. placebo in hours	-29	---
P value	0.0167	---
<b>&gt;24 to ≤ 36 hours</b>	<b>N=113</b>	<b>N=119</b>
Median in hours (95% CI*)	71 (56.4, 91.7)	110 (92.7, 137.8)
Difference vs. placebo in hours	-39	---
P value	0.0004	---
<b>&gt;36 to ≤ 48 hours</b>	<b>N=94</b>	<b>N=74</b>
Median in hours (95% CI*)	93 (76.9, 116.2)	102 (78.7, 125.4)
Difference vs. placebo in hours	-9	
P value	0.8249	

\*CI = confidence interval

Source: Clinical Study Report T0832, Table 11-47, page 190-191.

The time to improvement of symptoms was shorter in the baloxavir marboxil arm compared to the placebo arm in each of the time periods. The median time to improvement of symptoms was similar among subjects treated with baloxavir within 36 hours of symptom onset; while the difference in median time to improvement of symptoms between the baloxavir marboxil arm and the placebo arm was smallest in the time period from > 36 hours to ≤ 48 hours. Although this may be related to improved response to treatment prior to host effects such as destructive changes in the respiratory tract, the exact reason is unknown, but similar results have been described with oseltamivir. Efficacy in subjects with onset of symptoms longer than 48 hours prior to treatment was not evaluated in this trial.

*Time to improvement of symptoms by presence or absence of pre-existing and worsening symptoms*

The time to improvement of symptoms was analyzed for the subgroups of subjects who had pre-existing symptoms that overlapped with symptoms of influenza (cough, muscle or joint pain, and/or fatigue) that worsened with their influenza infection and for those who did not.

**Table13: Median Time to Improvement of Symptoms by Presence of Pre-Existing and Worsening Symptoms (Intent-to-Treat-Infected Population)**

	<b>Baloxavir marboxil</b>	<b>Placebo</b>
<b>Pre-existing and worsened symptoms</b>	<b>N=70</b>	<b>N=76</b>
Median in hours (95% CI*)	73 (56.8, 98.3)	102 (77.9, 142.7)
Difference vs. placebo in hours	-29	---
P value	0.0118	
<b>No pre-existing and worsened symptoms</b>	<b>N=315</b>	<b>N=309</b>
Median in hours (95% CI*)	74 (65.2, 97.7)	102 (91.8, 113.1)
Difference vs. placebo in hours	-28	---
P value	0.0010	---

\*CI = confidence interval

Source: Clinical Study Report T0832, Table 11-42, page 179.

The median time to improvement of symptoms was similar in both subgroups and reached statistical significance in both subjects who had pre-existing and worsened symptoms and those who did not.

### **Efficacy Results for Selected Secondary Efficacy Endpoints**

#### *Incidence of influenza-related complications*

Influenza-related complications were reported in 11 subjects (3%) in the baloxavir marboxil arm and in 40 subjects (10%) in the placebo arm. Influenza-related complications diagnosed in subjects in the baloxavir marboxil arm were bronchitis (N=7) and sinusitis (N=1). The influenza-related complications diagnosed in the placebo arm were bronchitis (N=23), sinusitis (N=8) and pneumonia (N=3). There was a statistically significant difference in the percentage of subjects with bronchitis and sinusitis between the two study arms. However, the criteria for the diagnoses of the individual conditions were not described in the protocol, discussed with FDA, or determined by an adjudication committee. For this reason, in the opinion of this reviewer, these analyses are not clinically meaningful, (b) (4).

No treatment-emergent deaths were reported in either the baloxavir marboxil or placebo arm. Three subjects in the baloxavir marboxil arm and five in the placebo arm were hospitalized. There was no significant difference in the percentage of subjects with hospitalization or death.

#### *Antibiotic use*

Systemic antibiotics were prescribed for 3% of subjects in the baloxavir marboxil arm and for 8% in the placebo arm. Specific criteria for the use of antibiotics were not included in the trial protocol. Because the use of antibiotics varies widely by individual and institution and because there were no pre-defined criteria for the use of antibiotics, this analysis may not be clinically meaningful, (b) (4).

## **Efficacy Summary and Conclusions**

The efficacy of baloxavir marboxil in the treatment of acute, uncomplicated influenza in patients with underlying health factors placing them at high risk of influenza complications was demonstrated in this Phase 3 efficacy and safety trial. The median time to improvement of symptoms was 73 hours in the baloxavir marboxil arm compared to 102 hours in the placebo arm ( $p < 0.0001$ ). The efficacy results were also supported by the results of multiple secondary efficacy endpoints and subgroup analyses. The results for the primary endpoint of Trial T0832 will be added to Section 14 of the package insert.

## **8. Safety**

The data from Trial 1601T0832 support the safety of baloxavir marboxil in patients with acute, uncomplicated influenza 12 years of age and older, who have a health factor that places them at high risk of influenza complications. Safety results from this trial were similar to those from the Phase 2 dose-finding trial, 1518T0821, and the Phase 3 safety and efficacy trial, 1601T8031, which supported the initial approval of baloxavir marboxil. Safety results from these two trials are described in Section 6.0 ADVERSE REACTIONS of the baloxavir marboxil package insert.

The methods used to assess safety in the individual trials and in the integrated summary of safety were considered appropriate. For the FDA review, ADAM and SDTM datasets for Trial 1601T8032 were analyzed using JMP. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and are unlikely to impact the overall assessment of the safety profile of baloxavir marboxil. All of the safety assessments and conclusions in this review are those of the FDA clinical reviewer unless otherwise specified.

As agreed upon at the pre-NDA meeting, the Applicant submitted a Safety Update Report on May 3, 2019. The report was reviewed thoroughly, and important findings were incorporated into the relevant sections of this review.

### **Relevant Characteristics of the Safety Population**

The safety population included all subjects who received at least one dose of study drug. Study treatment was dispensed in error for two subjects. One subject was randomized to placebo but received baloxavir marboxil, and one subject who was randomized to oseltamivir received baloxavir marboxil. In addition, four randomized subjects were withdrawn prior to receipt of study drug (1 in the baloxavir marboxil arm and 3 in the oseltamivir arm). As a result, a total of 730 study subjects were exposed to a single dose of baloxavir marboxil, 727 received placebo, and 727 received oseltamivir in T0832.

The demographics of the safety population were similar to that of the ITTI population except that a higher percentage of the safety population were White, and a lower percentage were Asian. When the demographics of the T0832 trial population are compared to the demographics of the two trials that supported the original NDA, the demographics of T0832 more accurately represent the racial/ethnic diversity of the U.S.

The number and percentage of subjects with health factors placing them at high risk of influenza complications by CDC criteria are shown in the following table for the safety population. Some subjects had more than one health factor placing them at high risk; therefore, the number of subjects in this table adds up to more than the total number of study subjects.

**Table 14: Number and Percentage of Subjects with High Risk Factors by High Risk Category (Based on CDC Criteria\*)**

	<b>Placebo N=729</b>	<b>Baloxavir N=730</b>	<b>Oseltamivir N=725</b>
Respiratory / Chronic lung disease	301 (42%)	308 (42%)	300 (41%)
Endocrine disorders	257 (32%)	232 (32%)	243 (34%)
Age ≥ 65 years	203 (28%)	209 (29%)	190 (26%)
Heart disease	87 (12%)	83 (11%)	78 (11%)
Morbid obesity	77 (11%)	75 (10%)	96 (13%)
Metabolic disorders	74 (10%)	64 (9%)	71 (10%)
Neurologic and neurodevelopment disorders	37 (5%)	45 (6%)	50 (7%)
Compromised immune system	27 (4%)	26 (4%)	26 (4%)
Blood disorders	18 (3%)	19 (3%)	13 (2%)
Native American / Alaskan Native	7 (1%)	7 (1%)	6 (1%)
Residents of long-term care facilities	1 (<1%)	2 (<1%)	0
Women within 2 weeks postpartum	1 (<1%)	1 (<1%)	0

\*CDC criteria for high risk factors accessed at URL <https://www.cdc.gov/flu/highrisk/index.htm>  
Source: Response to FDA Information Request, SN 131, Table, pages 1-5.

The type and number of high-risk health factors were similar across the three treatment arms. The majority of subjects in the trial had respiratory/chronic lung disease (42%), endocrine disorders (34%), or were 65 years of age or older (28%). There was an adequate representation of most health factor categories except for Native American/Alaskan Native, residents of long-term care facilities, and women within 2 weeks postpartum who were not breastfeeding. These categories may have been difficult to enroll because of site locations (Native American/Alaskan Native and residents of long-term care facilities) or because the population is difficult to enroll (women within 2 weeks of giving birth). Therefore, the representation across health factors is acceptable.

Individual high-risk health factors reported in 5% or more of total subjects are shown in the following table. While the CDC criteria list high risk health factors, few specific examples of each health factor are provided. Specific diseases placing patients at high risk of influenza complications that are included by CDC include asthma, sickle cell disease, COPD, cystic fibrosis, diabetes mellitus, congenital heart disease, congestive heart failure, coronary artery disease, and receipt of immunomodulators. As a result, the types of individual health factors within each category were largely up to investigator discretion.

**Table 15: Number and Percentage of Subjects with Individual High-Risk Factors Reported in ≥ 5% of Total Subjects**

High Risk Factor	Placebo N=729	Baloxavir N=730	Oseltamivir N=725
Asthma	245 (34%)	243 (33%)	249 (34%)
Diabetes mellitus Type 2	152 (21%)	140 (19%)	129 (18%)
Diabetes mellitus (unspecified)	53 (7%)	45 (6%)	58 (8%)
Diabetes mellitus Type 1	6 (1%)	2 (<1%)	3 (<1%)
COPD	51 (7%)	57 (8%)	40 (6%)
Obesity	53 (7%)	52 (7%)	56 (8%)

\*Diabetes mellitus was reported as three different high-risk factors (diabetes mellitus, type 1 diabetes, and type 2 diabetes)

Source: Response to FDA Information Request, SN 131, Table, pages 1-5.

The types and numbers of individual high-risk health factors were similar between the three arms. Asthma and diabetes mellitus were reported much more commonly than other individual high-risk factors. Asthma has been demonstrated to be a risk factor for the development of influenza complications in multiple studies, and has been reported most commonly in pediatric patients and in patients with influenza during the 2009 H1N1 epidemic.<sup>1,2</sup> Diabetes has been demonstrated to be a risk factor for complications of influenza in both a meta-analysis<sup>3</sup> and a population based review.<sup>1</sup> Therefore, while asthma and diabetes mellitus were more common than other high risk factors, they represent common and important conditions that place patients at risk of influenza complications.

### Adverse Events

In Trial T0832, adverse events (AEs) were collected through Day 22. AEs were classified by System Organ Class and Preferred Terms of the MedDRA system. The severity of AEs was categorized according the Common Terminology Criteria for Adverse Events (CTCAE version) 4.0.

The overall summary of adverse events with the numbers of each type of AE is shown in the following table.

**Table 16: Overall Summary of Adverse Events (Safety Population)**

	Placebo N=727	Baloxavir N=730	Oseltamivir N=727
Number (%) of subjects with any AE	216 (30%)	183 (25%)	202 (28%)
Number of deaths	0	1	1
Number (%) of subjects with SAE	9 (1%)	5 (1%)	8 (1%)
Number (%) of subjects with AE leading to premature study discontinuation	5 (1%)	5 (1%)	4 (1%)

Source: CSR T0832, Table 12-6, page 223

As shown in the table, the percentage of subjects who experienced an adverse event was somewhat lower in the baloxavir marboxil arm (25%) compared to the placebo arm (30%) and the oseltamivir arm (28%). The percentage of subjects with a serious adverse event or an adverse event leading to premature study discontinuation was the same in all three treatment arms.

## Deaths and Other Serious Adverse Events

There were two deaths in Trial T0832: one in the baloxavir arm and one in the oseltamivir arm. Subject (b) (6) in the baloxavir arm was a 66-year-old male who was high risk due to his age. He was enrolled and received a single 80 mg dose of baloxavir marboxil. His Day 1 electrocardiogram (obtained prior to dosing) was read by a cardiologist after dosing on Day 1, and the subject had ECG evidence of a myocardial infarction. The subject was withdrawn due to the ECG finding, and he was admitted for cardiac catheterization. The subject subsequently had a coronary artery bypass on Day 12 for occlusion of the right coronary artery. He developed post-operative complications (right ventricular failure, *Pseudomonas* bacteremia and pneumonia, and brain death) and died on Day 24. This death was not considered treatment-related since the initial AE (myocardial infarction) occurred prior to treatment with baloxavir marboxil.

Subject (b) (6) was an 81-year-old Asian male a history of carotid artery stenosis, dyslipidemia, hypertension, and interstitial lung disease. He was RT-PCR positive for influenza B and was treated with oseltamivir. The subject was hospitalized on Day 12 for pneumonia. His hospital course was complicated by cardiac failure, cerebral infarction, pneumothorax, acute respiratory distress syndrome, and septic shock (staphylococcal infection). He died on Day 38. His death was considered to be unrelated to study drug.

Serious adverse events were reported in 1% of subjects in each treatment arm. Seven SAEs were reported in 5 subjects in the baloxavir marboxil arm, 9 SAEs in 9 subjects in the placebo arm, and 16 AEs in 8 subjects in the oseltamivir arm. The only SAEs reported in more than one subject within a treatment arm were cholelithiasis, which was reported in two subjects in the baloxavir marboxil arm, and increased/abnormal liver function tests, which was reported in two subjects in the oseltamivir arm. SAEs reported in more than one study subject (e.g., all treatment arms together) were pneumonia, which was reported in one subject in each of the three treatment arms) and pneumothorax, which was reported in one subject in the baloxavir marboxil arm and one in the oseltamivir arm. The individual SAEs reported by treatment arm were as follows:

- Baloxavir marboxil arm: influenza B pneumonia, pneumonia, pneumothorax, acute cholecystitis, bile duct stone, and cholelithiasis (in two subjects)
- Placebo arm: hypotension, nausea, headache, ureterolithiasis, urinary retention, hyperglycemia, and hyperbilirubinemia.
- Oseltamivir arm: aspiration pneumonia, vulvar abscess, hypotension, uncontrolled diabetes, arachnoid cyst, and increased/abnormal LFTs (in two subjects). Nine SAEs were reported for Subject (b) (6) who died on Day 38; his case was previously described.

## Discontinuations due to Adverse Events

Fourteen subjects prematurely discontinued the trial because of an adverse event: 5 in the baloxavir marboxil arm, 5 in the placebo arm, and 4 in the oseltamivir arm. The premature discontinuations in the baloxavir marboxil arm included:

- A 62-year-old female with diabetes who was RT-PCR-positive for influenza B and developed an increase in cough on Day 3. She had evidence of pneumonia on chest radiograph. She was taken off study and treated with oseltamivir and levofloxacin.
- A 29-year-old male with asthma and diabetes mellitus who was RT-PCR negative for influenza. On the day of enrollment, he developed difficulty breathing and was hospitalized with left lower lobe pneumonia. He was taken off study and treated with oseltamivir and doxycycline.

- A 26-year-old female with obesity and chronic lung disease with influenza B had Grade 1 vomiting on Day 1 after receiving a single dose of baloxavir. She was taken off study and treated with ondansetron and oseltamivir.
- A 66-year-old female with a complicated medical history including asthma, diabetes mellitus, obesity, osteoarthritis, and gastroesophageal reflux developed Grade 1 abdominal pain and vomiting on Day 3. She was influenza negative by RT-PCR.
- A 68-year-old female with COPD developed urticaria 48 hours after receipt of a single dose of baloxavir. She was taken off study and treated with steroids and antihistamines.

In these five subjects, the adverse events of vomiting and of urticaria were considered related to baloxavir marboxil.

The AEs that resulted in premature discontinuation were varied in subjects who received placebo: acute bronchitis, bronchitis with asthma exacerbation, headache, nausea, and atrial fibrillation. Three subjects who received oseltamivir were prematurely discontinued from the study due to gastrointestinal AEs (abdominal pain or discomfort, nausea, decreased appetite, and dysgeusia) that were attributed to study drug. One subject in the oseltamivir arm was prematurely discontinued due to pneumonia that was judged as not related to study drug.

### **Adverse Events of Interest**

The adverse events described in this section were selected by the Applicant as AEs of special interest and were analyzed separately in the Clinical Summary of Safety and the Safety Update Report.

#### Neuropsychiatric Adverse Events

Abnormal behavior has been reported in patients infected with influenza. In addition, cases of neuropsychiatric adverse events have been reported postmarketing in patients who have received oseltamivir and other neuraminidase inhibitors. The neuropsychiatric adverse events described in the Warnings and Precautions section of Tamiflu® package insert are abnormal behavior, delirium, and hallucinations. These cases have been reported primarily in pediatric patients and adolescents. The mechanism of these neuropsychiatric AEs is unknown, and the Tamiflu label states that the contribution of Tamiflu to these events has not been established. The Applicant conducted an analysis of neuropsychiatric adverse events in Trial T0832. Only one subject in the baloxavir marboxil arm reported a neuropsychiatric adverse event (anxiety). Five neuropsychiatric adverse events were reported in the placebo arm (delirium, altered mood, nightmare, insomnia, and depression), and three neuropsychiatric adverse events were reported in the oseltamivir arm (insomnia, anxiety, and depression). There was no clear increase in any individual neuropsychiatric adverse event in any treatment arm in this trial. See the postmarketing safety section of this review for a summary of neuropsychiatric adverse events in patients who received baloxavir marboxil.

#### Hepatic Adverse Events

In nonclinical repeat dose oral toxicity studies in rats, liver effects were observed at the high baloxavir marboxil dose. Abnormal findings were noted on gross and microscopic examination of the liver, but findings were minimal or mild and resolved during recovery. In nonclinical repeat dose oral toxicity studies in monkeys, increases in liver enzymes were observed after baloxavir marboxil doses of 20 mg/kg/day or higher. Because of these findings, hepatic adverse events were considered adverse events of special interest.

No cases of drug-induced liver injury or cases fitting Hy's Law criteria were reported in subjects who received baloxavir marboxil in Trial T0832. No hepatic adverse events, other than increases in liver enzymes, were reported in subjects who received baloxavir marboxil.

Abnormalities in liver enzymes in Trial T0832 (obtained between Days 2 and 22 after dosing) are shown in the following table.

**Table 17: Number of Subjects with Abnormal Liver Enzymes (Safety Population)**

	Category	Baloxavir marboxil N=730	Placebo N=727	Oseltamivir N=721
ALT	> 3 to ≤ 5 x ULN	3 (<1%)	4 (1%)	5 (1%)
	>5 to ≤ 20 x ULN	3 (<1%)	1 (<1%)	6 (1%)
	>20 x ULN	0	0	0
AST	> 3 to ≤ 5 x ULN	2 (<1%)	3 (<1%)	7 (1%)
	>5 to ≤ 20 x ULN	1 (<1%)	1 (<1%)	2 (<1%)
	>20 x ULN	0	0	0
Total bilirubin	> 1.5 to ≤ 3 x ULN	6 (1%)	2 (<1%)	5 (1%)
	>3 to ≤ 10 x ULN	0	2 (<1%)	0
	>10 x ULN	0	0	0

Source: Summary of Clinical Safety, Table 18, page 49

As shown in the preceding table, the proportion of subjects with increased liver enzyme tests was similar in the baloxavir marboxil, placebo arms, and oseltamivir arms. In the opinion of this reviewer, no hepatotoxicity was associated with baloxavir marboxil use this trial.

#### **Adverse Events with Severe or Life-threatening Intensity**

The percentage of subjects with Grade 3 or 4 adverse events was similar in the three treatment arms: 1.5% in the baloxavir marboxil arm, 1.8% in the placebo arm, and 1.7% in the oseltamivir arm. Grade 4 AEs were uncommon, and none were reported in the baloxavir marboxil arm; Grade 4 AEs were reported in 3 subjects in the placebo arm and in 2 in the oseltamivir arm. The Grade 4 AEs reported in the placebo arm were loss of consciousness, atrial ventricular block, and COPD. All but one Grade 4 and 5 AEs reported in the oseltamivir arm were reported in the subject who died with pneumonia, septic shock, staphylococcal infection, acute kidney injury, and cardiac failure. Another subject in the oseltamivir arm had a Grade 4 arachnoid cyst. The only Grade 3 adverse event reported in more than one subject in any treatment arm was bronchitis, which was reported in two subjects who received baloxavir marboxil, three who received placebo, and three who received oseltamivir. In addition, two subjects in the baloxavir marboxil arm reported cholelithiasis; one had acute cholecystitis and the other had a bile duct stone. There were two subjects in the placebo arm with nausea, and two in the oseltamivir arm with vomiting. Grade 3 AEs reported once each in the baloxavir arm were primarily in the Infections and Respiratory System Organ Classes: pneumonia, influenza pneumonia, cough, wheezing, dyspnea, COPD, and pneumothorax. These Grade 3 AEs were all uncommon and were consistent with underlying influenza and/or chronic respiratory disease. In the opinion of this reviewer, baloxavir marboxil was not associated with any severe or life-threatening adverse events in this trial.

#### **Common Adverse Events**

##### Adverse events of any causality

The following table displays all adverse events reported in at least 1% of subjects who received baloxavir marboxil in Trial T0832. There were no treatment-emergent adverse events reported in more than 5% of subjects in any arm in the pivotal trials.

**Table 18: Number and Percentage of Subjects with Treatment-Emergent Adverse Events (Reported in ≥1% of Subjects, Safety Population)**

	<b>Placebo N=727</b>	<b>Baloxavir N=730</b>	<b>Oseltamivir N=727</b>
Subjects with at least one AE	216 (30%)	183 (25%)	202 (28%)
Bronchitis	33 (5%)	21 (3%)	30 (4%)
Nausea	29 (4%)	20 (3%)	34 (5%)
Diarrhea	21 (3%)	20 (3%)	23 (3%)
Sinusitis	21 (3%)	14 (2%)	22 (3%)
Vomiting	6 (1%)	8 (1%)	14 (2%)
Headache	7 (1%)	6 (1%)	9 (1%)
Abdominal pain	12 (2%)	5 (1%)	3 (<1%)
Pneumonia	4 (1%)	5 (1%)	8 (1%)
Dizziness	6 (1%)	4 (1%)	7 (1%)
Otitis media	6 (1%)	3 (<1%)	6 (1%)
Asthma	5 (1%)	4 (1%)	4 (1%)
Acute sinusitis	7 (1%)	2 (<1%)	2 (<1%)
Decreased appetite	3 (<1%)	4 (1%)	2 (<1%)
Pharyngitis	4 (1%)	2 (<1%)	3 (<1%)
Urinary tract infection	4 (1%)	2 (<1%)	2 (<1%)
Back pain	1 (<1%)	5 (1%)	2 (<1%)
Rash	2 (<1%)	4 (1%)	1 (<1%)
Epistaxis	4 (1%)	2 (<1%)	1 (<1%)

Source: Clinical Study Report 1602T0832: Table 12-8, pages 225-232

Bronchitis was the only adverse event reported in at least 5% of subjects who received baloxavir marboxil. Adverse events reported in ≥ 2% of subjects in the baloxavir marboxil arm were bronchitis, nausea, diarrhea, and sinusitis. The incidence of all four of these adverse events (2% to 5%) was similar in the baloxavir marboxil arm, the placebo arm, and the oseltamivir arm. There was no single adverse event that was observed at an incidence that was more than 2% higher in the baloxavir marboxil arm than in the placebo arm. The percentage of subjects with any individual treatment-emergent adverse event was low in each treatment arm, and the percentages for each AE were similar between the three treatment arms. No pregnancies were reported in Trial T0832.

The only adverse events considered related to study drug that were reported in 1% or more of subjects who received baloxavir marboxil were nausea (2%) and diarrhea (1%). Treatment-related nausea was reported in 3% of subjects in the placebo arm and 3% of subjects in the oseltamivir arm; treatment-related diarrhea was also reported in 1% of subjects in both the placebo and oseltamivir arm.

These results are similar to those in the safety results observed in the Phase 2 and the Phase 3 trials submitted to support baloxavir safety and efficacy in the original NDA and are similar to the safety results already described in the Xofluza package insert.

#### **Analyses of Adverse Events by Subgroup**

Among baloxavir-treated subjects, the types of adverse events reported in the two weight groups (< 80 kg and ≥ 80 kg) were similar, and safety did not appear to vary by weight group or baloxavir marboxil dose.

Only 21 subjects from 12 to < 18 years of age were enrolled in Trial T0832. Therefore, there were too few subjects to analyze safety in adolescents as compared to adults. However, there were no serious AEs, Grade 3 adverse events, or Grade 4 adverse events reported in adolescents participating in the trial, regardless of treatment arm.

In Trial T0832, 209 subjects 65 years of age and older and 500 subjects from 18 to < 65 years of age received a single dose of baloxavir. Adverse events were reported in 26% of subjects 65 years of age and older and in 25% of subjects from 18 to < 65 years of age. Adverse events reported in 2% or more of subjects 65 years and older were nausea (6%), diarrhea (3%), bronchitis (2%), and abdominal pain (2%). Adverse events reported in 2% or more of subjects from 18 to < 65 years of age were bronchitis (3%), diarrhea (3%), and sinusitis (2%). The percentage of subjects with nausea was considerably higher in subjects 65 years of age who received baloxavir marboxil and older compared to those from 18 to 64 years of age. However, the percentage of subjects 65 years and older in the placebo arm who reported nausea (8%) was also higher than the percentage of subjects 18 to 64 years of age with nausea (1%). It appears that although not associated with baloxavir marboxil specifically, nausea was more common in elderly subjects with influenza than in younger adults in this trial. Section 8.5, Geriatric Use, of the package insert will include the increased incidence of nausea in subjects 65 years of age and older.

A total of 440 Whites, 201 Asians, and 72 Blacks/African Americans received a single dose of baloxavir marboxil in Trial T0832. The percentage of subjects in the baloxavir marboxil arm with at least one adverse event was 22% in Whites, 30% in Asians, and 26% in Blacks/African Americans. Because the number of Black/African American subjects was relatively small, individual AEs were compared between the White and Asian subgroups only. Adverse events reported in 2% or more of White subjects were bronchitis (3%), diarrhea (3%), and sinusitis (2%), which was similar to the entire population of subjects who received baloxavir marboxil. In the subgroup of Asian subjects, AEs reported in at least 2% of subjects were nausea (7%), diarrhea (2%), nasopharyngitis (2%), and decreased appetite (2%). Bronchitis was reported in 2 (1%) Asian subjects, and sinusitis was reported in 1 subject (1%). Nausea was considerably higher in Asian subjects compared to White subjects (7% vs. < 1%, respectively). Other AEs were reported in 1 to 3% of subjects in either racial subgroup, and therefore, were observed at a similar incidence in the two racial subgroups.

*Reviewer comment:* Two ongoing trials (CP40617 and MV40618) are enrolling subjects in the United States and should enroll additional Black/African Americans (see Table 20).

### **Laboratory Abnormalities**

Clinical safety laboratory tests were obtained on Days 1, 5, 15, and 22. The Clinical Study Report, Summary of Clinical Safety, and laboratory datasets for Trial T0832 were reviewed for Grade 3 and 4 laboratory abnormalities. See the section of this review entitled, Adverse Events of Interest, for a discussion of abnormal liver function tests. Treatment-emergent Grade 3 and 4 abnormalities in other laboratory values were uncommon and are shown in the following table.

**Table 19: Total Number of Subjects with Treatment-Emergent Grade 3 and 4 Abnormalities in Select Laboratory Parameters**

	Grade 3			Grade 4		
	Placebo N=727	Baloxavir N=730	Oseltamivir N=727	Placebo N=727	Baloxavir N=730	Oseltamivir N=727
↑ Creatinine	10	8	6	3	0	1
↓ Neutrophil count	1	0	0	0	0	1
↓ Platelet count	0	0	0	0	0	1
↓ Hemoglobin	2	3	2	0	0	1

Source: Clinical Study Report 1602T0832: Table 12-8, pages 225-232

As shown in the table above, the number of subjects with Grade 3 and 4 laboratory abnormalities was low in each treatment arm. The number of subjects with Grade 3 creatinine, neutrophil count, and platelet count was lower in the baloxavir marboxil arm compared to the placebo arm. The number of subjects with a Grade 3 decrease in hemoglobin was slightly higher in the baloxavir marboxil arm compared to the placebo arm. There were no Grade 4 laboratory abnormalities in the baloxavir marboxil arm. Overall, there was no safety signal observed on analysis of individual laboratory values in this trial.

### Overdose

DAVP was notified by the Division of Medication Error Prevention and Analysis (DMEPA) of eight cases of baloxavir marboxil overdose that have been reported to the FDA Adverse Reporting System (FAERS) to date. In each of these cases, subjects who were prescribed a single 40 mg dose received 80 mg. Adverse events following overdose were reported in two subjects. A 16-year-old female developed dizziness, a mild headache, and poor short-term memory; she reported felt like she had a mild concussion. A 14-year-old female had an “allergic reaction” after overdose; no other information was provided. Several of the reports note that the overdose was due to either pharmacy or prescribing error.

DMEPA was consulted and sent an information request to the Applicant on June 7, 2019 requesting an analysis of their cases and complaints and for their plans to prevent medication errors. The Applicant identified one additional case of overdose. A 51-year-old female was given an 80 mg dose instead of a 40 mg dose. This patient had a history of irritable bowel syndrome and developed watery diarrhea after taking baloxavir.

Baloxavir marboxil is currently approved and provided in blister cards, each blister card containing either 2 x 20 mg tablets, 4 x 20 mg tablets, 1 x 40 mg tablets, or 2 x 40 mg tablets. In the overdose cases, it appears that patients were given 2 x 40 mg tablets instead of a single 40 mg tablet. DMEPA recommended revisions to the DOSING AND ADMINISTRATION section of the package insert and to the “How should I take Xofluza” section of the patient package insert to help prevent dosing errors. These recommendations were conveyed to the Applicant. The Applicant will no longer market the blister cards containing 4 x 20 mg tablets and 1 x 40 mg tablets in the United States. DMEPA suggested removing information regarding blister cards containing these strengths from the package insert. The Applicant agreed to these changes. Finally, DMEPA recommended changes to the carton labeling to minimize confusion (by dispensing pharmacy or by the patient) regarding baloxavir marboxil dosing. (b) (4)

The Applicant states that they are taking steps to minimize confusion to health care providers, pharmacists, and patients. The Applicant has developed stand-alone dosing cards and

additional information that will be made available to health care providers. The Applicant will also add dosing instructions to the Xofluza website and plans to develop patient brochures.

(b) (4)

### **Safety Update Report**

The Safety Update Report (SUR) was submitted on May 3, 2019. It included an overview of safety from clinical studies completed and ongoing from February 27, 2018 to the February 22, 2019 data lock point and data from postmarketing adverse events reported since the marketing approval of baloxavir marboxil in Japan on February 23, 2018.

DAVP requested an analysis of anaphylaxis, hypersensitivity, and related allergic adverse events in an information request dated March 1, 2019 after multiple FAERS reports of anaphylaxis were identified by reviewers in the Office of Surveillance and Epidemiology. This analysis, which included data from both clinical trials and from postmarketing adverse event reports, is reviewed separately below.

After DAVP made recommendations for the inclusion of a Postmarketing Experience section to Section 6, Adverse Reactions section of the baloxavir marboxil package insert, the Applicant submitted a response with additional data on August 3, 2019. This information is included in this review. Labeling negotiations with the Applicant are ongoing.

#### *Safety Update from Clinical Studies*

During the dates covered by the SUR, three clinical trials were completed. One of the completed trials was T0832. Safety follow-up was completed and included in the Clinical Study Report for T0832, so no additional information is provided in the SUR for Trial T0832. Six clinical trials were ongoing during this period; three were conducted in a blinded fashion and three were not blinded (i.e., open-label). The completed trials, with the exception of T0832, and the ongoing trials are described in the following table. The numbers of subjects exposed to baloxavir marboxil in the ongoing blinded trials is estimated based on the number of subjects enrolled and the randomization scheme.

**Table 20: Clinical Trials of Baloxavir Marboxil Completed or Ongoing between February 2018 and February 2019**

Study Number	Study Design	Study Population	No. Subjects Exposed to Baloxavir
(b) (4)			
CP40559	Phase 3, single arm, open-label, safety, PK and efficacy	Pediatric subjects from birth to < 12 months of age with influenza	1
(b) (4)			
CP40563	Phase 3, single arm, open-label, safety, PK and efficacy	Pediatric subjects from 12 months to < 12 years of age with influenza	115*
CP40617	Phase 3, randomized, double-blind placebo-controlled trial	Subjects ≥ 12 years of age hospitalized due to influenza	51*#
(b) (4)			
MV40618 <sup>^</sup>	Phase 3, randomized, double-blind, placebo-controlled, prevention of transmission	Index cases ≥ 12 years to ≤ 64 years of age with influenza	1,130

\*Number of subjects exposed to baloxavir marboxil estimated based on number of subjects enrolled and randomization schema

#Baloxavir marboxil administered in combination with a neuraminidase inhibitor

<sup>^</sup>Subjects were not enrolled in this trial during the SUR reporting period.

Source: SUR, Table 1, page 9-10 and Appendix 1, pages 48-51.

In total, 118 subjects have received baloxavir marboxil (unblinded), and 541 are estimated to have received baloxavir marboxil but study drug is blinded. SAEs were listed in tabular form, and the table included SAEs from all studies of baloxavir marboxil and was not limited to the reporting period for the SUR. Therefore, the SAEs were from the (b) (4) Phase 1 studies, the Phase 2 and Phase 3 registrational trials, Trial T0832, as well as the trials in the previous table. Overall, there have been a total of 11 serious adverse events in completed or unblinded trials and 8 serious adverse events in trials that remain blinded. Of the 11 serious adverse events reported in unblinded studies, 8 occurred in Trial T0832 and are discussed in the safety review of this clinical review. Two SAEs occurred in the Phase 3, safety, PK, and efficacy trial in

otherwise healthy adolescents and adults with acute uncomplicated influenza (Trial T0831). These two SAEs, viral meningitis and incarcerated inguinal hernia, were discussed in the clinical review of the original NDA. No additional information was presented for the final SAE, increased hepatic enzymes. Eight SAEs have been reported in trials that are still blinded, and it is not known whether these subjects received baloxavir. These eight SAEs included two SAEs of interstitial lung disease and one each of asthma, viral lower respiratory tract infection, urinary tract infection, cerebral artery embolism, accidental overdose, and spinal compression fracture. Because the treatment for these subjects remains blinded, these SAEs are not discussed further in this review.

During the time period covered by the SUR, six subjects prematurely discontinued clinical trials due to an adverse event. Two subjects who had received baloxavir marboxil discontinued prematurely due to adverse events: one subject due to vomiting and the other due to an increased AST. A subject who received oseltamivir discontinued prematurely due to liver dysfunction. The treatment for the remaining three subjects remains blinded.

Hypersensitivity reactions and related events observed in clinical trials are discussed along with allergic-type adverse events from postmarketing adverse event reports later in this section of this review.

#### *Postmarketing Safety Data*

The post marketing adverse event reports include a tabular summary of all postmarketing adverse events, a brief discussion of postmarketing adverse events report by System Organ Class, and an analysis of all adverse events of anaphylaxis, hypersensitivity, and related allergic adverse events.

The Applicant searched the Roche Global Safety Database from the time of initial commercial distribution of baloxavir marboxil in Japan on March 14, 2018 until February 2019. During that time period, an estimated (b) (4) patients in Japan and (b) (4) patients in the U.S. were treated with baloxavir marboxil. Baloxavir marboxil is not approved for use in any other countries at this time. A total of 2,695 adverse postmarketing events were reported to the Applicant's safety database; 436 of these were considered serious. A serious postmarketing AE is one with any of the following outcomes, death, hospitalization, life-threatening, disability, or congenital anomaly, documented in the AE report. The majority of postmarketing adverse events (94%) were reported from Japan. The number of postmarketing reports from Japan may have been affected by the Japanese Post-Marketing Phase Vigilance program. In this program, drug companies are to contact medical institutions by visit, letter, fax or e-mail for six months after drug approval (every two weeks for two months then once a month for four months) to promote proper use of the new drug and to encourage adverse events reporting. The Post-Marketing Phase Vigilance program for baloxavir marboxil was conducted from March 14, 2018 to September 13, 2018.

A total of 2,695 postmarketing adverse event reports were submitted to the Roche Safety Database during the time period from March 14, 2018 to February 22, 2019. Of these, 436 were serious adverse events, 2,235 were non-serious, and 24 were reported in non-interventional post-marketing studies. The most commonly reported postmarketing AEs were in the gastrointestinal (GI) System Organ Class (SOC). GI symptoms have been reported with influenza, particularly in pediatric patients, and diarrhea, nausea, and vomiting are included in the Tamiflu package insert. Of the 813 gastrointestinal AEs after with baloxavir marboxil use, there were 326 reports of diarrhea and 276 reports of vomiting. The majority of these were non-serious (308 reports and 267 reports, respectively). Diarrhea was reported in 3% of subjects in

the clinical trials conducted in otherwise healthy subjects (T0821 and T0831) and in subjects at high risk of influenza complications (T0832). The incidence of diarrhea is included in Section 6.1, Clinical Trials Experience of the baloxavir marboxil package insert.

Serious gastrointestinal AEs reported postmarketing included 12 SAEs of melena, 6 of ischemic colitis, 2 of hemorrhagic colitis, one of GI hemorrhage, and one of hemorrhagic diarrhea. The CIOMS reports for these gastrointestinal AEs were reviewed. Four SAEs of melena were described without further clinical information and were judged as mild. Three SAEs of melena were in subjects who developed severe diarrhea that progressed to bloody stools. In one SAE of melena, the patient was actually diagnosed with ischemic colitis. The remaining SAEs of melena were confounded by the use of multiple oral antibiotics (N=1) or did not contain sufficient information for interpretation (N=3).

All of the patients with serious AEs reported as ischemic colitis, hemorrhagic diarrhea, and hemorrhagic colitis were described as abdominal pain and diarrhea. Two subjects had endoscopies that revealed inflammation of the large intestine wall; a third subject had an ultrasound showing inflammation of the large intestine wall. These procedures showed evidence of colitis, but subjects were not definitively diagnosed with ischemic colitis. Two subjects were admitted, placed on intravenous fluids, and were not permitted to take anything by mouth. Another patient refused hospitalization. Because of the seriousness of these cases, DAVP recommended that “colitis” be included in the postmarketing experience section of the package insert.

The Applicant has agreed to inclusion of vomiting, bloody diarrhea, melena, and colitis under the heading of gastrointestinal disorders in Section 6.2 Postmarketing Experience section of the baloxavir marboxil package insert.

Neuropsychiatric events are included in the WARNING AND PRECAUTIONS section of the Tamiflu® package insert. Although influenza can be associated with neurologic and behavioral symptoms such as hallucinations, delirium, and abnormal behavior, neuropsychiatric adverse events were included in the Tamiflu (oseltamivir) package insert because of a high number postmarketing reports of delirium and abnormal behavior. The neuropsychiatric AEs were primarily reported in pediatric and adolescent patients, and the majority of reports were from Japan. While the incidence of neuropsychiatric AEs after oseltamivir cannot be calculated from the postmarketing AE reports and these reports do not prove causality, the number of reports were concerning. Neuropsychiatric AEs associated with oseltamivir were from October 1999 to August 2012 were reported in the British Medical Journal<sup>4</sup>. During the time period covered in this report, there were 980 reports of abnormal behavior, 317 of delirium, and 477 of hallucination associated with oseltamivir use. As a result of the concern about neuropsychiatric AEs with oseltamivir, the Japanese regulatory authorities advise against prescribing oseltamivir in adolescents aged 10 to 19 years. Because of the perceived risk of neuropsychiatric adverse events with oseltamivir, it is important to analyze the postmarketing neuropsychiatric adverse events reported with baloxavir marboxil. In addition, the Applicant has proposed an

(b) (4)

Among the postmarketing adverse events reported to this sNDA, there were a total of 129 AEs in the SOC, psychiatric disorders, including 26 serious AEs, and 234 AEs in the SOC, Nervous System disorders, including 67 serious adverse events. Of these, there were 43 AEs of abnormal behavior including 13 SAEs, 5 reports of delirium all of which were SAEs, and 29 reports of hallucinations (preferred terms of hallucination, auditory hallucination, visual

hallucination, and mixed hallucination) including 5 serious reports. All of these AE reports were from Japan. Patient age was provided for 25 of the AE reports for abnormal behavior, hallucinations, and delirium and ranged from 4 years to 85 years of age. Eighteen of these AEs were reported in pediatric patients. Due to the seriousness of these reports and the association of neuropsychiatric AEs with oseltamivir, DAVP recommended inclusion of delirium, abnormal behavior, and hallucinations in the postmarketing section of the baloxavir marboxil package insert. The Applicant has agreed to include psychiatric adverse events in the postmarketing experience section of the package insert; including delirium, abnormal behavior, and hallucinations.

In the SOC Musculoskeletal and Connective Tissue Disorders, there were 17 serious adverse events of rhabdomyolysis. Because all of these reports were serious, DAVP initially proposed including rhabdomyolysis in the postmarketing experience section. Review of the requested CIOMS reports for serious AEs of rhabdomyolysis, determined that there was sufficient information to confirm the diagnosis of rhabdomyolysis in only five of the 17 cases. Most of these reports were either confounded by pre-existing symptoms (N=2), concomitant medications (N=1), or concomitant/pre-existing illnesses (N=3) or contained too little information for confirmation of the diagnosis (N=6). However, because rhabdomyolysis can be observed with viral infections and because there was no clear excess of cases, DAVP agreed not to include rhabdomyolysis in the package insert at this time.

There were 20 postmarketing AE reports of pregnancy. None of these reports included information on pregnancy outcome. No pregnancies have been reported in clinical trials of baloxavir marboxil. Therefore, there are currently no clinical data to guide the use of baloxavir marboxil during pregnancy.

#### *Anaphylaxis, Hypersensitivity, and Related Adverse Events*

The Applicant searched all clinical trial safety data using the SMQ, hypersensitivity. This SMQ was designed retrieve all types of cases of drug-related adverse reactions that are possibly related to hypersensitivity/allergic reactions. It is intended to be a broader search term than specific SMQs of anaphylactic reaction and angioedema. [ICH, Introductory Guide for Standardized MedDRA Queries (SMQs) Version 16.0; [https://www.meddra.org/sites/default/files/guidance/file/smq\\_intguide\\_16\\_0\\_english.pdf](https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_16_0_english.pdf)]. The hypersensitivity SMQ includes more than 75 different preferred terms (PTs) for adverse events including 18 different preferred terms for angioedema, 22 preferred terms that include anaphylactic/anaphylaxis in the name of the PT, and 37 PTs for different types of urticaria. (<http://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=20000214>).

A total of 52 hypersensitivity adverse events in subjects who received baloxavir were identified in the Applicant's clinical trials database. Nineteen of these hypersensitivity AEs (reported in 18 subjects) occurred with 2 days of administration of baloxavir marboxil, and thus were temporally related to baloxavir marboxil and more likely to be have a causal relationship with baloxavir marboxil. None of these 19 hypersensitivity AEs was a serious adverse event; all were assessed as Grade 1 or Grade 2 intensity. However, all 19 of these AEs were mild or moderate, and there were no reports of more serious allergic type AEs such as anaphylaxis, hypersensitivity reaction, or angioedema.

The Applicant also searched postmarketing data using the MedDRA Standardized MedDRA query (SMQ), hypersensitivity. A total of 285 hypersensitivity adverse events were identified in the database search. This included 217 non-serious events and 68 serious events. The

serious postmarketing hypersensitivity AEs reported from the Roche Safety Database search are listed in the following table.

**Table 21: Postmarketing Reports of Serious Adverse Events for Baloxavir Marboxil in the MedDRA SMQ “Hypersensitivity”**

<b>Serious Adverse Event</b>	<b>Number of Serious Adverse Events</b>
Anaphylactic reaction	15
Anaphylactic shock	10
Erythema multiforme	7
Shock	5
Drug eruption	5
Anaphylactoid reaction	4
Urticaria	3
Facial swelling	2
Stevens-Johnson syndrome	2
Interstitial lung disease	2
Shock syndrome	1
Acute respiratory failure	1
Asthma	1
Pneumonitis	1
Respiratory arrest	1
Respiratory failure	1
Gastrointestinal edema	1
Acute generalized exanthematous Pustulosis	1
Angioedema	1
Eczema	1
Erythema	1
Rash	1
Generalized rash	1

Source: sNDA 218054/001, SUR, Table 4, pages 32-33

The Applicant analyzed the serious AEs reported in the System Organ Class, Immune System Disorders, for evidence of a causal association between baloxavir marboxil and anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, or drug hypersensitivity. Serious adverse events in Immune System Disorders were anaphylactic reaction (N=15), anaphylactic shock (N=10), and anaphylactoid reaction (N=4). The criteria used by the Applicant to identify a causal association between each SAE in this class and baloxavir marboxil were 1) fulfillment of Samson’s criteria for anaphylaxis, 2) occurrence within 2 days of receipt of baloxavir marboxil, 3) sufficient information to permit assessment of the AE, and 4) AE was not confounded by concomitant medication or concurrent illness. Samson’s criteria to define anaphylaxis were developed at the second National Institute of Allergy and Infectious Disease / Food Allergy and Anaphylaxis Network Symposium.<sup>5</sup> Sampson’s criteria state that anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset (minutes to hours) with involvement of skin, mucosal tissue or both plus either:
  - a. respiratory compromise or
  - b. reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly (minutes to hours) after exposure to a likely allergen:
  - a. Involvement of the skin-mucosal tissue
  - b. Respiratory compromise
  - c. Reduced blood pressure or associated symptoms, such as syncope or hypotonia
  - d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure after known allergen for that patient.

Of the 29 serious adverse events reported as Immune System Disorders, the Applicant identified five cases that met their criteria for a causal association with baloxavir. Some SAEs had more than one reason for not being included in the analysis, reasons for exclusion included insufficient information provided (N=16), AE occurred more than 2 days of baloxavir treatment (N=8), AE confounded by concomitant medication or illness (N=4) and did not meet Samson's criteria for anaphylaxis (N=4). The five serious adverse events that met the Applicant's criteria for anaphylaxis associated with baloxavir marboxil are described in the following table.

**Table 22: Serious Postmarketing Adverse Event Reports of Anaphylaxis Causally Associated with Baloxavir (Applicant Analysis)**

Age (Yrs.)	Sex	Onset*	Diagnosis on Report	Symptoms
7	M	< 2 hrs.	Anaphylactic reaction	Swelling of eyelids, generalized urticaria, vomiting
7	M	2 hrs.	Anaphylactic reaction	Generalized urticaria, pruritus, abdominal pain
36	F	10 mins	Anaphylactic shock	Eye swelling, generalized pruritus, loss of consciousness, vomiting
27	F	Same day	Anaphylactic shock	Redness and swelling of eyes, skin eruption, dyspnea, diarrhea, and loss of consciousness, abdominal pain
29	F	<1 hr.	Anaphylactoid reaction	Dyspnea, urticaria on trunk and legs, generalized itching

\*Onset is time since ingestion of baloxavir marboxil  
Source: sNDA 218054/001, SUR, text, pages 34-35

Four patients were described as recovered or recovering; the outcome for one patient (27-year-old with anaphylactic shock) was not provided.

Four of the 29 patients with serious adverse reactions in the Immune System Disorders SOC did not meet Samson's criteria and are not included in Table 22 but were categorized by the Applicant as hypersensitivity or allergic reactions. The SAEs reported for these patients are described in the following table. The Applicant stated that these adverse reactions were potentially related to the use of baloxavir marboxil.

**Table 23: Serious Postmarketing Adverse Event Reports of Hypersensitivity Reactions or Allergic Reactions (Applicant Analysis)**

Age (Yrs.)	Sex	Onset*	Diagnosis on Report	Symptoms
21	M	3.5 hrs.	Anaphylactic reaction	Flushed face, lip swelling, skin eruption, generalized pruritus
40	F	< 1 hr.	Anaphylactic shock	Pain in mouth and pharynx,

				conjunctival hyperemia, pruritus, rash, urticaria
25	F	2 hrs.	Anaphylactic shock	Face swelling, throat swelling, difficulty vocalizing
47	F	30 mins	Anaphylactic shock	Pruritus, redness on face, upper limbs and chest, teary eyes, hoarseness, hypotension (BP not provided)

\*Onset is time since ingestion of baloxavir marboxil

Source: sNDA 218054/001, SUR, text, page 35

The case describing the 47-year-old patient with hypotension was not included by the Applicant as an anaphylactic reaction because the blood pressure reading was not provided. Of note, that patient required fluid resuscitation and was hospitalized for four days, so an anaphylactic reaction seems likely. Three of the subjects recovered from the SAE; the outcome was not provided for the fourth patient.

The Applicant identified five serious adverse events of anaphylactic reaction, anaphylactic shock, or anaphylactoid reactions and four SAEs of hypersensitivity reactions which they considered causally related to baloxavir marboxil. These nine adverse events were identified using strict criteria including temporal relationship to receipt of baloxavir, lack of other possible cause, and the availability of sufficient documentation. The association of baloxavir marboxil with these nine serious adverse events is clearly documented; DAVP and the Applicant agreed that serious allergic reactions such as anaphylaxis should be included in the baloxavir marboxil package insert. DAVP and the Applicant agree to the addition of Section 5.1, Hypersensitivity to the WARNINGS AND PRECAUTIONS section of the Xofluza package insert to describe the possibility of anaphylaxis, urticaria, angioedema, and erythema multiforme with baloxavir marboxil. Section 6.2, Postmarketing Experience of 6 ADVERSE REACTIONS will include adverse events reported in the “Body as a Whole: Swelling of the face, eyelids or tongue, dysphonia, angioedema, anaphylactic reactions, anaphylactic shock, anaphylactoid reactions.”

The Office of Surveillance and Epidemiology (OSE) reviewed the FDA’s Adverse Event Reporting System (FAERS) and the scientific literature for reports of anaphylaxis or angioedema associated with baloxavir marboxil. OSE reviewers also analyzed the Safety Update Report provided by the Applicant. The FAERS search identified 12 cases of anaphylaxis. All 12 cases were serious adverse events; 5 of these cases had a probable association with baloxavir marboxil and 7 had a possible association. The OSE FAERS search also identified 12 cases of angioedema; all 12 were serious. Two cases of angioedema were judged as having a probable association with baloxavir marboxil and 10 as having a possible association. OSE agreed with DAVP’s decision to add anaphylaxis and angioedema to the WARNINGS AND PRECAUTIONS section of the Xofluza package insert.

The Applicant also assessed postmarketing reports using the SMQ of angioedema. This SMQ is a subset of the SMQ of hypersensitivity. A total of 73 adverse events were reported in 64 patients; seven adverse events were serious AEs. According to the Applicant, only one SAE could be included in their analysis because four were confounded and one had insufficient information. This single case along with six cases that were non-serious are discussed in the following table. Although six of the cases are not serious, they are included in the table because of the need for treatment with steroids, the need for hospitalization, or concerning symptoms such as difficulty breathing.

**Table 24: Postmarketing Adverse Event Reports of Angioedema**

Age (Yrs.)	Sex	Onset*	Serious Adverse Event	Symptoms
40	F	< 24 hrs.	Yes	Generalized urticaria, facial edema, hospitalized and treated with steroids
7	F	< 1 hr.	No	Face edema, pharyngeal edema, dyspnea, unable to swallow medications, hospitalized and treated with steroids
17	M	< 2 hrs.	No	Mild dyspnea, swelling of eyelid and lips, erythema of lips, slight difficulty breathing
60	F	2 hrs.	No	Urticaria, oropharyngeal swelling, dysphonia, treated with steroids and antihistamine
74	M	4 hrs.	No	Face edema, pharyngeal edema, treated with steroids and antihistamines
39	F	2 hrs.	No	Eyelid edema, urticaria on trunk, pruritus, treated with steroids and antihistamines
38	M	40 mins	No	Facial swelling, urticaria,

\*Onset is time since ingestion of baloxavir marboxil

Source: sNDA 218054/001, SUR, text, pages 36, 40-41

Seven postmarketing adverse event reports of angioedema were identified; these AEs are clearly related to baloxavir marboxil because of the temporal relationship, the lack of other possible explanation for angioedema, and the availability of sufficient information for the AE. It is unclear why only one of the AEs was considered serious, because two patients were hospitalized. In addition, it is concerning that four patients had airway involvement, and that five had treatment with steroids documented. The Applicant agreed to include angioedema in the WARNING AND PRECAUTIONS section and Postmarketing Experience section of the baloxavir marboxil package insert.

The SMQ hypersensitivity also identifies all adverse events for rashes. There were 75 AEs for rash and generalized rash, 14 AEs of pruritus and pruritic rash, and 41 AEs of urticaria reported in the postmarketing database. These 41 patients include the patients with urticaria as part of anaphylaxis, a hypersensitivity reaction, or angioedema that were previously discussed in this review. Sixty patients had rash with no other associated events. The Applicant notes that the majority of rashes and pruritic rashes occurred within 2 days after baloxavir marboxil treatment. Most of the rashes and pruritic rashes resolved spontaneously. Urticaria typically appeared within 24 hours of receiving baloxavir marboxil. Of the patients with rash, pruritic rash, or urticaria, five had serious adverse events; two with rash and three with urticaria. Both SAEs for rash were reported in elderly patients but one SAE was confounded, and the other SAE report contained insufficient information. Two of the SAE reports of urticaria were considered confounded and the third subject with a serious AE of urticaria also had facial edema and is described in the previous table. Postmarketing reports reveal multiple adverse events of rash and urticaria that are temporally related to receipt of baloxavir. Because of the sizeable number of rash and urticaria adverse event reports; urticaria will be added to the WARNINGS AND PRECAUTIONS section because it was reported in association with anaphylaxis or angioedema. Additionally, both rash and urticaria will be added to the Postmarketing Section of the baloxavir marboxil label.

When the Roche Safety Database was searched using the hypersensitivity SMQ, 15 serious cutaneous reactions were identified. This included erythema multiforme (N=7), drug eruption (N=5), Stevens-Johnson syndrome (N=2), and acute generalized exanthematous pustulosis (N=1). According to the Applicant, all adverse event reports for patients with erythema multiforme, drug eruption, and Stevens-Johnson were either confounded by concomitant medications or contained insufficient information to assess. Acute generalized exanthematous pustulosis (AGEP) is a rare skin reaction that is related to medication administration in 90% of cases. AGEP was reported in a 12-year-old male with a history of atopic dermatitis. He developed facial erythema; fever; and pruritus, erythema, and urticaria on his trunk and extremities on the same day he was treated with baloxavir marboxil. He was observed as an outpatient but required hospitalization on day 5 of symptoms due to decreased food intake and continued fever, urticaria, and erythema. On the day of hospitalization, he was noted to have an increased eosinophil count (17.5% percent with normal laboratory range of 0.2% to 8.4%). The patient then developed desquamation at an unspecified time later.

Because of the seriousness of erythema multiforme and Stevens-Johnson syndrome, the individual AE reports were reviewed for these patients.

- A female in her fifth decade of life was diagnosed with influenza A by rapid test and received a 20 mg dose of baloxavir. She was treated with a lower dose (20 mg) of baloxavir than recommended. Two days later, she developed a rash on her arms and was diagnosed with “erythema multiforme exudativum”. Her only concomitant medications were aspirin and tranexamic acid. No information on her past medical history, illness course, or outcome was provided. The rash completely resolved.
- A 64-year-old female with a negative rapid influenza test was diagnosed with influenza based on signs and symptoms. She was treated with a single 40 mg dose of baloxavir marboxil, vitamins, electrolytes, and tranexamic acid. She was diagnosed with “erythema multiforme exudativum” three days later. However, she visited the hospital one day after her erythema multiforme exudativum diagnosis and was told she had urticaria. She was treated with anti-allergy medication. At the time of the AE report, the erythema multiforme exudativum was improving. Her physician attributed the AE to baloxavir marboxil and dextromethorphan.
- A 7-year-old was started on amoxicillin for laryngobronchitis on (b) (6). Four days later he was diagnosed with influenza A by a rapid test and treated with a single 20 mg dose of baloxavir marboxil. He developed a rash on his face and body four days after receiving baloxavir marboxil and was diagnosed with “erythema multiforme exudativum”. He was hospitalized for treatment at a different hospital, and no further information was available. The reporting physician was uncertain whether erythema multiforme exudativum was due to amoxicillin or baloxavir marboxil.
- A 5-year-old male with cardiac disease was diagnosed with influenza A and treated with a single 20 mg dose of baloxavir marboxil. He was seen by a physician five days later and diagnosed with “erythema multiforme exudativum”. The erythema multiforme exudativum was not treated because of his underlying cardiac disease. No information about other medications or outcome was provided.
- An 80-year-old male was diagnosed with influenza B and treated with a single 40 mg dose of baloxavir, paracetamol, carbocisteine (a mucolytic), and ebastine (an antihistamine). Two days later he developed a rash and was seen by a dermatologist who diagnosed him with erythema multiforme. Three days after diagnosis with erythema multiforme, he was hospitalized for fever and difficulty walking. Follow-up and information regarding his past medical history and medications were not provided.

- A 60-year-old male was diagnosed with influenza and treated with an unknown dose of baloxavir and antipyretics. He developed a rash 2 days later. He was diagnosed with erythema multiforme by a dermatologist and treated with steroids and anti-allergy medication. No information about his past medical history or medications was provided.
- A male in his seventh decade was treated with baloxavir (unknown dose, unknown date, and unknown concomitant medications) and developed a rash on the same day. He was diagnosed with erythema multiforme by his physician. No other information was provided.

In all seven AE reports, erythema multiforme was temporally related to receipt of baloxavir marboxil. The diagnosis of erythema multiforme was made by a physician (not reported to be a dermatologist) in six cases and by a dermatologist in at least two cases. Four of AEs were judged as possibly related to baloxavir marboxil, one was judged as related to baloxavir marboxil or amoxicillin, one as related to baloxavir marboxil or dextromethorphan, and one as not related to baloxavir marboxil. In addition, two were diagnosed as “erythema multiforme exudativum”, a term which suggests a more serious disease (e.g. Stevens-Johnson Syndrome or similar serious skin reaction). None of the AE reports contained information on the patient’s past medical history or what other medications the patients were taking at the time of diagnosis; therefore, these cases were not included in the Applicant’s analysis. The Applicant agreed to include erythema multiforme in both the WARNINGS AND PRECAUTIONS and in the ADVERSE REACTIONS/Postmarketing Experience sections of the Xofluza package insert.

There were two adverse event reports for Stevens-Johnson syndrome (SJS). The first patient was a 47-year-old female who was treated with a single 40 mg dose of baloxavir for influenza A. She developed a rash on her face and trunk three days later. On the following day, the rash was generalized, and she had swelling of her ocular mucosa. She was diagnosed with Stevens-Johnson syndrome by a dermatologist, admitted to the hospital and treated with steroids. The second patient was a 58-year-old female who was treated with a single 40 mg dose of baloxavir for influenza and developed a rash one hour later. She returned to the hospital was diagnosed with Stevens Johnson syndrome, and was treated with steroids. No additional information was provided. No past medical history was provided for either patient. Although there were only two reports of Stevens-Johnson syndrome; this condition is rare but can be fatal. Therefore, DAVP initially recommended inclusion of Stevens-Johnson syndrome in the Warnings and Precaution section of the package insert. However, the Applicant did not agree with the inclusion of Stevens-Johnson syndrome in the package insert because the two AE reports were “poorly documented” without diagnostic confirmation and neither case had skin peeling. OSE was consulted to determine if more cases of SJS were reported in FAERS. OSE confirmed that no additional SJS cases have been reported to date, and DAVP agreed with the Applicant not to include SJS in the package insert at this time.

The mechanism of anaphylaxis with baloxavir marboxil is not known. The Division of Applied Regulatory Science (DARS) was consulted regarding possible mechanisms and to recommend studies that might provide additional information on the mechanism of or risk factors for anaphylaxis or hypersensitivity with baloxavir marboxil. Reviewers from DARS conducted molecular similarity analysis but did not identify structural motifs or similarities with other drugs known to cause hypersensitivity reactions. The allergic reactions reported with baloxavir marboxil could be mediated through IgE or non-IgE pathways. The DARS consult stated that laboratory studies can be conducted to test baloxavir marboxil for activation of mast cells and basophils. However, the DARS reviewer noted that the incidence of anaphylaxis and hypersensitivity reactions was too low to conduct a clinical trial to study the mechanism. However, they recommended that the Applicant further evaluate patients who do have

anaphylactic reactions to specifically investigate the role of classic IgE pathways and possible MRGPRX2 receptor polymorphisms in these patients. The Applicant should also consider obtaining HLA typing in patients who experience anaphylaxis. The Division has asked the Applicant to assess all possible cases of anaphylaxis or hypersensitivity that occur in a clinical trial or other situation in which the patient can be examined, and blood can be drawn in a timely fashion.

### **Safety Summary**

The safety analysis of this supplemental BLA was based the results of Trial T0832, postmarketing safety reports, and consults from DMEPA and OSE. The safety results from Trial T0832 are consistent with safety results from the pivotal trials of baloxavir marboxil that are described in the package insert. Minor revisions were made to Section 6.1, Clinical Trials Experience, of the package insert. However, multiple serious cases of anaphylaxis and angioedema were identified in postmarketing reports for baloxavir marboxil. A causal association with baloxavir marboxil was identified by the Applicant for 5 reports of anaphylaxis and 7 reports of angioedema. DAVP and the Applicant have agreed to the addition of Section 5.1, Hypersensitivity to the WARNINGS AND PRECAUTIONS section of the package insert. This subsection will state that anaphylaxis, urticaria, angioedema, and erythema multiforme have been reported in post-marketing experience. In addition, DAVP and the Applicant have agreed to revise the ADVERSE REACTIONS section of the Xofluza package insert to include a Postmarketing Experience subsection. Postmarketing cases of angioedema, anaphylaxis, erythema multiforme, and urticaria will be included in this section. Other adverse events reported postmarketing that will be added to the Postmarketing Experience subsection are gastrointestinal adverse events, which were commonly reported, and neuropsychiatric adverse events (abnormal behavior, hallucinations, and delirium), which have also been observed postmarketing with neuraminidase inhibitors. Overall, the findings in this clinical trial of subjects with health factors placing them at high risk of influenza complications are consistent with previously described adverse events observed with the use of baloxavir marboxil in otherwise healthy subjects with acute, uncomplicated influenza; and the safety concerns identified postmarketing, such as anaphylaxis and angioedema can be adequately described in baloxavir marboxil labeling to minimize any risks associated with baloxavir marboxil use.

### **9. Advisory Committee Meeting**

Not applicable.

### **10. Pediatrics**

This application contains pediatric data for subjects from 12 to < 18 years of age. This sNDA did not trigger PREA because it was not submitted for a new dosing regimen, a new dosage form, a new active ingredient, or a new route of administration. Note that initially, the Applicant proposed a new indication, i.e. Treatment of influenza in patients 12 years of age and older who have been symptomatic for more than 48 hours and are at high risk of developing influenza-related complications. However, DAVP determined that the indication remained the same, i.e. treatment of acute, uncomplicated influenza, but rather, the population was extended to patients at high risk for influenza complications. Therefore, PREA was not triggered by a new indication in this case.

### **11. Other Relevant Regulatory Issues**

No additional regulatory issues have been identified.

## 12. Baloxavir Marboxil Labeling

The baloxavir marboxil labeling has been updated to reflect changes in the indication, extending the population to subjects with health factors that place them at high risk of influenza related complications. The changes with this efficacy supplement primarily affected the following sections.

### 1 INDICATIONS AND USAGE

The indication was revised to include the treatment of patients with health factors that place them at high risk of influenza complications.

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 and who are:

- otherwise healthy, or
- at high risk of developing influenza-related complications<sup>1</sup> [see Clinical Studies (14.2)].

### 2 DOSAGE AND ADMINISTRATION

Table 1 was revised to prevent medication errors.

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

Patient Body Weight (kg)	Recommended Single Oral Dose
40 kg to less than 80 kg	Two 20 mg tablets taken at the same time for a total single dose of 40 mg (blister card contains two 20 mg tablets)
At least 80 kg	Two 40 mg tablets taken at the same time for a total single dose of 80 mg (blister card contains two 40 mg tablets)

### 4 CONTRAINDICATIONS

A sentence regarding serious allergic reactions was added because of the postmarketing reports of anaphylaxis, angioedema, and hypersensitivity reactions.

Serious allergic reactions have included anaphylaxis, angioedema, urticaria and erythema multiforme [see Warnings and Precautions (5.1)]

#### 5.1 WARNINGS AND PRECAUTIONS, Hypersensitivity

This section was added because of the serious postmarketing reports of anaphylaxis, urticaria, angioedema, and erythema multiforme.

Cases of anaphylaxis, urticaria, angioedema, and erythema multiforme have been reported in post-marketing experience with XOFLUZA. Appropriate treatment should be instituted if an allergic-like reaction occurs or is suspected. The use of XOFLUZA is contraindicated in patients with known hypersensitivity to XOFLUZA [see Contraindications (4) and Adverse Reactions (6.2)]

#### 6.1 Clinical Trials Experience

Safety results in trial T0832 were similar to those reported previously in the current baloxavir marboxil label. The number of subjects exposed to baloxavir marboxil and the age ranges of

the subjects were updated. Sinusitis was added to the table of adverse events occurring in at least 1% of subjects receiving Xofluza.

#### 6.2 Postmarketing Experience

This section was added and the following postmarketing adverse reactions were included based on postmarketing reports of serious adverse events.

*Body as a Whole:* Swelling of the face, eyelids or tongue, dysphonia, angioedema, anaphylactic reactions, anaphylactic shock, anaphylactoid reactions

*Skin and Subcutaneous Tissue Disorders:* Rash, urticaria, erythema multiforme

*Gastrointestinal disorders:* Vomiting, bloody diarrhea, melena, colitis

*Psychiatric:* Delirium, abnormal behavior, and hallucinations

#### 8.4 Pediatric Use

This section was revised to add information from Trial T0832.

##### *Treatment of Acute Uncomplicated Influenza in Pediatric Patients at High Risk for Influenza Complications*

The safety and effectiveness of XOFLUZA in pediatric patients 12 years of age and older weighing at least 40 kg who are at high risk of developing influenza-related complications is supported by extrapolation from a clinical trial in otherwise healthy adults and adolescents with acute uncomplicated influenza (Trial 2), and from one randomized, double-blind, phase 3 controlled trial in patients at high risk for influenza complications (Trial 3) in which 38 adolescents aged 12 to 17 years were randomized and received either XOFLUZA (N=21) or placebo (N=17). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years who were infected with influenza was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively) [see *Clinical Studies (14.2)*]. Adverse events reported in adolescents were similar to those reported in adults [see *Adverse Reactions (6.1)*].

#### 8.5 Geriatric Use

This section was revised to add the results of Trial T0832. The revisions included the number of subjects 65 years of age and older (N=209) who received baloxavir marboxil in T0832 and to provide information on both the efficacy and safety of baloxavir marboxil. Revisions included the following.

The median time to improvement of influenza symptoms in subjects 65 years of age and older was 70 hours in subjects who received XOFLUZA (N=112) and 88 hours in those who received placebo (N=102). The safety profile observed for this population was similar to that reported in the overall trial population except for nausea, which was reported in 6% of elderly subjects compared to 1% of subjects from 18 to 64 years of age.

#### 10. OVERDOSE

This section was revised to remove the statement that there have been no reports of Xofluza overdoses.

#### 14 Clinical Studies

The Clinical Trials section of the package insert was revised to update the section describing efficacy in otherwise healthy subjects and to add a section on efficacy in high-risk subjects in Trial 0832.

#### 14.1 Treatment of acute, uncomplicated influenza in otherwise healthy subjects

Revisions were made in this section to clarify the difference in the numbers of subjects randomized and those with influenza.

#### 14.2 Treatment of acute, uncomplicated influenza in otherwise healthy subjects

This section was added to describe the results of Trial T0832. The section includes descriptions of the trial designs, study population, and demographics. The high-risk factors for influenza complications were revised. The results for the primary endpoint were included as were the results for the subgroup of adolescents and for the secondary endpoint, efficacy of baloxavir marboxil compared to oseltamivir. The results for efficacy against influenza B in T0832 were also included in the package insert. (b) (4)

The following labeling information was agreed upon with the Applicant:

Trial 3 (NCT02949011) was a randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy and safety of a single oral dose of XOFLUZA compared with placebo or oseltamivir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza-related complications.

A total of 2,182 subjects with signs and symptoms of influenza were randomized to receive a single oral dose of 40 mg or 80 mg of XOFLUZA according to body weight (subjects who weighed 40 to less than 80 kg received 40 mg and subjects who weighed 80 kg and above received 80 mg) (N=729), oseltamivir 75 mg twice daily for 5 days (N=725), or placebo (N=728). Twenty-eight percent of subjects were Asian, 59% were White, and 10% were Black or African American. The mean age was 52 years, and 3% of subjects were less than 18 years of age; 43% of subjects were male and 57% female.

High risk factors were based on the Centers for Disease Control definition<sup>1</sup> of health factors known to increase the risk of developing serious complications from influenza. The majority of subjects had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity, or were 65 years of age or older.

In Trial 3, (b) (4) of the 2,182 enrolled subjects had influenza confirmed by RT-PCR and were included in the efficacy analysis (XOFLUZA N=385 placebo N=385 or oseltamivir N=(b) (4)). Among subjects in whom only one type/subtype of influenza virus was identified, 50% were infected with subtype A/H3N2, 43% were infected with type B, and 7% were infected with subtype A/H1N1.

Eligible subjects had an axillary temperature of at least 38°C, at least one moderate or severe respiratory symptom (cough, nasal congestion, or sore throat), and at least one moderate or severe systemic symptom (headache, feverishness or chills, muscle or joint pain, or fatigue) and all were treated within 48 hours of symptom onset. Subjects participating in the trial were required to self-assess their influenza symptoms as “none”, “mild”, “moderate” or “severe” twice daily. A total of 215 subjects (19%) had pre-existing symptoms (cough, muscle or joint pain, or fatigue) associated with their underlying high-risk condition that were worsened due to influenza infection. The primary efficacy endpoint was time to improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). This endpoint included alleviation of new symptoms and improvement of any pre-

existing symptoms that had worsened due to influenza. A statistically significant improvement in the primary endpoint was observed for XOFLUZA when compared with placebo, see Table 7.

**Table 7 Time to Improvement of Symptoms After Single Dose in High Risk Subjects 12 Years of Age and Older with Acute Uncomplicated Influenza in Trial 3 (Median Hours)**

XOFLUZA 40/80 mg (95% CI <sup>a</sup> ) N=385	Placebo (95% CI <sup>a</sup> ) N=385
73 <sup>b</sup> (67, 85)	102 <sup>b</sup> (93, 113)

<sup>a</sup>CI: Confidence Interval

<sup>b</sup>XOFLUZA treatment resulted a significant reduction in Time to Improvement of Influenza Symptoms compared to placebo using Peto-Prentice's generalized Wilcoxon test (p-value: <0.001)

There was no statistically significant difference in the median time to improvement of influenza symptoms in the subjects who received XOFLUZA (73 hours) and those who received oseltamivir (81 hours). The median time to improvement of influenza symptoms in the limited number of adolescent subjects aged 12 to 17 years infected with influenza virus was similar for subjects who received XOFLUZA (188 hours) or placebo (191 hours) (N=13 and N=12, respectively).

For subjects infected with type B virus, the median time to improvement of influenza symptoms was 75 hours in the XOFLUZA group (95% CI: 67, 90) compared to 101 hours in the placebo group (95% CI: 83, 116).

### 13. Outstanding Issues

(b) (4) are currently ongoing.

### 14. Recommendations / Risk Benefit Assessment

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of baloxavir marboxil for the treatment of acute, uncomplicated influenza in patients who have health factors that place them at high risk of influenza complications and who have been symptomatic for 48 hours or less.

Throughout the review of this sNDA, no deficiencies that would preclude the approval were identified. Baloxavir marboxil was studied in a Phase 3, randomized, placebo- and active-controlled trial, in which 2,184 subjects with health factors placing them at increased risk of influenza complications were randomized to receive baloxavir marboxil, placebo, or oseltamivir. The trial enrolled subjects 12 years of age and older in North America/Europe, Asia, and the Southern Hemisphere. Subjects with acute, uncomplicated influenza, as diagnosed by RT-PCR were followed until alleviation or improvement of seven influenza symptoms.

The median time to improvement of influenza symptoms was shorter in subjects who received baloxavir marboxil (73 hours) compared to those who received placebo (N=102 hours) (p value <0.001). In addition, the results for the primary endpoint were supported by the results for secondary endpoints such as time to resolution of fever, time to improvement of systemic symptoms, and time to improvement of respiratory symptoms.

Efficacy results were also analyzed for subgroups that were either not represented or not well represented in the Phase 3 trial T0831, which was submitted in the original NDA. The median time to improvement of symptoms was shorter in subjects 65 years of age and older who received baloxavir marboxil compared to those who received placebo. This study enrolled a larger percentage of the study population in the United States, and efficacy was demonstrated in subjects in North America/Europe and in Asia. In addition, a larger percentage of subjects weighed 80 kg or more and received the baloxavir marboxil 80 mg dose. Efficacy was demonstrated in both subjects weighing < 80 kg and those weighing ≥ 80 kg.

The Applicant demonstrated an acceptable safety profile for baloxavir marboxil in patients 12 years of age and older with influenza who have health factors placing them at high risk of influenza complications. Baloxavir was generally safe and well tolerated in subjects enrolled in trial T0832. The only adverse events reported in at least 2% of subjects receiving baloxavir marboxil were diarrhea (3%), bronchitis (3%), nausea (3%), and sinusitis (2%). No deaths were reported, and serious adverse events were uncommon. No new safety concerns were identified in the trial, and Section 6.1 of the baloxavir marboxil package insert was revised to include safety information from T0832.

Postmarketing safety reports were provided from the U.S. and Japan and were reviewed with this supplement. Serious adverse events of anaphylaxis, angioedema, and hypersensitivity and urticaria have been reported. While there have been no deaths due to serious allergic reactions, the WARNINGS AND PRECAUTIONS section of the package insert was revised to include information on hypersensitivity reactions including anaphylaxis, urticaria, angioedema, and erythema multiforme. Although this safety finding is new, the risks are adequately described in the package insert. In addition, serious hypersensitivity reactions have been reported with the other anti-influenza antivirals approved in the U.S. Other safety concerns observed in review of postmarketing reports, such as neuropsychiatric adverse events and skin reactions, were added to a new postmarketing experience section of the package insert.

#### **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None

#### **Recommendation for Other Postmarketing Requirements and Commitments**

None

## 15. Clinical Investigator Disclosure Review Template for sNDA 22187/S-024

Submission Date(s): January 4, 2019  
 Applicant: Genentech, Incorporated  
 Product: Xofluza (baloxavir marboxil)

Reviewer: Melisse Baylor, MD  
 Date of Review: September 1, 2019  
 Covered Clinical Trial (Name and/or Number): 1602T0832

Was a list of clinical investigators provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <b>2,352</b>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <b>0</b>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <b>0</b>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <b>0</b> Significant payments of other sorts: <b>0</b> Proprietary interest in the product tested held by investigator: <b>0</b> Significant equity interest held by investigator in sponsor of covered study: <b>0</b>		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <b>0</b>		
Is an attachment provided with the reason? N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*.

## References

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/s/  
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CHRISTINE KIM  
10/16/2019 02:02:51 PM  
Signing on behalf of Melisse Baylor, MD

MARY E SINGER  
10/16/2019 02:11:12 PM  
I concur with Dr. Baylor's review and recommendations.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**PRODUCT QUALITY REVIEW(S)**

**Office of Lifecycle Drug Products  
Division of Post-Marketing Activities I  
Review of Chemistry, Manufacturing, and Controls**

**1. NDA Supplement Number: NDA 210-854/ S-001**

**2. Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	01/04/2019	01/04/2019	01/29/2019	11/04/2019	10/04/2019

**3. Provides For:** Fulfilling PMC 3503-7 and to seek an indication for the use of XOFLUZA to treat patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications.

**4. Review #: 1**

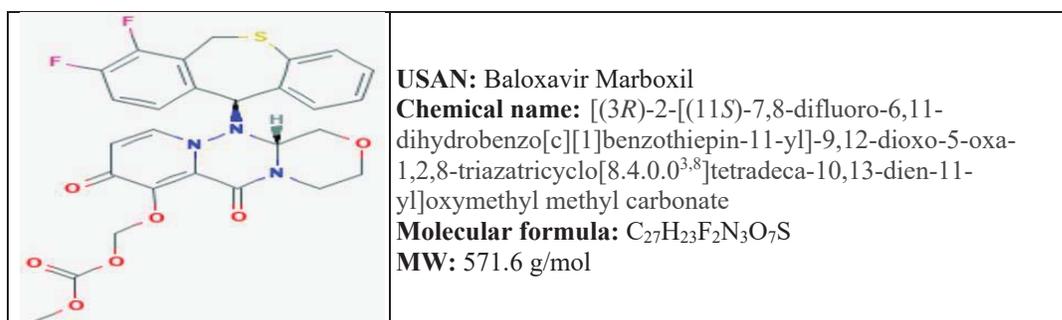
**5. Clinical Review Division: DAVP**

**6. Name and Address of Applicant:** Genentech Inc.  
1 DNA Way  
So. San Francisco, CA 94080

**7. Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Xofluza (Baloxavir Marboxil; S-033188; RO7191686)	Tablets	20 mg and 40 mg	Oral	Rx	No

**8. Chemical Name and Structure of Drug Substance:**



**9. Indication:** Treatment of influenza

**10. Supporting/Relating Documents:** None

**11. Consults:** None

**12. Executive Summary:** This Prior Approval Efficacy Supplement provides for fulfilment of the referenced PMC 3503-7 and to seek an indication for the use of XOFLUZA to treat patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications. The final study report and data from the pivotal study 1602T0832 are provided. The proposed U.S. Prescribing Information (USPI) draft documents including clean, redlined and annotated versions based on the efficacy and safety data from study 1602T0832 are provided.

The proposed labeling (Prescribing Information) does not include changes in the *CMC-related Sections 3, 11 or 16*. The request for Categorical Exclusion from preparation of Environmental Assessment (EA) is acceptable.

**13. Conclusions & Recommendations:**

This supplement is recommended for approval.

**14. Comments/Deficiencies to be Conveyed to Applicant:** None

**15. Primary Reviewer:**

Libaniel Rodriguez, Ph.D., CMC reviewer, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

**16. Secondary Reviewer:**

David Lewis, Ph.D., Branch Chief, Branch II, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

**I. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety:** Low.



Libaniel  
Rodriguez

Digitally signed by Libaniel Rodriguez  
Date: 10/04/2019 08:27:20AM  
GUID: 508da72000029f7c881e93501194d445



David  
Lewis

Digitally signed by David Lewis  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 210854

**Supplement #:** S-001

**Drug Name:** XOFLUZA™ (baloxavir marboxil, S-033188) 40 or 80 mg (b) (4)

**Indication(s):** For the treatment of acute uncomplicated influenza in patients at high risk of influenza complications who are 12 years of age and older who have been symptomatic for no more than 48 hours

**Applicant:** Genentech Inc.

**Date(s):** Date Submitted: 01-04-19  
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**Review Priority:** Standard

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## 1 EXECUTIVE SUMMARY

Genentech Inc. submitted this supplemental NDA for XOFLUZA™ (baloxavir marboxil, S-033188) based on a single dose of 40 or 80 mg (b) (4) for the treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications. This review will focus on the applicant's prospective, randomized, double-blind, placebo-controlled, phase 3 clinical trial (study 1602T0832) to evaluate the safety and efficacy of baloxavir marboxil for the proposed indication. This phase 3 trial was conducted primarily in Japan and the United States with additional sites in other Asian countries, Europe, and the Southern Hemisphere. Subjects with influenza A and/or B infection were randomized using 1:1:1 allocation to receive a single weight-based dose of 40 or 80 mg of baloxavir marboxil, oseltamivir 75 mg twice daily for five days or placebo.

The time to alleviation of symptoms (TTAS) was defined by the applicant as the time from the start of treatment to the alleviation of influenza symptoms (measured in hours) when all of the seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of approximately one day (at least 21.5 hours). The primary efficacy endpoint was the time to improvement of symptoms (TTIS), defined by the applicant as the time between the initiation of the study treatment and the time when all of a patient's influenza symptoms had been alleviated, maintained, or improved for a duration of at least 21.5 hours. The TTIS was similar to the TTAS except time to improvement could occur earlier than TTAS because symptoms could be moderate if they were severe at baseline and it would take longer for them to become mild or absent.

In the primary efficacy analysis comparing the distribution of TTIS in the baloxavir marboxil (n=385) and placebo (n=385) treated subjects who had a confirmed diagnosis of influenza virus infection at Day 1, a statistically significant difference was observed in favor of baloxavir marboxil over placebo ( $p < 0.001$ ). The median TTIS was 73 hours in baloxavir marboxil patients compared to 102 hours in placebo subjects with a median difference in TTIS between the two treatment groups of 21 hours. There was no statistically significant difference observed ( $p = 0.83$ ) in the secondary efficacy analysis comparing the TTIS in baloxavir marboxil and oseltamivir subjects (n=388) where the median TTIS in oseltamivir subjects was 81 hours.

The majority of subjects in the trials were infected with the type A/H3N2 and B strains of the influenza virus. There were far fewer subjects with the type A/H3N1 strain. A statistically significant difference in TTIS was observed between baloxavir marboxil and placebo subjects who were infected with Influenza A/H3N2 and B ( $p = 0.014$  in both subgroups) while there was no statistical significance between the TTIS in baloxavir marboxil and placebo subjects with type A/H1N1 strain ( $p = 0.11$ ).

## 2 INTRODUCTION

### 2.1 Overview

Baloxavir marboxil is an anti-influenza virus drug. This supplemental NDA was submitted to fulfill post-marketing commitment (PMC) 3503-7 entitled: “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.”

Subsequently in this review baloxavir marboxil will be referred to as baloxavir or S-033188. The applicant stated that they submitted this efficacy supplement to fulfill the above referenced PMC 3503-7 and to seek an indication for the use of baloxavir to treat patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications. In addition, the applicant noted that while Genentech, Inc. is the current Sponsor of the IND, study 1602T0832 was conducted and completed by Shionogi Inc. under IND 126653 prior to transfer from Shionogi Inc. to Genentech Inc.

There was one pivotal trial that was reviewed in this NDA. Study 1602T0832 (T0832) was conducted primarily in Japan and the United States with additional sites in APAC (including Australia, New Zealand, Philippines, and South Korea), 98 sites in Europe and 21 sites in South Africa.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
1602T0832	Phase 3, Randomized, Double-Blind Trial in Asia (mostly Japan), USA/Europe, Southern Hemisphere	One day for S-033188  Five days for oseltamivir	22 days	385 on S-033188 385 on Placebo 388 on Oseltamivir	Otherwise healthy patients 12 years of age and older with influenza who were symptomatic for no more than 48 hours

## 2.2 Data Sources

The application package is located at \\CDSESUB1\evsprod\NDA210854\0066.

Datasets are located in \\CDSESUB1\evsprod\NDA210854\0066\m5\datasets\cv40818.

The clinical study report is located in \\CDSESUB1\evsprod\NDA210854\0066\m5\53-clin-stud-rep\535-rep-effic-safety-stud\high-risk\5351-stud-rep-contr\cv40818.

The dataset called “adtte” contains data for the time to event endpoints including the primary efficacy endpoint. Other variables for baseline and demographic characteristics are in the adsl dataset.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

The applicant submitted SDTM, listing and analysis datasets along with define.pdf files and SAS programs used to analyze and create analysis datasets. The applicant’s submitted data were well-defined along with the summary tables and figures in the clinical study report. There were some discrepancies noticed with respect to consistently defining the censoring variable. The Analysis Data Reviewer’s Guides (ADRG) from the original NDA submission stated that the censored data was indicated as CNSR=0 which was true for the adtte dataset and the SAS program adtte.sas for T0821. However, for T0831 and T0832 and the ISE, time to event data were censored when CNSR=1. In response to the FDA Information Request dated July 6, 2018, the applicant confirmed this and confirmed that the primary analyses were correct for studies T0821, T0831 and the ISE and did not change based on the updated ADRGs.

The protocol and statistical analysis plan (SAP) and relevant analyses decisions were reviewed prior to unblinding of the trial. The statistics review of the amended protocol was finalized on April 19, 2018 while the statistics review of the SAP was completed on April 30, 2018. According to the applicant, the SAP was finalized on June 19, 2018 just prior to database unblinding on June 25, 2018.

### 3.2 Evaluation of Efficacy

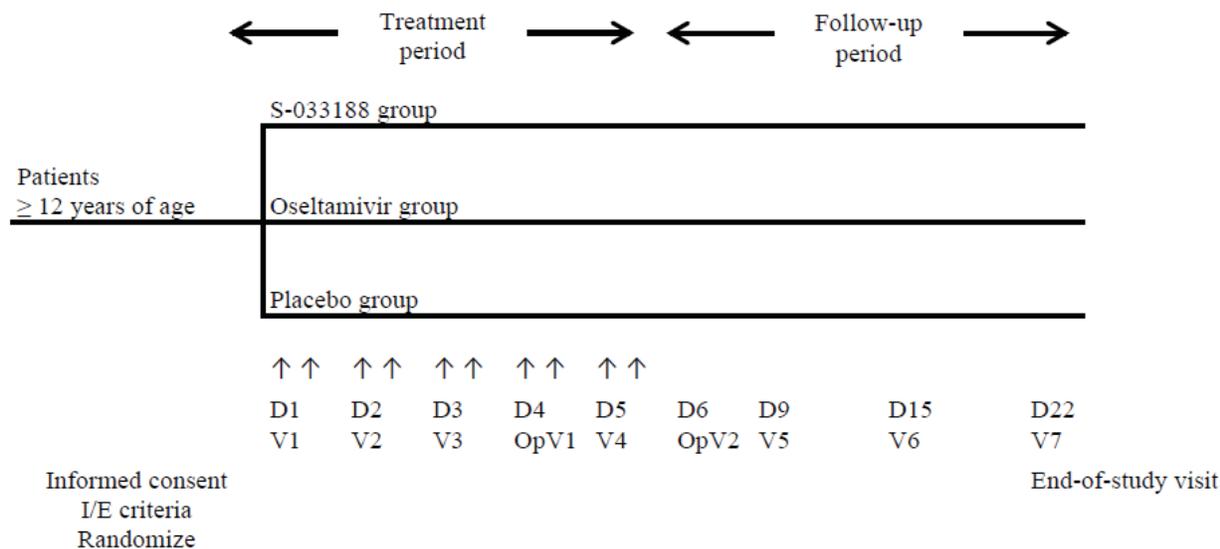
#### 3.2.1 Study Design and Endpoints

Note that the summary in Section 3.2.1 is either directly taken from the sponsor’s NDA or previous IND submissions, or paraphrased, unless otherwise specified.

T0831 was a randomized, phase 3, double-blind, multicenter trial in otherwise healthy patients with influenza in Japan and the United States. Subjects 12 years of age and older were

randomized in a 1:1:1 ratio to receive a single dose of 40 or 80 mg of S-033188 according to their weight category, 75 mg BID of oseltamivir for 5 days, or placebo. In order to achieve comparable exposure to the drug, patients who weighed < 80 kg at Screening received 40 mg of S-033188, and patients who weighed ≥ 80 kg at Screening received 80 mg of S-033188.

**Figure 1: Schematic Diagram**



D = day; I/E = inclusion/exclusion; OpV1 = optional Visit 1; OpV2 = optional Visit 2; S-033188 = baloxavir marboxil; V = visit

Up arrows demonstrate the administrations of study drug.

Source: Figure 9-1 of the Clinical Study Report

The applicant provided the following description of study blinding in Section 9.4.6 of the Clinical Study Report: “The study was conducted in a double-blind, double-dummy fashion by using placebo matching baloxavir marboxil and oseltamivir in appearance, labeling, and packaging. An interactive web response system (IWRS) was used for central patient randomization and study drug assignment. The IWRS assigned drug identifiers according to a randomization schedule. Only unblinded staff members of the contract research organization (CRO) or designee had the authority to assign the drug identifiers. All patients, investigators, study personnel, and data analysts were blinded to the treatment assigned at randomization until database lock. The randomization schedule was kept confidential and was not accessible to anyone until unblinding, except for Drug Supply Management staff, IWRS clinical coordinators, IWRS vendor staff, the unblinded statistician on the Data Safety Monitoring Board (DSMB), and Drug Safety personnel for reporting suspected unexpected serious adverse reactions (SUSARs), as required by local regulations.”

Randomization was stratified by

- Baseline composite symptom score ( $\leq 14$  or  $\geq 15$ )
- Pre-existing and worsened symptom (yes or no; if a patient had at least 1 of 3 symptoms [namely cough, muscle or joint pain, or fatigue] that was Pre-existing and worsened, the patients was assigned to the “Yes” category, otherwise “No”)
- Region (Asia, North America/Europe, Southern Hemisphere)
- Weight (< 80 kg or  $\geq 80$  kg)

The time to alleviation of symptoms (TTAS) was defined by the applicant as the time from the start of treatment to the alleviation of influenza symptoms (measured in hours) when all of the seven influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were assessed by the patient as 0 (None) or 1 (Mild) in the patient eDiary, for a duration of approximately one day (at least 21.5 hours).

The primary efficacy endpoint was the time to improvement of symptoms (TTIS), defined by the applicant as the time between the initiation of the study treatment and the time when all of a patient's influenza symptoms had been alleviated, maintained, or improved for a duration of at least 21.5 hours. The TTIS was similar to the TTAS for the majority of subjects. However, for a few subjects the time to improvement occurred earlier than the TTAS because symptoms could be moderate if they were severe at baseline and it would take longer for the symptoms to become mild or absent.

Patients with pre-existing symptoms (i.e., cough, fatigue, or muscle/joint pain that existed prior to developing influenza) that were judged by the patient to NOT be worse at baseline (i.e., the pre-dose examinations) must have had their baseline severity maintained. For example, severe at baseline to severe or less than severe post-baseline, moderate at baseline to moderate or less than moderate post-baseline, mild or absent at baseline to mild or absent post-baseline.

Secondary objectives of T0831 were

- to evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg daily (BID) for 5 days by measuring the TTIS in patients with uncomplicated influenza virus infection.
- to evaluate the efficacy of a single, oral dose of S-033188 compared with placebo by measuring the secondary endpoints in patients with uncomplicated influenza virus infection.
- to evaluate the efficacy of a single, oral dose of S-033188 compared with oseltamivir 75 mg BID for 5 days by measuring the secondary endpoints in patients with uncomplicated influenza virus infection.

### **3.2.2 Statistical Methodologies**

The Intent-to-Treat-Infected (ITTI) population was the primary efficacy analysis population that consisted of the patients who received the study drug with a confirmed diagnosis of influenza and were enrolled at sites with Good Clinical Practice (GCP) compliance. Confirmation of influenza was based on the results of the reverse transcription polymerase chain reaction (RT-PCR) test on Day 1. The population was analyzed according to the treatment to which the patients were randomized. The Safety population was the primary population used for analyses of adverse events and consisted of all randomized patients who received at least one dose of the study drug.

Kaplan-Meier plots, median survival time and 95% CI were obtained without stratification. Patients who did not experience improvement of symptoms were censored at the last observation time point. For the primary endpoint, if at least one of the seven influenza symptom scores (except for the pre-existing symptoms judged as ‘not worsened’ and ‘severe’ at baseline) were missing at the time of assessment, the missing assessment of influenza symptoms were to be treated conservatively as failures at the corresponding date and time of assessment. If influenza symptom scores were missing for the preexisting symptoms judged as ‘not worsened’ and ‘severe’ at baseline, these symptoms were not to be evaluated for assessment of the primary endpoint. For TTAS if at least one of the seven influenza symptom scores was missing but the date and time of assessment were recorded, this missing assessment was to be conservatively be treated as a moderate or severe symptom (as failures) at the corresponding date and time of assessment.

The Statistical Analysis Plan (SAP) pre-specified the Peto-Prentice version of the generalized Wilcoxon test as the primary analysis method. The reviewer used the Peto-Prentice Wilcoxon test for the primary analysis as this is the method of choice for most applicants, was pre-specified in the SAP, and unlike the Gehan Wilcoxon test, the Peto-Prentice Wilcoxon test does not assume that censoring rates are the same in each treatment group.

The reviewer also performed sensitivity analyses using the log rank and the Gehan and modified Peto-Prentice versions of the generalized Wilcoxon test. Note that the Peto-Prentice generalized Wilcoxon test is sometimes referred to as the Peto Wilcoxon or Peto test.

The applicant reported differences between the median TTIS obtained separately for each treatment group using the method by Brookmeyer and Crowley (1982) to calculate of the CIs for the quantiles (25<sup>th</sup> percentile, median and 75<sup>th</sup> percentile) in each treatment group. The applicant computed the difference of median times and the associated 95% CI using the bootstrap percentile method. In addition to the applicant’s approach, the reviewer used the Hodges-Lehmann estimator of the median of all pairwise treatment differences between subjects in the two treatment groups and the corresponding asymptotic 95% CI for the median treatment difference. In the reviewer’s analysis, censored values were set to the maximum follow-up time for efficacy of 14 days. This will be discussed in Section 5.1.

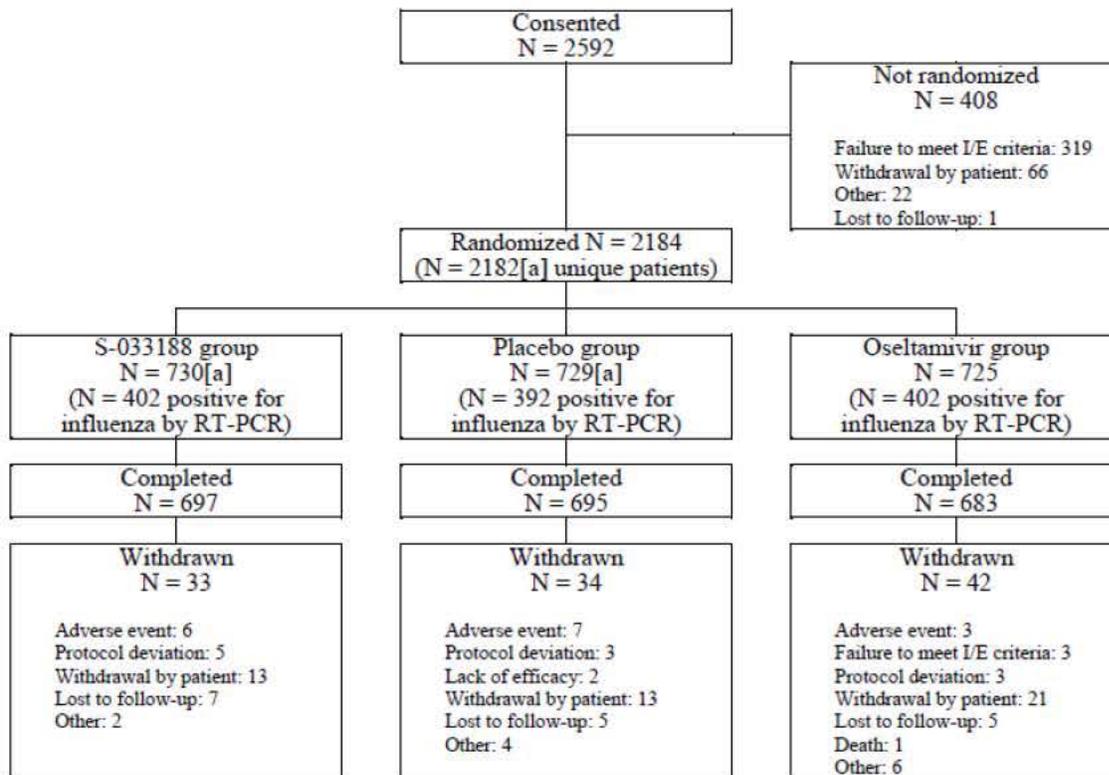
Numerous subgroup analyses were pre-specified by the applicant for primary and secondary endpoints without applying any statistical adjustments for multiplicity. Therefore, all subgroup analyses were considered to be exploratory and used to assess the robustness of the baloxavir treatment effect.

### **3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

In T0831, there were 2592 subjects who consented to participate in the study; 408 were not randomized mostly due to the 319 subjects who failed to meet the inclusion/exclusion criteria. The remaining 2184 subjects were randomized with 730 subjects randomized to the S-033188 treatment group, 729 randomized to the placebo treatment group and 725 randomized to the oseltamivir treatment group. A total of 33, 34, and 42 subjects respectively in the S-033188, placebo and oseltamivir treatment groups withdrew from the study prior to completion.

Withdrawal by the subject was the most prevalent reason for study discontinuation, followed by loss to follow-up, adverse events, protocol deviation, failure to meet inclusion/exclusion criteria, lack of efficacy, death and other reasons.

**Figure 2: Patient Disposition**



ID = identification; RT-PCR = reverse transcriptase-polymerase chain reaction

[a] Two patients were each assigned 2 patient IDs (1 patient was initially assigned ID (b) (6) [baloxavir marboxil group] and was re-assigned ID (b) (6) [oseltamivir group] before dosing and 1 patient was initially assigned ID (b) (6) [placebo group] and was re-assigned ID (b) (6) [oseltamivir group] before dosing); therefore, there were a total of 2182 unique patients (729 patients in the baloxavir marboxil group, 725 patients in the oseltamivir group, and 728 patients in the placebo group).

Source: Figure 10-1 of the Clinical Study Report

The applicant summarized baseline and demographic characteristics as shown below in Table 2. The number of subjects in each treatment arm in Table 2 was much smaller than the numbers shown above in the Disposition of Patients (Figure 2) because the former only included subjects who were in the ITT-I population while the latter included all randomized subjects regardless of whether or not they were confirmed to have influenza.

Age, height, weight and BMI appeared to be similar in the three treatment groups. Slightly more than half of the subjects in each treatment group were female. Approximately 405 of the subjects in each treatment group were from Asia, while approximately 55% of the subjects in each treatment group were from US/Europe while only 4-5% of the subjects in each treatment group were from the southern hemisphere. The majority of subjects (45-50%) in each treatment group were White, while slightly more than 40% of the subjects in each treatment group were Asian and 7.5-10% of the subjects in each treatment group were Black or African American. Approximately 15% of the subjects in each treatment arm were Hispanic or Latino.

Slightly more than 15% of the subjects in each treatment arm were smokers. There appeared to be similar composite symptom scores (CSS) and body temperatures in each treatment arm at baseline with approximately half of the CSS scores  $\leq 14$  and the remaining half  $\geq 15$ . The majority of subjects in the baloxavir and placebo treatment arms had influenza for >12 to 24 hours followed by subjects with influenza >24 to 36 hours while the opposite was true for the oseltamivir subjects. Based on the RT-PCR test, almost half of the subjects were diagnosed as having the influenza A/H3 subtype of the virus, followed by 38-44% of the subjects in each treatment group having influenza B and 4-9% of the subjects in each treatment group having the influenza A/H1N1 subtype. The percentage of subjects who received influenza vaccination ranged from 23% for the S-033188 arm to 27% in the oseltamivir treatment group.

**Table 2: Demographics and Baseline Characteristics (ITT-Infected population)**

		S-033188 N = 388 n (%)	Placebo N = 386 n (%)	Oseltamivir N = 389 n (%)
Age (years)	n	388	386	389
	Mean	52.3	51.9	51.1
	SD	16.8	16.7	17.0
	Min	12	12	12
	Median	55.0	53.0	53.0
	Max	84	86	89
	≥ 12 to ≤ 19	19 (4.9)	17 (4.4)	22 (5.7)
	≥ 20 to ≤ 29	29 (7.5)	22 (5.7)	27 (6.9)
	≥ 30 to ≤ 39	42 (10.8)	58 (15.0)	44 (11.3)
	≥ 40 to ≤ 49	63 (16.2)	55 (14.2)	75 (19.3)
	≥ 50 to ≤ 59	83 (21.4)	101 (26.2)	83 (21.3)
	≥ 60 to ≤ 64	39 (10.1)	30 (7.8)	35 (9.0)
	≥ 65 to ≤ 74	85 (21.9)	76 (19.7)	78 (20.1)
≥ 75	28 (7.2)	27 (7.0)	25 (6.4)	
Height (cm)	n	388	386	389
	Mean	165.80	165.51	165.52
	SD	9.68	10.05	9.98
	Min	121.9	130.4	135.0
	Median	166.00	165.00	165.10
	Max	185.4	193.0	191.0
Weight (kg)	n	388	386	389
	Mean	77.69	78.98	79.49
	SD	21.58	23.76	23.37
	Min	40.1	40.2	40.2
	Median	73.85	73.00	74.60
	Max	158.2	165.6	167.4
	< 80	239 (61.6)	232 (60.1)	233 (59.9)
≥ 80	149 (38.4)	154 (39.9)	156 (40.1)	
BMI (kg/m <sup>2</sup> )	n	388	386	389
	Mean	28.10	28.65	28.87
	SD	6.85	7.58	7.61
	Min	15.8	16.3	16.2
	Median	26.80	26.75	27.10
Sex	Max	51.6	58.6	58.0
	Male	193 (49.7)	180 (46.6)	191 (49.1)
	Female	195 (50.3)	206 (53.4)	198 (50.9)
Region	Asia	159 (41.0)	151 (39.1)	152 (39.1)
	North America/Europe	212 (54.6)	216 (56.0)	220 (56.6)
	Southern Hemisphere	17 (4.4)	19 (4.9)	17 (4.4)

		<b>S-033188</b> N = 388 n (%)	<b>Placebo</b> N = 386 n (%)	<b>Oseltamivir</b> N = 389 n (%)
Race	American Indian or Alaska Native	1 (0.3)	2 (0.5)	3 (0.8)
	Asian	167 (43.0)	157 (40.7)	163 (41.9)
	Black or African American	39 (10.1)	30 (7.8)	29 (7.5)
	White	178 (45.9)	194 (50.3)	188 (48.3)
	Other	3 (0.8)	3 (0.8)	6 (1.5)
Ethnicity	Hispanic or Latino	62 (16.0)	59 (15.3)	56 (14.4)
	Not Hispanic or Latino	325 (83.8)	327 (84.7)	331 (85.1)
	Not reported	1 (0.3)	0	1 (0.3)
	Unknown	0	0	1 (0.3)
Prior medication	Yes	329 (84.8)	336 (87.0)	329 (84.6)
	No	59 (15.2)	50 (13.0)	60 (15.4)
Prior procedure	Yes	3 (0.8)	7 (1.8)	2 (0.5)
	No	385 (99.2)	379 (98.2)	387 (99.5)
Medical history	Yes	379 (97.7)	381 (98.7)	382 (98.2)
	No	9 (2.3)	5 (1.3)	7 (1.8)
Smoking habits	Yes	59 (15.2)	58 (15.0)	66 (17.0)
	No	329 (84.8)	328 (85.0)	323 (83.0)
Meal before administration	Yes	246 (63.4)	234 (60.6)	248 (63.8)
	No	142 (36.6)	152 (39.4)	141 (36.2)
	Missing	0	0	0
Meal after administration	Yes	281 (72.4)	263 (68.1)	274 (70.4)
	No	105 (27.1)	120 (31.1)	112 (28.8)
	Missing	2 (0.5)	3 (0.8)	3 (0.8)
Duration between meal and administration (hours)	< 2	140 (36.1)	137 (35.5)	138 (35.5)
	≥ 2 to ≤ 4	112 (28.9)	87 (22.5)	98 (25.2)
	> 4	85 (21.9)	108 (28.0)	109 (28.0)
Composite symptom scores at baseline	n	388	386	389
	Mean	14.3	14.4	14.2
	SD	3.7	3.6	3.5
	Min	5	4	5
	Median	15.0	15.0	14.0
	Max	21	21	21
	≤ 14	188 (48.5)	188 (48.7)	201 (51.7)
	≥ 15	200 (51.5)	198 (51.3)	188 (48.3)

		<b>S-033188</b> <b>N = 388</b> <b>n (%)</b>	<b>Placebo</b> <b>N = 386</b> <b>n (%)</b>	<b>Oseltamivir</b> <b>N = 389</b> <b>n (%)</b>
Body temperature (degrees Celsius) at baseline	n	386	386	386
	Mean	38.40	38.42	38.40
	SD	0.42	0.44	0.42
	Min	36.9	37.0	37.2
	Median	38.30	38.30	38.30
	Max	40.5	40.3	40.3
Time to treatment from flu onset (hours)	≥ 0 to ≤ 12	27 (7.0)	42 (10.9)	37 (9.5)
	> 12 to ≤ 24	151 (38.9)	150 (38.9)	119 (30.6)
	> 24 to ≤ 36	114 (29.4)	120 (31.1)	141 (36.2)
	> 36 to ≤ 48	95 (24.5)	74 (19.2)	92 (23.7)
	Missing	1 (0.3)	0	0
Influenza virus subtype A by rapid influenza diagnostic test		179 (46.1)	171 (44.3)	204 (52.4)
	B	143 (36.9)	155 (40.2)	144 (37.0)
	A and B	6 (1.5)	3 (0.8)	0
	Negative	60 (15.5)	56 (14.5)	41 (10.5)
	Unknown	0	1 (0.3)	0
Influenza virus subtype based on RT-PCR	A/H1N1pdm	28 (7.2)	17 (4.4)	35 (9.0)
	A/H3	182 (46.9)	185 (47.9)	190 (48.8)
	B	167 (43.0)	168 (43.5)	149 (38.3)
	Mixed infection	4 (1.0)	5 (1.3)	5 (1.3)
	Other	7 (1.8)	11 (2.8)	10 (2.6)
	Negative	0	0	0
Influenza vaccination	Yes	91 (23.5)	99 (25.6)	104 (26.7)
	No	297 (76.5)	287 (74.4)	285 (73.3)
Influenza virus titer at baseline [log <sub>10</sub> (TCID <sub>50</sub> /mL)]	n	378	377	380
	Mean	4.96	5.27	5.25
	SD	2.28	2.39	2.27
	Min	0.7	0.7	0.7
	Median	5.20	6.00	5.70
	Max	10.0	9.5	9.7
Amount of influenza virus RNA at baseline [log <sub>10</sub> (virus particles/mL)]	n	385	378	387
	Mean	6.72	6.87	6.81
	SD	1.43	1.54	1.37

	S-033188 N = 388 n (%)	Placebo N = 386 n (%)	Oseltamivir N = 389 n (%)
Min	2.2	2.2	2.2
Median	7.00	7.30	7.00
Max	9.0	9.7	9.3

BMI = body mass index; ITTI = Intention-to-Treat Infected; Max = maximum; Min = minimum; RT-PCR = reverse transcription polymerase chain reaction; SD = standard deviation; TCID<sub>50</sub> = 50% tissue culture infective dose

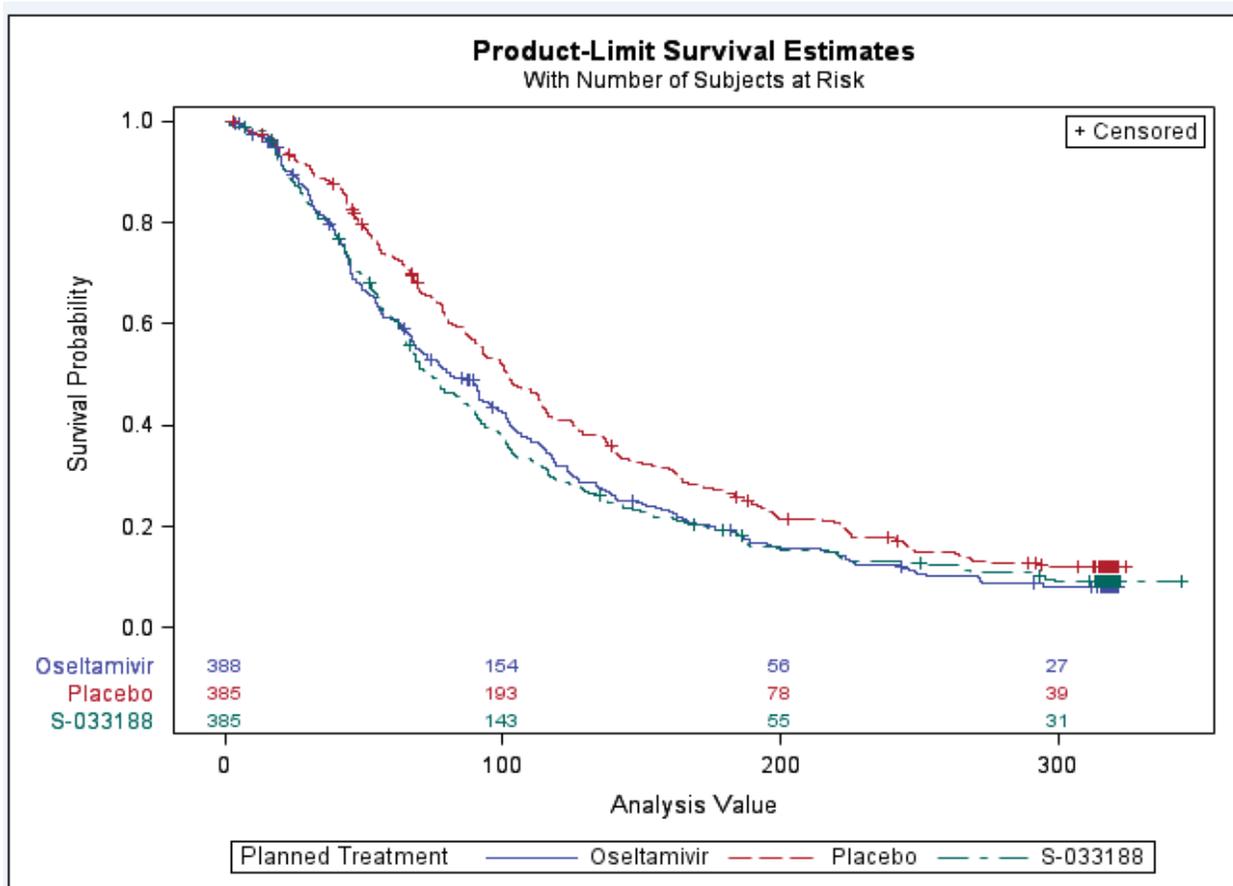
Source: Table 11-2 in the Clinical Study Report

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Results for Time to Improvement of Symptoms

As shown in the Kaplan-Meier plot below, influenza symptoms for the baloxavir and oseltamivir treatment groups improved more rapidly than for subjects in the placebo treatment arm.

**Figure 3: Kaplan-Meier plot for the Time to Improvement of Symptoms Study 1602T0832, ITT-Infected Population**



Source: Reviewer's analysis

Statistical significance between S-033188 and placebo was achieved for the primary analysis of time to improvement of symptoms [p<0.001 using the applicant’s pre-specified Peto Wilcoxon test (Table 3)]. The reviewer’s sensitivity analyses (p<0.001 using the modified Peto Wilcoxon and log rank tests and p=0.0046 using the Gehan Wilcoxon test) corroborated the findings.

**Table 3: Summary of Primary Efficacy and Sensitivity analyses**

Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	11.3369	1	0.0008
Wilcoxon	8.0168	1	0.0046
Peto	16.2849	1	<.0001
Modified Peto	16.0117	1	<.0001

Wilcoxon test refers to the Gehan generalized Wilcoxon test p-value was adjusted for

- composite symptom score at baseline ( $\leq 14, \geq 15$ ),
- pre-existing and worsening symptom (yes or no),
- region (Asia, North America/Europe, Southern Hemisphere)

Source: Reviewer’s analysis

As given in Table 4, median TTIS was 73 hours for the baloxavir treatment arm compared to 81 hours for the oseltamivir active control arm and 102 hours for the placebo subjects. The median difference, calculated by the reviewer, between TTIS in baloxavir and placebo subjects was 21 hours. The 25<sup>th</sup> percentiles of TTIS ranged from 43 hours for baloxavir subjects to 56 hours for placebo subjects while the 75<sup>th</sup> percentiles of TTIS ranged from 138 hours for baloxavir subjects to 188 hours for placebo subjects.

**Table 4: Median Time to Improvement of Symptoms**

Treatment Group	N	25 <sup>th</sup> Percentile (95% CI)	Median (95% CI)	75 <sup>th</sup> Percentile (95% CI)
S-033188	385	43 (38, 47)	73 (67, 85)	138 (118, 165)
Placebo	385	56 (50, 67)	102 (93, 113)	188 (164, 222)
Oseltamivir	388	43 (38, 45)	81 (69, 92)	143 (127, 169)
Placebo – S-0331888			21 (11, 32)*	

\*Hodges-Lehmann estimator and asymptotic 95% confidence interval

Source: Reviewer’s analysis

The applicant used stratified Peto-Prentice Wilcoxon and log-rank tests to compare the TTIS in baloxavir subjects with the TTIS in the placebo and active control arms and computed a difference between medians of baloxavir and placebo equal to 29 hours. The median difference calculated by the reviewer was 21 hours.

**Table 5: Applicant’s Analysis of Time to Improvement of Symptoms**

	<b>S-033188</b>	<b>Placebo</b>	<b>Oseltamivir</b>
<b>Summary statistics</b>			
- n	385	385	388
- Median (hours)	73.2	102.3	81.0
- 95% CI (hours)	67.2, 85.1	92.7, 113.1	69.4, 91.5
<b>Comparison with placebo</b>			
- Median difference (hours)	-29.1	---	---
- 95% CI for median difference (hours) [a]	-42.8, -14.6	---	---
- P-value derived from stratified generalized Wilcoxon test [b]	<.0001	---	---
- P-value derived from stratified log-rank test [b]	0.0008	---	---
<b>Comparison with oseltamivir</b>			
- Median difference (hours)	-7.7	---	---
- 95% CI for median difference (hours) [a]	-22.7, 7.9	---	---
- P-value derived from stratified generalized Wilcoxon test [b]	0.8347	---	---
- P-value derived from stratified log-rank test [b]	0.8449	---	---

CI = confidence interval; ITTI = Intention-to-Treat Infected

[a] Bootstrap estimates.

[b] Stratification factors: region, composite symptom scores at baseline, and preexisting and worsened symptom

Patients who did not experience improvement of symptoms were treated as censored at the last observation time point.

Subset of patients whose time to improvement of symptoms were not missing.

Source: Table 11-5 of the Clinical Study Report

Median time to alleviation of symptoms was only slightly smaller than time to improvement of symptoms in all three treatment arms. For most subjects the improvement of symptoms occurred at the same time when symptoms were alleviated. Only a few subjects had symptoms that were moderate when the symptoms were severe at baseline and it longer for these symptoms to become alleviated (i.e., mild or absent).

**Table 6: Median Time to Improvement vs. Alleviation of Symptoms**

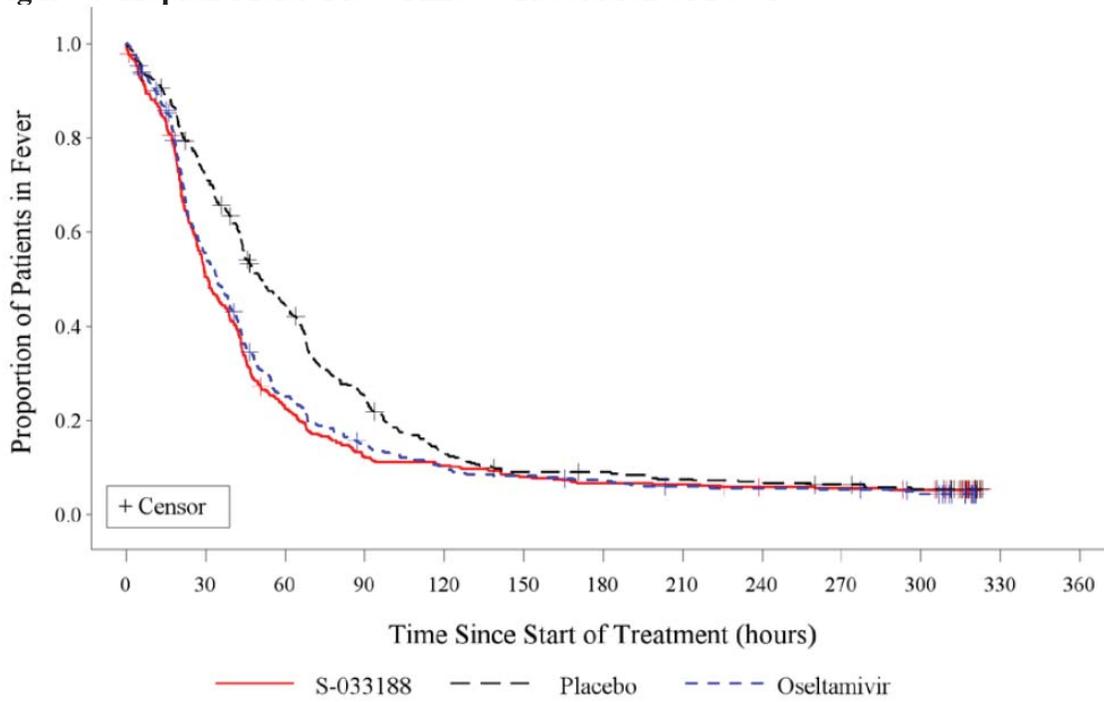
Treatment Group	N	Time to Improvement (hours)	Time to Alleviation (hours)
S-033188	385	73	77
Placebo	385	102	103
Oseltamivir	388	81	86

Source: Reviewer's analysis

### 3.2.4.2 Secondary efficacy results for Time to Resolution of Fever

The superiority of S-033188 compared to placebo was demonstrated for the secondary efficacy endpoint of time to resolution of fever ( $p < 0.001$ ). Although time to resolution of fever was found to be statistically significant, the findings could be confounded by many factors including time and the way it was measured, antipyretics and other NSAID use of patients.

**Figure 4: Kaplan-Meier Plot: Time to Resolution of Fever**



ITTI = Intention-to-Treat Infected

Patients who did not experience resolution of fever by the last observation time point were censored at that time point.

Subset of patients whose body temperature at baseline was more than 37 degrees.

Subset of patients whose time to resolution of fever was not missing.

Source: Figure 11-13 of the Clinical Study Report

The applicant computed median times to resolution of fever of 31 hours for subjects in the S-033188 treatment group, 34 hours for subjects in the oseltamivir active controls and 51 hours for subjects in the placebo treatment group.

**Table 7: Analysis of Time to Resolution of Fever**

	<b>S-033188</b>	<b>Placebo</b>	<b>Oseltamivir</b>
Summary statistics			
- n	380	385	383
- Median (hours)	30.8	50.7	34.3
- 95% CI (hours)	28.2, 35.4	44.6, 58.8	30.0, 38.9
Comparison with Placebo			
- Median difference (hours)	-19.8	---	---
- 95% CI for median difference (hours) [a]	-28.8, -12.5	---	---
- P-value derived from stratified generalized Wilcoxon test [b]	<.0001	---	---
Comparison with Oseltamivir			
- Median difference (hours)	-3.5	---	---
- 95% CI for median difference (hours) [a]	-9.1, 2.7	---	---
- P-value derived from stratified generalized Wilcoxon test [b]	0.2425	---	---

CI = confidence interval; ITTI = Intention-to-Treat Infected

[a] Bootstrap estimates.

[b] Stratification factors: region, composite symptom scores at baseline, and preexisting and worsened symptom

Patients whose body temperature was not resolved were treated as censored at the last observation time point.

Subset of patients whose body temperature at baseline was more than 37 degree.

Subset of patients whose time to resolution of fever was not missing.

Source: Table 11-34 of the Clinical Study Report

### 3.2.4.3 Secondary efficacy results for individual symptoms

The applicant's results for the individual seven symptoms that were included in the primary efficacy endpoint are shown below. With the exception of sore throat, comparisons of the TTIS between baloxavir and placebo using the Peto Wilcoxon test for each of the individual seven symptoms were all statistically significant. There were no statistically significant differences between baloxavir and oseltamivir for any of the seven individual symptoms.

**Table 8: Analyses of Time to Improvement of Individual Symptoms**

	S-033188	Placebo	Oseltamivir
<b>Cough</b>			
Summary statistics			
- n	314	312	317
- Median (hours)	47.3	70.4	47.5
- 95% CI (hours)	42.8, 52.7	56.5, 79.5	43.0, 55.4
Comparison with Placebo			
- Median difference (hours)	-23.1	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0009	---	---
Comparison with Oseltamivir			
- Median difference (hours)	-0.2	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.4074	---	---
<b>Sore Throat</b>			
Summary statistics			
- n	249	243	226
- Median (hours)	40.2	46.5	39.3
- 95% CI (hours)	32.4, 46.1	39.0, 53.5	30.1, 42.8
Comparison with Placebo			
- Median difference (hours)	-6.3	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.2496	---	---
Comparison with Oseltamivir			
- Median difference (hours)	0.9	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.2963	---	---

	<b>S-033188</b>	<b>Placebo</b>	<b>Oseltamivir</b>
- Median difference (hours)	2.0	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.7877	---	---
<b>Headache</b>			
Summary statistics			
- n	251	258	266
- Median (hours)	33.4	43.9	31.3
- 95% CI (hours)	29.1, 40.5	33.6, 46.2	28.6, 37.0
Comparison with Placebo			
- Median difference (hours)	-10.6	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0390	---	---
Comparison with Oseltamivir			
- Median difference (hours)	2.0	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.7877	---	---
<b>Nasal Congestion</b>			
Summary statistics			
- n	240	267	257
- Median (hours)	45.6	57.7	44.0
- 95% CI (hours)	37.4, 54.3	48.7, 67.8	36.4, 50.3
Comparison with Placebo			
- Median difference (hours)	-12.1	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0017	---	---
Comparison with Oseltamivir			
- Median difference (hours)	1.5	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.8119	---	---

	S-033188	Placebo	Oseltamivir
<b>Feverishness or Chills</b>			
Summary statistics			
- n	348	347	347
- Median (hours)	28.3	31.9	29.1
- 95% CI (hours)	24.2, 31.8	28.6, 41.2	25.2, 30.8
Comparison with Placebo			
- Median difference (hours)	-3.6	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0070	---	---
Comparison with Oseltamivir			
- Median difference (hours)	-0.7	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.9191	---	---
<b>Muscle or Joint Pain</b>			
Summary statistics			
- n	311	302	312
- Median (hours)	37.2	44.9	33.2
- 95% CI (hours)	31.5, 41.6	42.2, 52.0	30.2, 39.5
Comparison with Placebo			
- Median difference (hours)	-7.7	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0232	---	---
Comparison with Oseltamivir			
- Median difference (hours)	4.0	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.5436	---	---

	<b>S-033188</b>	<b>Placebo</b>	<b>Oseltamivir</b>
<b>Fatigue</b>			
Summary statistics			
- n	332	330	325
- Median (hours)	41.3	48.8	43.2
- 95% CI (hours)	35.2, 46.1	42.7, 55.4	39.3, 47.4
Comparison with Placebo			
- Median difference (hours)	-7.5	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.0207	---	---
Comparison with Oseltamivir			
- Median difference (hours)	-1.9	---	---
- P-value derived from stratified generalized Wilcoxon test [a]	0.3710	---	---

CI = confidence interval; ITTI = Intention-to-Treat Infected

[a] Stratification factors: region, composite symptom scores at baseline, and preexisting and worsened symptom.

Patients whose symptoms at baseline are assessed as 0 (none), 1 (mild), 2 (moderate) but preexisting and not worsened, or 3 (severe) but preexisting and not worsened will be excluded from the analysis.

Subset of patients whose time to improvement of the symptom were not missing.

Patients who do not experience improvement of the symptom were treated as censored at the last observation time point.

Source: Table 11-33 of the Clinical Study Report

### **3.3 Evaluation of Safety**

The percentage of subjects with any adverse events ranged from 25% in the baloxavir treatment group to 30% in the placebo subjects. There was only one death in the trial, which occurred in the oseltamivir treatment group. According to the applicant this death was assessed as unrelated to study treatment by the investigator. The percentage of subjects with serious adverse events (excluding death) ranged from 0.7% in the baloxavir treatment group to 1.2% in the placebo subjects while the percentage of AEs leading to withdrawal of study drug was approximately 0.6-0.7% in each treatment group.

The percentage of subjects with any treatment-related adverse events ranged from 5.6% in the baloxavir treatment group to 8.3% in the placebo subjects. The percentage of subjects with treatment-related SAEs and the percentage of AEs leading to withdrawal of study drug was <1% in each treatment group.

**Table 9: Overall Summary of Adverse Events (Safety Population)**

	<b>S-033188</b> <b>N = 730</b>	<b>Placebo</b> <b>N = 727</b>	<b>Oseltamivir</b> <b>N = 721</b>
Adverse events			
- Number of patients	183	216	202
- (Number of events)	(282)	(342)	(332)
- Percentage of patients (%)	25.1	29.7	28.0
- 95% CI (%)	(22.0, 28.4)	(26.4, 33.2)	(24.8, 31.4)
Fisher's exact test			
- vs Placebo	0.0525	---	---
- vs Oseltamivir	0.2121	---	---
Death			
- Number of patients	0	0	1
- (Number of events)	(0)	(0)	(1)
- Percentage of patients (%)	0.0	0.0	0.1
- 95% CI (%)	(0.0, 0.5)	(0.0, 0.5)	(0.0, 0.8)
Fisher's exact test			
- vs Placebo	---	---	---
- vs Oseltamivir	0.4969	---	---
SAEs (excluding death)			
- Number of patients	5	9	8
- (Number of events)	(7)	(9)	(15)
- Percentage of patients (%)	0.7	1.2	1.1
- 95% CI (%)	(0.2, 1.6)	(0.6, 2.3)	(0.5, 2.2)
Fisher's exact test			
- vs Placebo	0.2986	---	---
- vs Oseltamivir	0.4192	---	---
AEs leading to withdrawal of study drug			
- Number of patients	5	5	4
- (Number of events)	(6)	(6)	(7)
- Percentage of patients (%)	0.7	0.7	0.6
- 95% CI (%)	(0.2, 1.6)	(0.2, 1.6)	(0.2, 1.4)
Fisher's exact test			
- vs Placebo	1.0000	---	---
- vs Oseltamivir	1.0000	---	---

AEs = adverse events; CI = confidence interval; SAEs = serious adverse events  
Source: Table 12-6 of the Clinical Study Report

**Table 10: Overall Summary of Treatment-related Adverse Events (Safety Population)**

	<b>S-033188</b> <b>N = 730</b>	<b>Placebo</b> <b>N = 727</b>	<b>Oseltamivir</b> <b>N = 721</b>
<b>Treatment-related AEs</b>			
- Number of patients	41	60	57
- (Number of events)	(49)	(76)	(72)
- Percentage of patients (%)	5.6	8.3	7.9
- 95% CI (%)	(4.1, 7.5)	(6.4, 10.5)	(6.0, 10.1)
<b>Fisher's exact test</b>			
- vs Placebo	0.0503	---	---
- vs Oseltamivir	0.0940	---	---
<b>Death</b>			
- Number of patients	0	0	0
- (Number of events)	(0)	(0)	(0)
- Percentage of patients (%)	0.0	0.0	0.0
- 95% CI (%)	(0.0, 0.5)	(0.0, 0.5)	(0.0, 0.5)
<b>Fisher's exact test</b>			
- vs Placebo	---	---	---
- vs Oseltamivir	---	---	---
<b>Treatment-related SAEs (excluding death)</b>			
- Number of patients	0	2	2
- (Number of events)	(0)	(2)	(2)
- Percentage of patients (%)	0.0	0.3	0.3
- 95% CI (%)	(0.0, 0.5)	(0.0, 1.0)	(0.0, 1.0)
<b>Fisher's exact test</b>			
- vs Placebo	0.2488	---	---
- vs Oseltamivir	0.2467	---	---
<b>Treatment-related AEs leading to withdrawal of study drug</b>			
- Number of patients	2	2	3
- (Number of events)	(2)	(2)	(5)
- Percentage of patients (%)	0.3	0.3	0.4
- 95% CI (%)	(0.0, 1.0)	(0.0, 1.0)	(0.1, 1.2)
<b>Fisher's exact test</b>			
- vs Placebo	1.0000	---	---
- vs Oseltamivir	0.6851	---	---

AE = adverse event; CI = confidence interval; SAEs = serious adverse events

Treatment-related is per investigator assessment.

Source: Table 12-7 of the Clinical Study Report

The incidence of adverse events occurring in at least 2% of subjects receiving baloxavir in acute uncomplicated influenza trials was similar in the placebo and baloxavir arms. The most frequent adverse events were bronchitis, diarrhea, nausea and sinusitis.

**Table 11: Adverse Events Occurring at an Incidence of  $\geq 2\%$  in Any of the Treatment Groups (Safety Population)**

<b>System Organ Class - Preferred Term</b>	<b>S-033188 N = 730 n (%)</b>	<b>Placebo N = 727 n (%)</b>	<b>Oseltamivir N = 721 n (%)</b>
Patients with any AEs	183 (25.1)	216 (29.7)	202 (28.0)
Infections and infestations	62 (8.5)	91 (12.5)	74 (10.3)
- Bronchitis	21 (2.9)	33 (4.5)	30 (4.2)
- Sinusitis	14 (1.9)	21 (2.9)	22 (3.1)
Gastrointestinal disorders	57 (7.8)	68 (9.4)	68 (9.4)
- Diarrhoea	20 (2.7)	21 (2.9)	23 (3.2)
- Nausea	20 (2.7)	29 (4.0)	34 (4.7)

AEs = adverse events

Data were presented as number of patients (percentage of patients).

Source: Table 12-9 of the Clinical Study Report

The Indications and Usage section of the label states that the 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. This section of the label also states that consideration should be given to available information on drug susceptibility patterns for circulating influenza virus strains when deciding whether to use baloxavir.

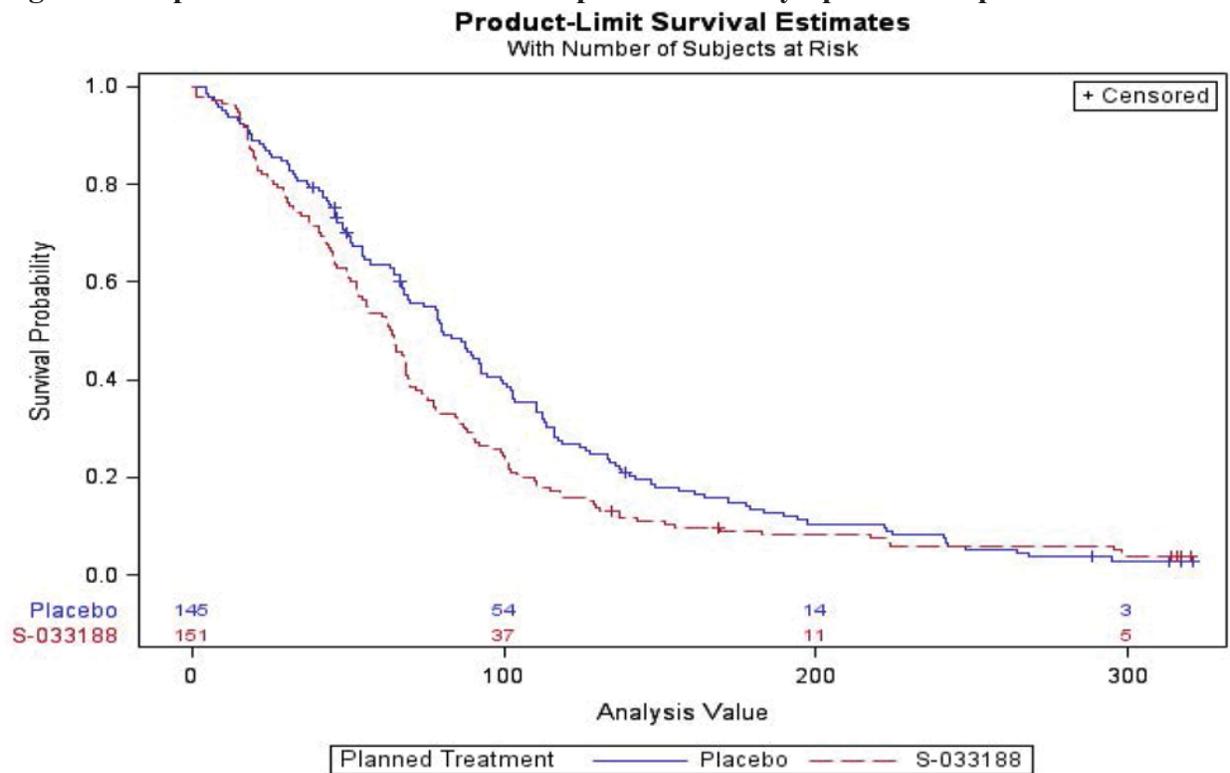
The Warnings and Precautions section of the label states that serious bacterial infections may begin with influenza-like symptoms and may coexist with or occur as a complication of influenza. Baloxavir has not been shown to prevent such complications. Prescribers should be alert to potential secondary bacterial infections and treat them as appropriate. See the clinical review for further evaluations of safety.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

Compared to placebo subjects, a statistically significant difference ( $p=0.022$ ) was observed for the time to improvement of symptoms in favor of S-033188 in Japanese subjects. Of note, the following analyses are based on various subgroups and the interpretation of the findings could potentially have several limitations including lack of adjustment for multiplicity that could lead to inflated type I error rates and low statistical power for small subgroups. Therefore, statistically significant findings are considered to be exploratory.

**Figure 5: Kaplan-Meier Plot of Time to Improvement of Symptoms in Japan**



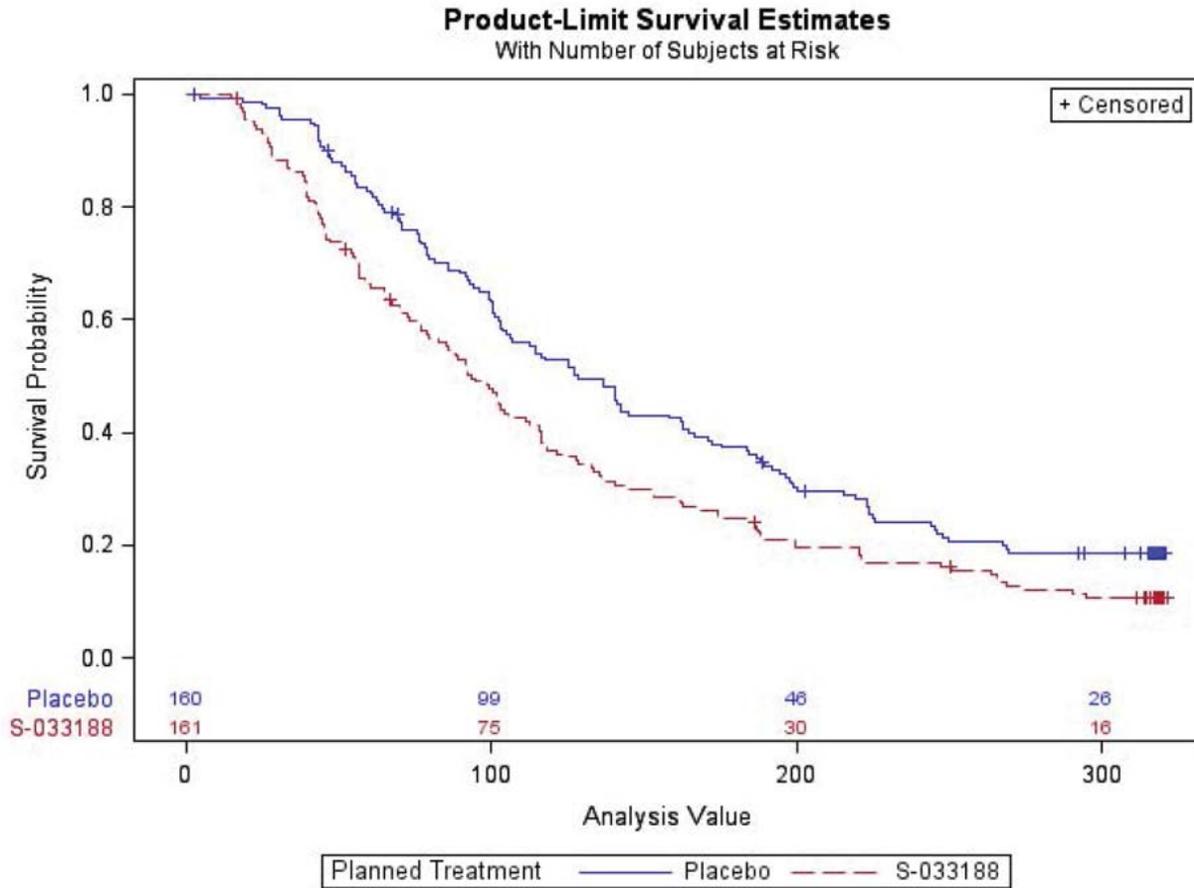
Medians: S-033188=64 hours, Placebo=81 hours

Stratified Peto Wilcoxon  $p$ -value = 0.022

Source: Reviewer's analysis

Compared to placebo subjects, statistical significance at the two-sided 0.05 level favoring the S-033188 arm was observed in the subgroup of U.S. subjects ( $p < 0.001$ ).

**Figure 6: Kaplan-Meier Plot of Time to Improvement of Symptoms in the U.S.**



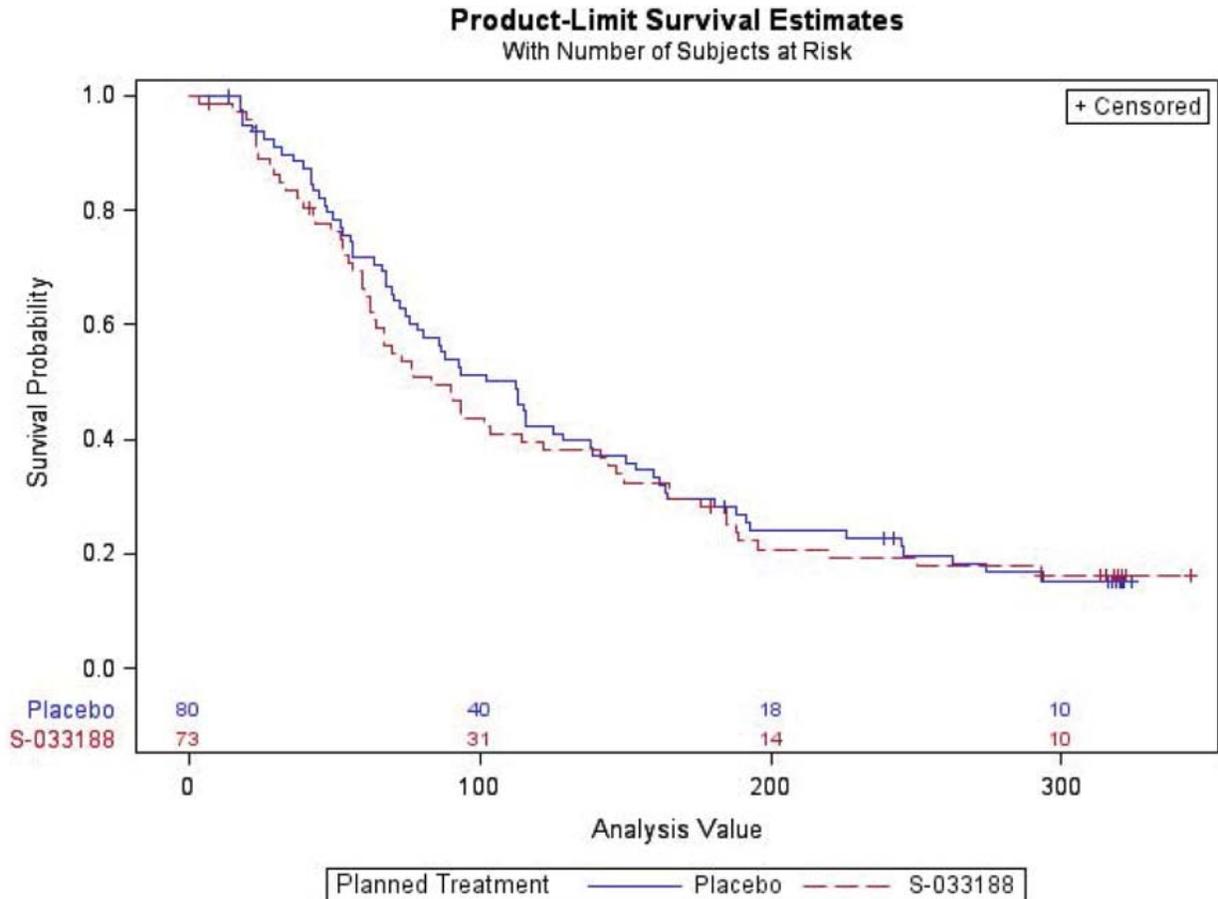
Medians: S-033188=93 hours, Placebo=128 hours

Stratified Peto Wilcoxon  $p$ -value  $< 0.001$

Source: Reviewer's analysis

In countries other than Japan and the US, there was no observed statistical significance at the two-sided 0.05 level between the S-033188 and placebo treatment groups ( $p=0.41$ ). Even though sample sizes were much smaller in the two treatment groups, there also appeared to be less separation between the survival curves in the two treatment groups than was observed in subjects in Japan and the U.S.

**Figure 7: Kaplan-Meier Plot of Time to Improvement of Symptoms in Other Countries**



Medians: S-033188=83 hours, Placebo=113 hours

Stratified Peto Wilcoxon  $p$ -value = 0.41

Source: Reviewer's analysis

Median differences between placebo and baloxavir ranged from 11 hours in Other Countries to 30 hours in the USA, all in favor of baloxavir. The 95% CI for the median difference in other countries included zero.

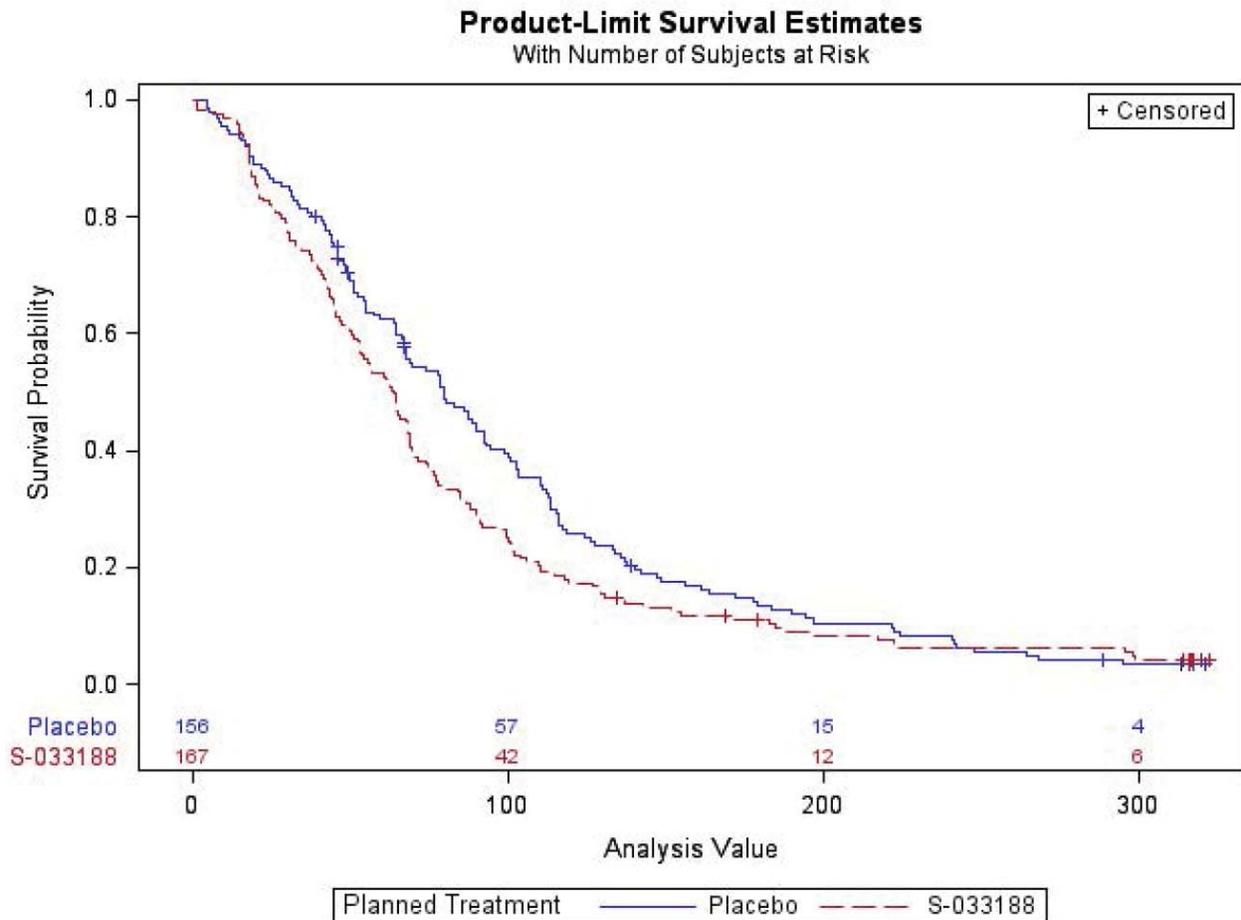
**Table 12: Median Time to Improvement of Symptoms by Region**

	Baloxavir Marboxil	Placebo
<b>Japan</b>	N=151	N=145
Median (95% CI) (hours)	64 (53, 69)	81 (68, 93)
Median Difference (95% CI)*		18 (5, 32)
<b>USA</b>	N=161	N=160
Median (95% CI) (hours)	93 (77, 112)	128 (104, 162)
Median Difference (95% CI)*		30 (10, 49)
<b>Other Countries</b>	N=73	N=80
Median (95% CI) (hours)	83 (63, 122)	113 (75, 138)
Median Difference (95% CI)*		11 (-11, 32)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Statistics Reviewer's analysis

As shown in the following figures, statistically significant differences were observed for the time to improvement of symptoms in favor of S-033188 in Asians ( $p=0.028$ ) and Whites ( $p=0.002$ ). Statistical significance was not observed in Blacks/African Americans ( $p=0.14$ ), but this subgroup only had 38 subjects in the S-033188 arm and 30 subjects in the placebo arm.

**Figure 8: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Race = Asian)**

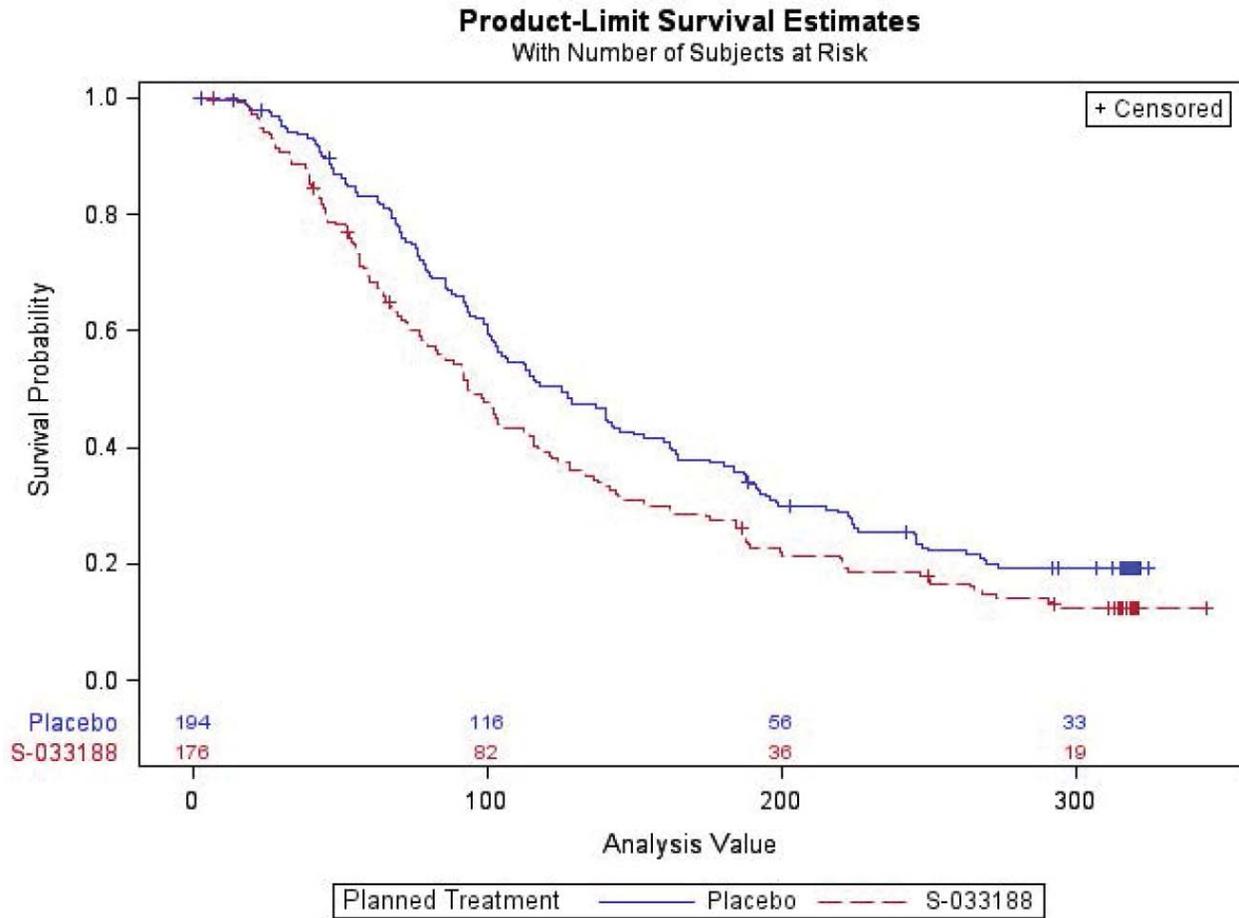


Medians: S-033188=64 hours, Placebo=80 hours

Stratified Peto Wilcoxon  $p$ -value =0.028

Source: Reviewer's analysis

**Figure 9: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Race = White)**

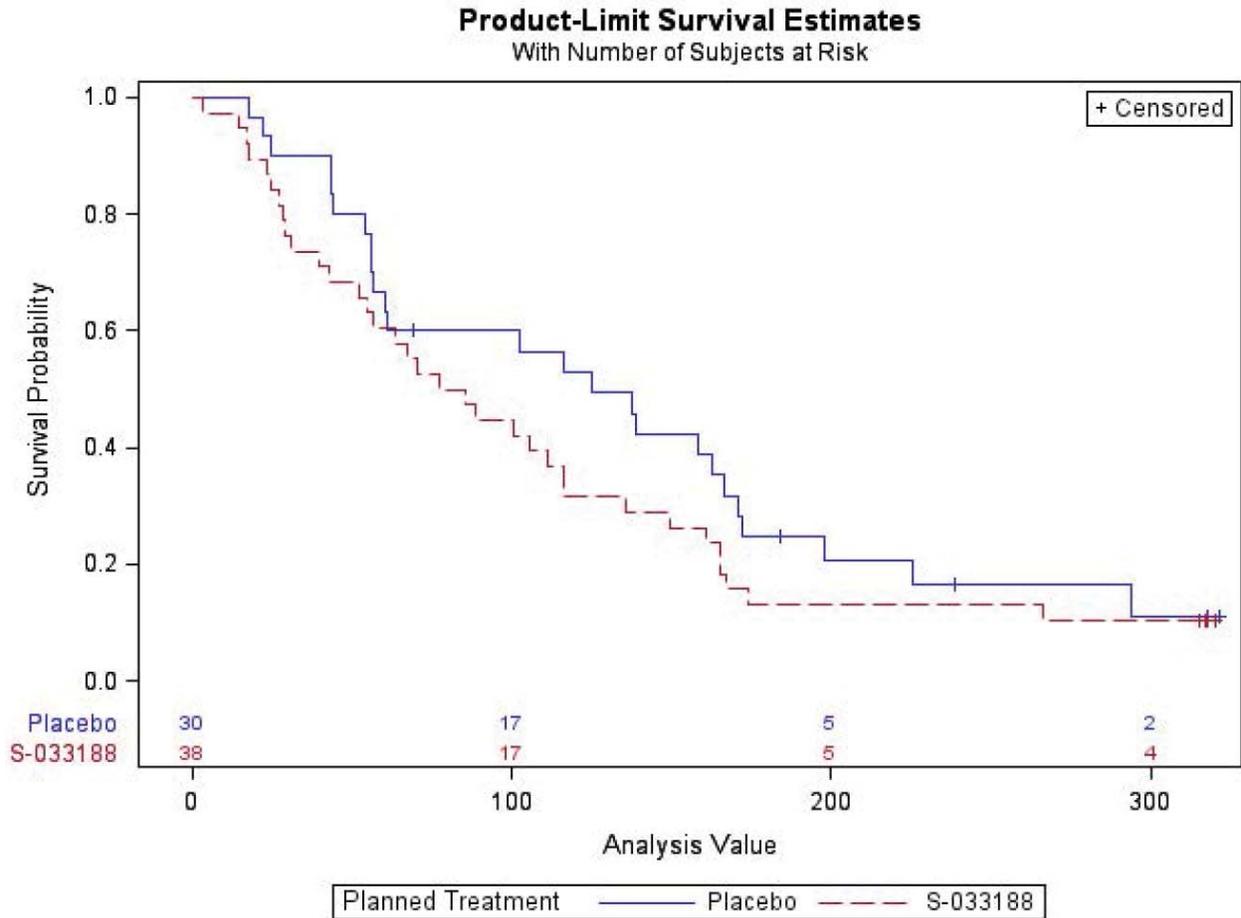


Medians: S-033188=94 hours, Placebo=125 hours

Stratified Peto Wilcoxon p-value =0.002

Source: Reviewer's analysis

**Figure 10: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Race = Black/African American)**



Medians: S-033188=81 hours, Placebo=125 hours

Stratified Peto Wilcoxon p-value =0.14

Source: Reviewer's analysis

Median differences between placebo and baloxavir ranged from 17 hours in Asians to 36 hours in Black/African Americans, all in favor of baloxavir. The 95% CI for the difference in Blacks/African Americans included zero.

**Table 13: Median Time to Improvement of Symptoms by Race**

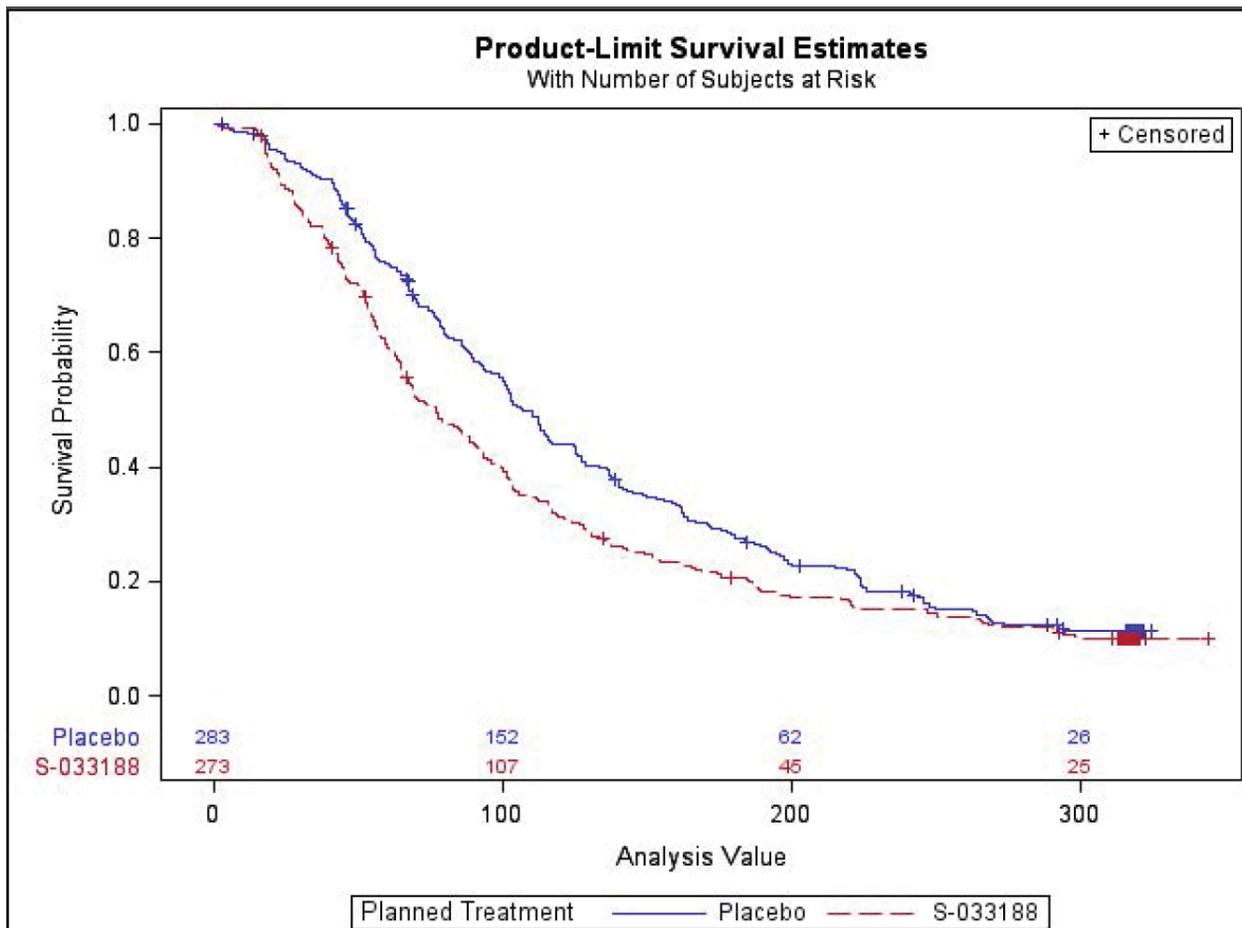
	Baloxavir Marboxil	Placebo
<b>Asians</b>	N=167	N=156
Median (95% CI) (hours)	64 (53, 69)	80 (67, 92)
Median Difference (95% CI)*		17 (4, 29)
<b>Whites</b>	N=176	N=194
Median (95% CI) (hours)	94 (79, 112)	125 (103, 145)
Median Difference (95% CI)*		22 (3, 41)
<b>Black/African American</b>	N=38	N=30
Median (95% CI) (hours)	81 (52, 116)	125 (56, 167)
Median Difference (95% CI)*		36 (-6, +77)

\* Hodges-Lehmann estimate and asymptotic 95% CI

Source: Reviewer's analysis

The following analyses figures evaluate the time to improvement in subjects who were <65 years and ≥65 years old. Due to the small number of adolescents, subjects between age 12-17 were pooled with other adult subjects <65 years of age and compared using Kaplan-Meier plots and Peto-Prentice Wilcoxon tests to subjects ≥65 years of age, where older subjects were thought to be at greater risk from influenza. The comparison between S-033188 and placebo was statistically significant in favor of S-033188 in subjects <65 years of age ( $p < 0.001$ ) and a trend in favor of S-033188 was also observed in adults age 65 years of age and older ( $p = 0.21$ ).

**Figure 11: Kaplan-Meier Plot of Time to Improvement of Symptoms in Subjects <65 years of age**

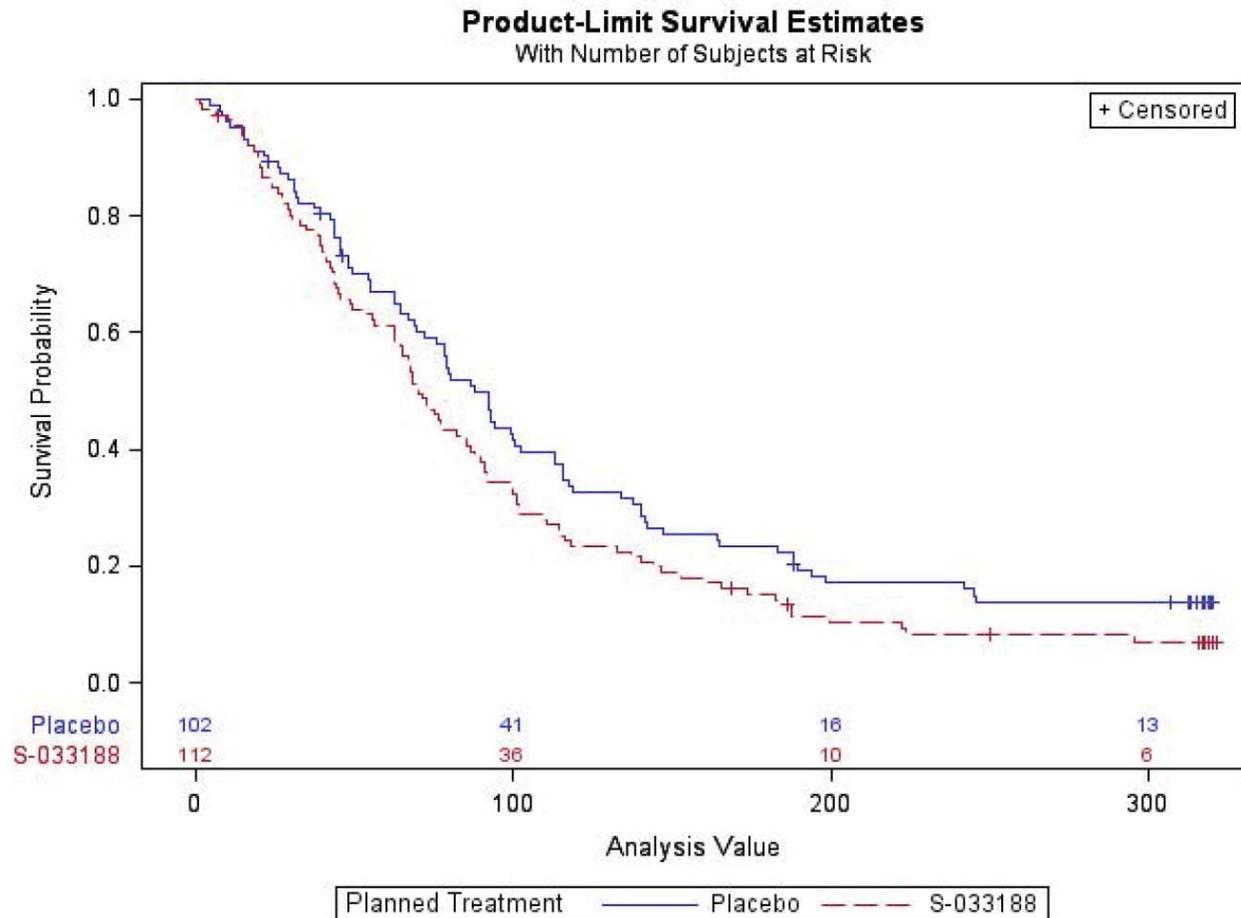


Medians: S-033188=77 hours, Placebo=107 hours

Stratified Peto Wilcoxon  $p$ -value <0.001

Source: Reviewer's analysis

**Figure 12: Kaplan-Meier Plot of Time to Improvement of Symptoms in Adults Subjects  $\geq 65$  years of age**



Medians: S-033188=70 hours, Placebo=88 hours

Stratified Peto Wilcoxon p-value =0.21

Source: Reviewer's analysis

With the exception of the small number of adolescent subjects, the median differences in TTIS between placebo and baloxavir were all positive in favor of S-033188 while the corresponding 95% CI for adolescents and for subjects 65-74 years of age included zero.

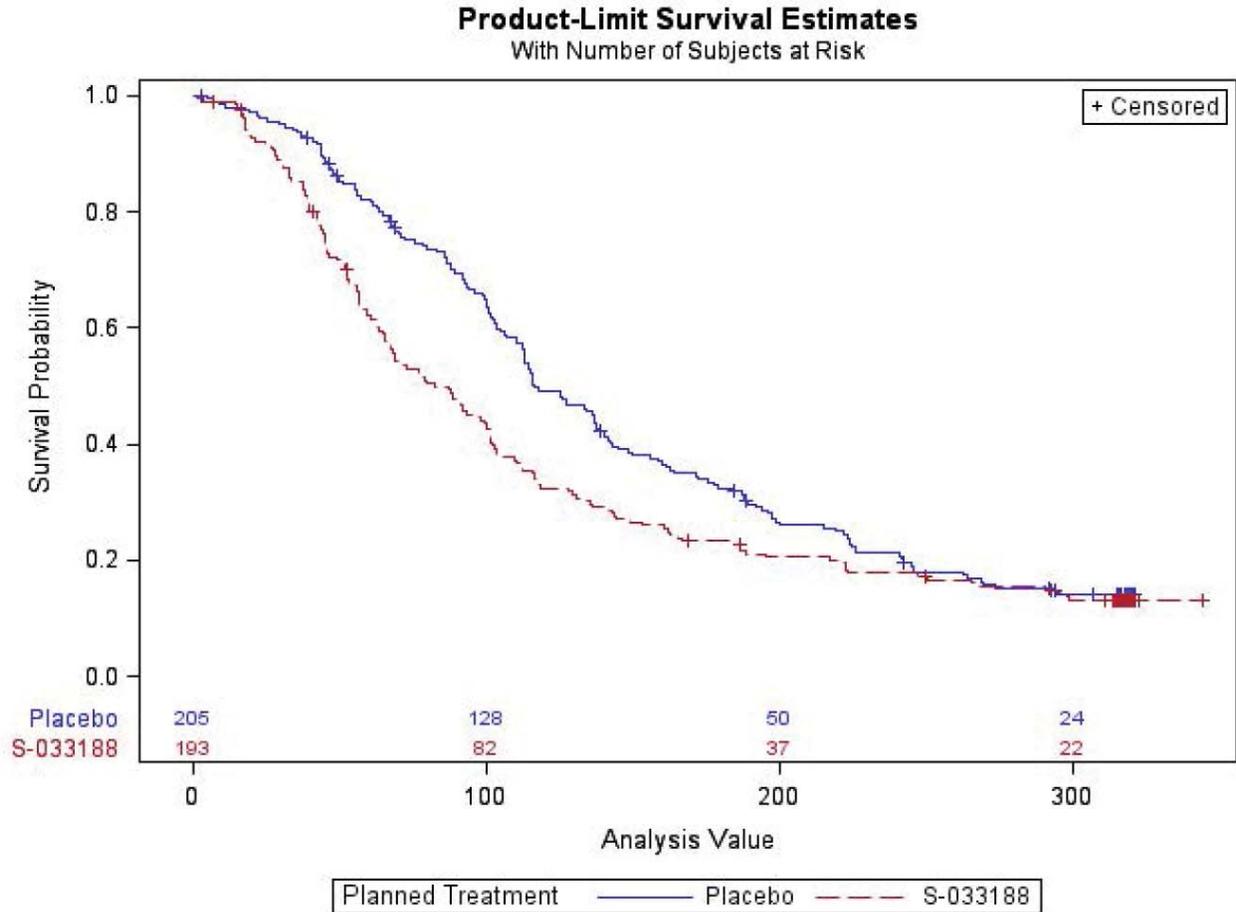
**Table 14: Median Time to Improvement of Symptoms by Age**

	Baloxavir Marboxil	Placebo
<b>Subjects <math>\geq 12</math> to <math>&lt;18</math> years</b>	N=13	N=12
Median (95% CI) (hours) Median Difference (95% CI)*	188 (53, ---)	192 (45, 224) -19 (-139, +100)
<b><math>\geq 18</math> to <math>\leq 64</math> years</b>	N=260	N=271
Median (95% CI) (hours) Median Difference (95% CI)*	74 (65, 88)	106 (96, 116) 24 (12, 37)
<b><math>\geq 65</math> to <math>\leq 74</math> years</b>	N=85	N=75
Median (95% CI) (hours) Median Difference (95% CI)*	73 (63, 91)	79 (63, 99) 7 (-12, 25)
<b><math>\geq 75</math> years</b>	N=27	N=27
Median (95% CI) (hours) Median Difference (95% CI)*	65 (39, 85)	116 (76, 147) 52 (7, 97)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

A statistically significant difference ( $p < 0.001$ ) was observed for the primary efficacy analysis in favor of S-033188 in females and a trend favoring S-033188 over placebo was observed in males ( $p = 0.15$ ).

**Figure 13: Kaplan-Meier plot for the Time to Improvement of Symptoms in Females**

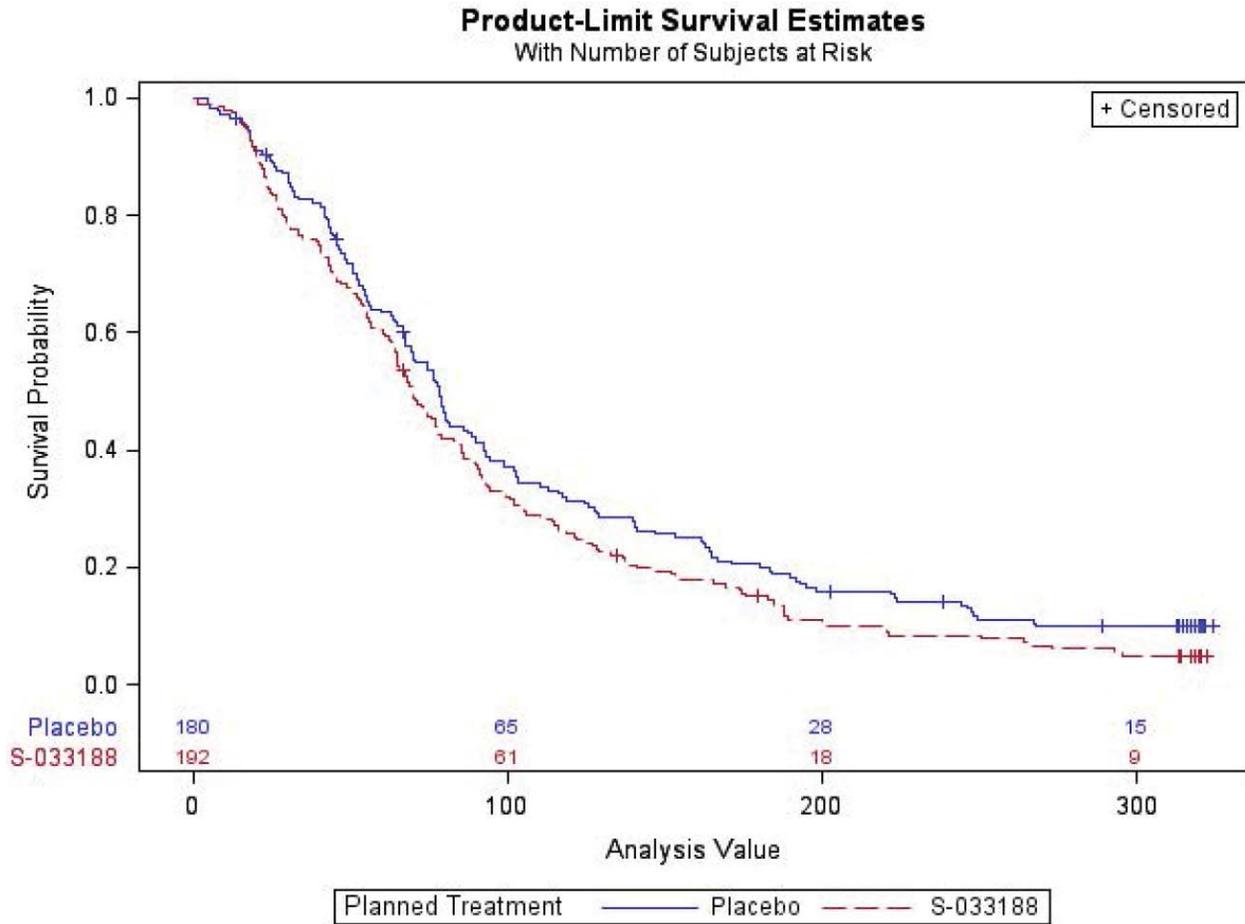


Medians: S-033188=82 hours, Placebo=116 hours

Stratified Peto Wilcoxon p-value  $< 0.001$

Source: Reviewer's analysis

**Figure 14: Kaplan-Meier plot for the Time to Improvement of Symptoms in Males**



Medians: S-033188=70 hours, Placebo=78 hours

Stratified Peto Wilcoxon p-value =0.15

Source: Reviewer's analysis

The median difference in TTIS between placebo and baloxavir was 31 hours in females and 11 hours in males. The 95% CI for males did not appear to indicate statistical significance for time to improvement of symptoms since the lower bound of the 95% CI was slightly less than zero.

**Table 15: Median Time to Improvement of Symptoms by Gender**

	Baloxavir Marboxil	Placebo
<b>Females</b>	N=193	N=205
Median (hours)	82	116
Median Difference (95% CI)*		31 (14, 48)
<b>Males</b>	N=192	N=180
Median (hours)	70 (64, 78)	78 (69, 88)
Median Difference (95% CI)*		11 (-0.4, 23)

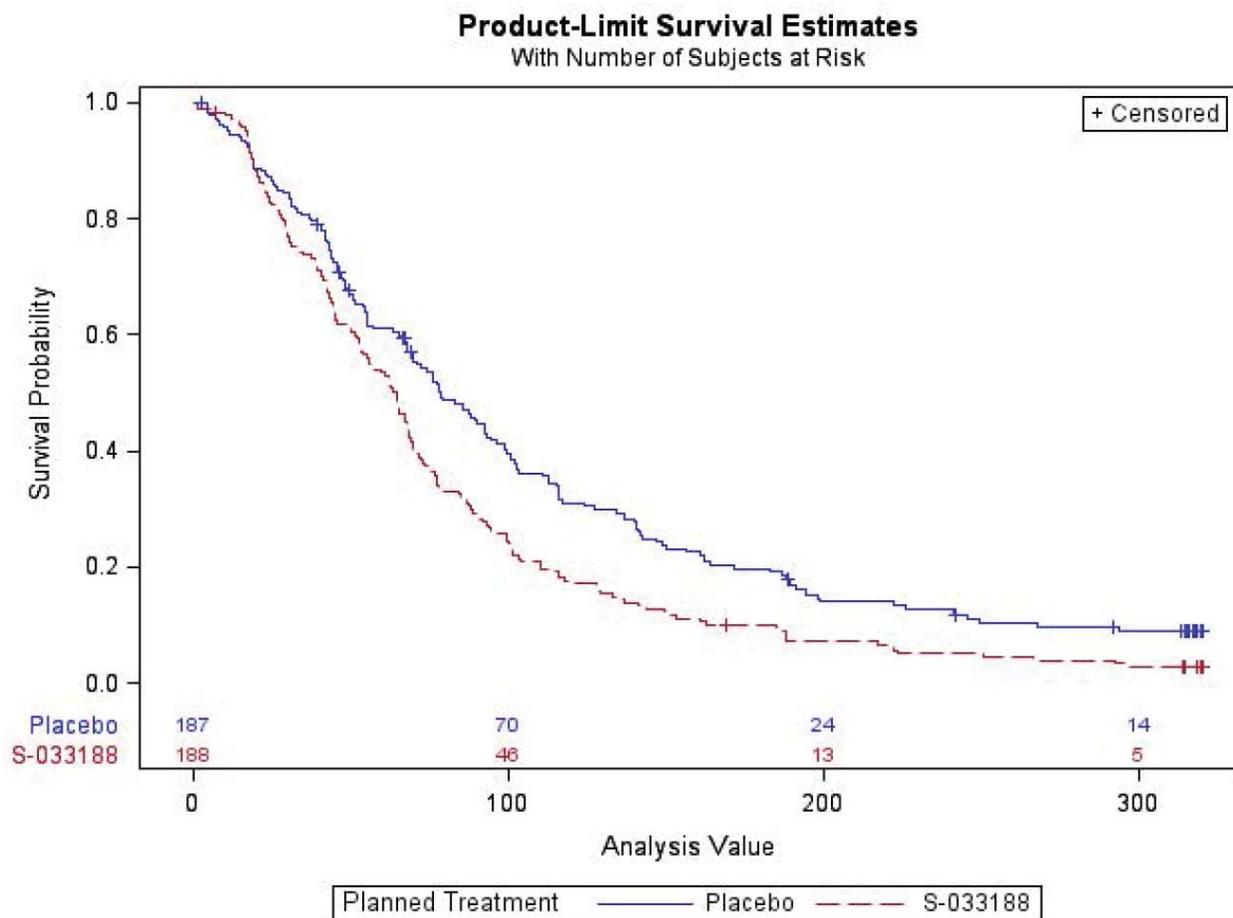
\* Hodges-Lehmann estimate and asymptotic 95% CI

Source: Reviewer's analysis

## 4.2 Other Special/Subgroup Populations

In special/subgroup populations, statistically significant differences were observed for time to improvement of symptoms in favor of S-033188 compared to placebo for both subgroups for the two composite symptom score strata used at randomization.

**Figure 15: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Composite Symptom Scores at Baseline q14)**

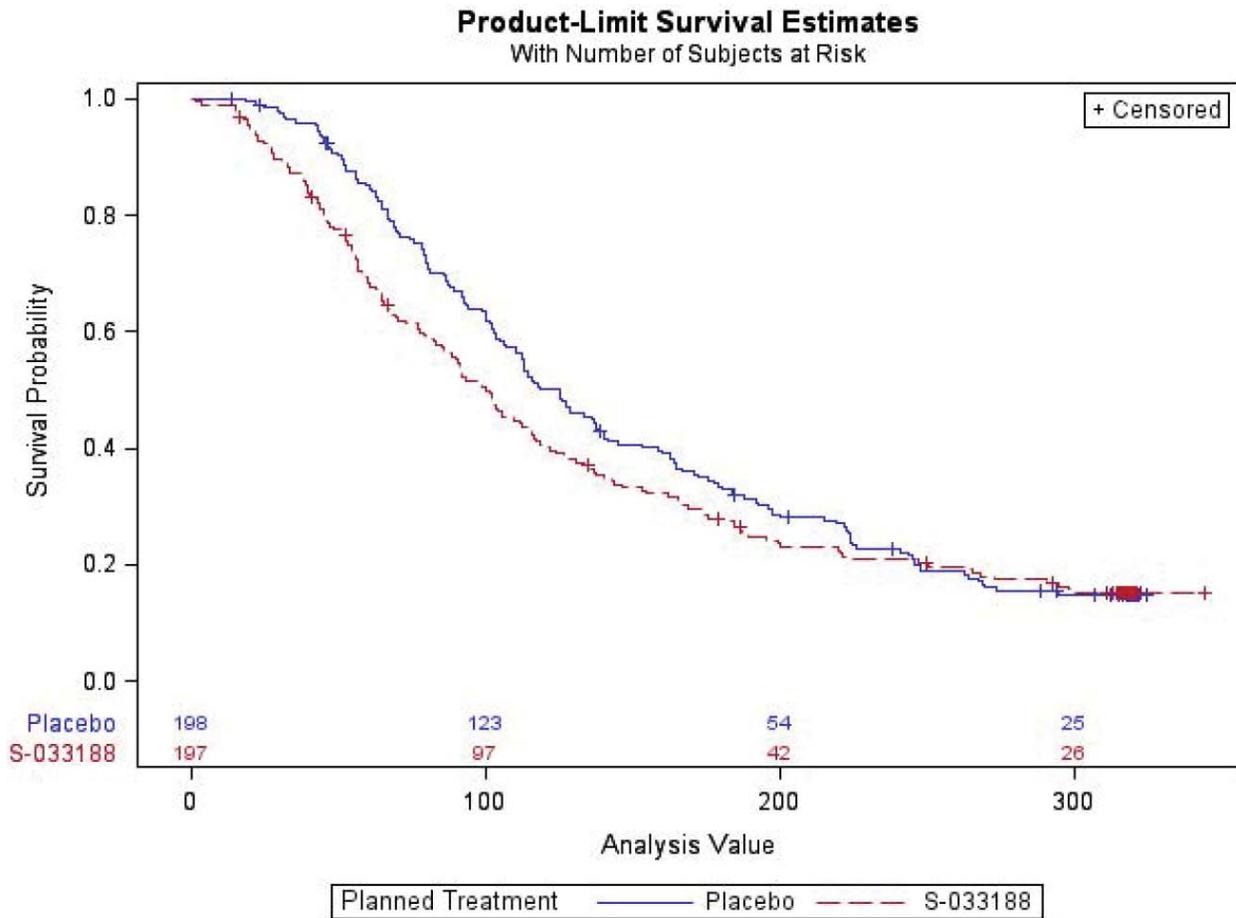


Medians: S-033188=64 hours, Placebo=78 hours

Stratified Peto Wilcoxon p-value =0.005

Source: Reviewer's analysis

**Figure 16: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Composite Symptom Scores at Baseline  $\geq 15$ )**



Medians: S-033188=101 hours, Placebo=125 hours

Stratified Peto Wilcoxon p-value =0.004

Source: Reviewer's analysis

The median difference in TTIS between placebo and baloxavir was approximately the same in both subgroups; 18 hours in the subjects with  $CSS \leq 14$  hours and 19 hours in subjects with  $CSS \geq 15$  hours, with both differences favoring baloxavir.

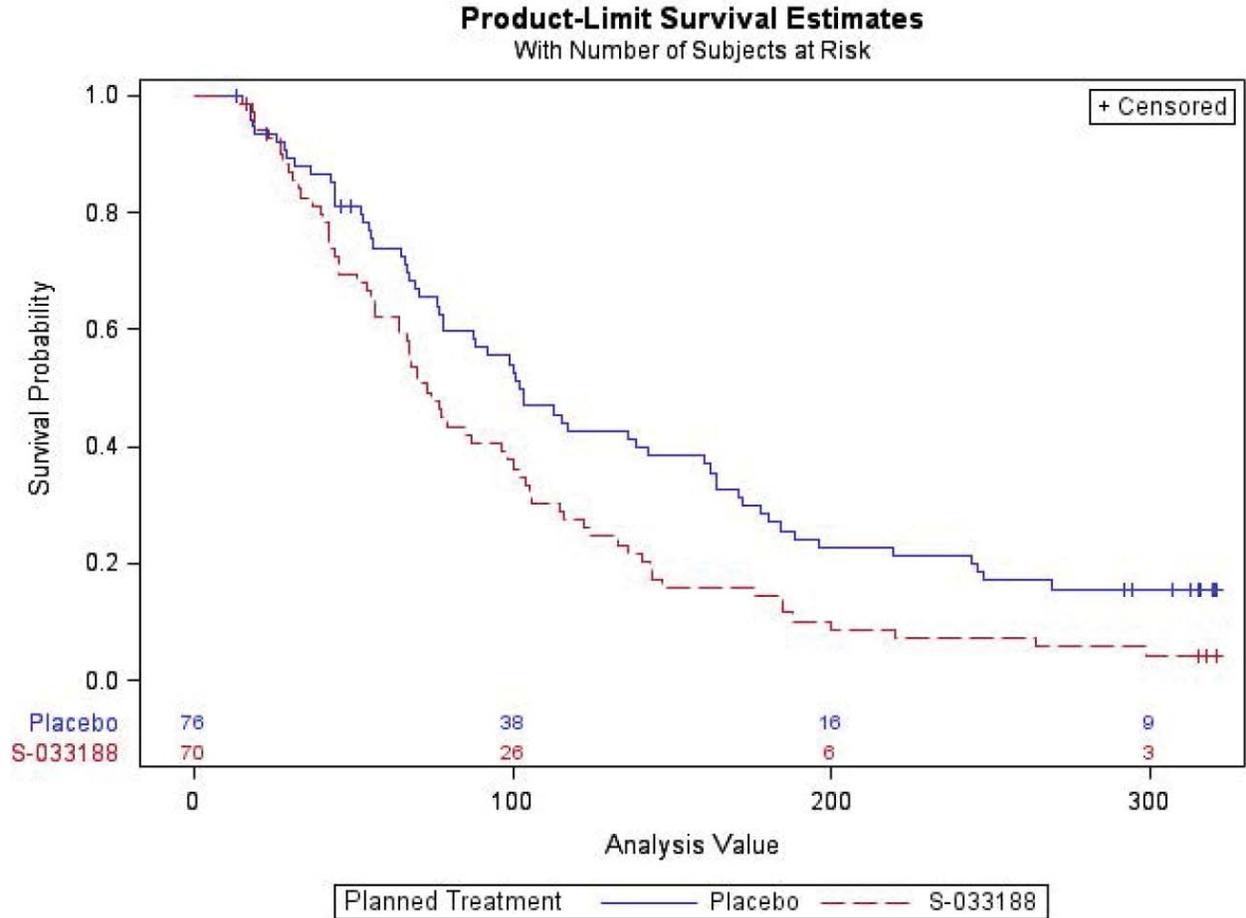
**Table 16: Time to Improvement of Symptoms by Composite Symptom Score at Baseline**

	Baloxavir Marboxil	Placebo
<b>CSS<math>\leq</math>14</b>	N=188	N=187
Median (95% CI) (hours)	64 (53, 69)	78 (68, 93)
Median Difference (95% CI)*		18 (6, 30)
<b>CSS<math>\geq</math>15</b>	N=197	N=198
Median (95% CI) (hours)	101 (86, 116)	125 (107, 139)
Median Difference (95% CI)*		19 (1, 36)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

In subjects with and without pre-existing and worsened symptoms at baseline, statistically significant differences were observed for time to improvement of symptoms in favor of S-033188 compared to placebo.

**Figure 17: Kaplan-Meier plot for the Time to Improvement of Symptoms in subjects with Pre-existing and Worsened Symptoms at Baseline**

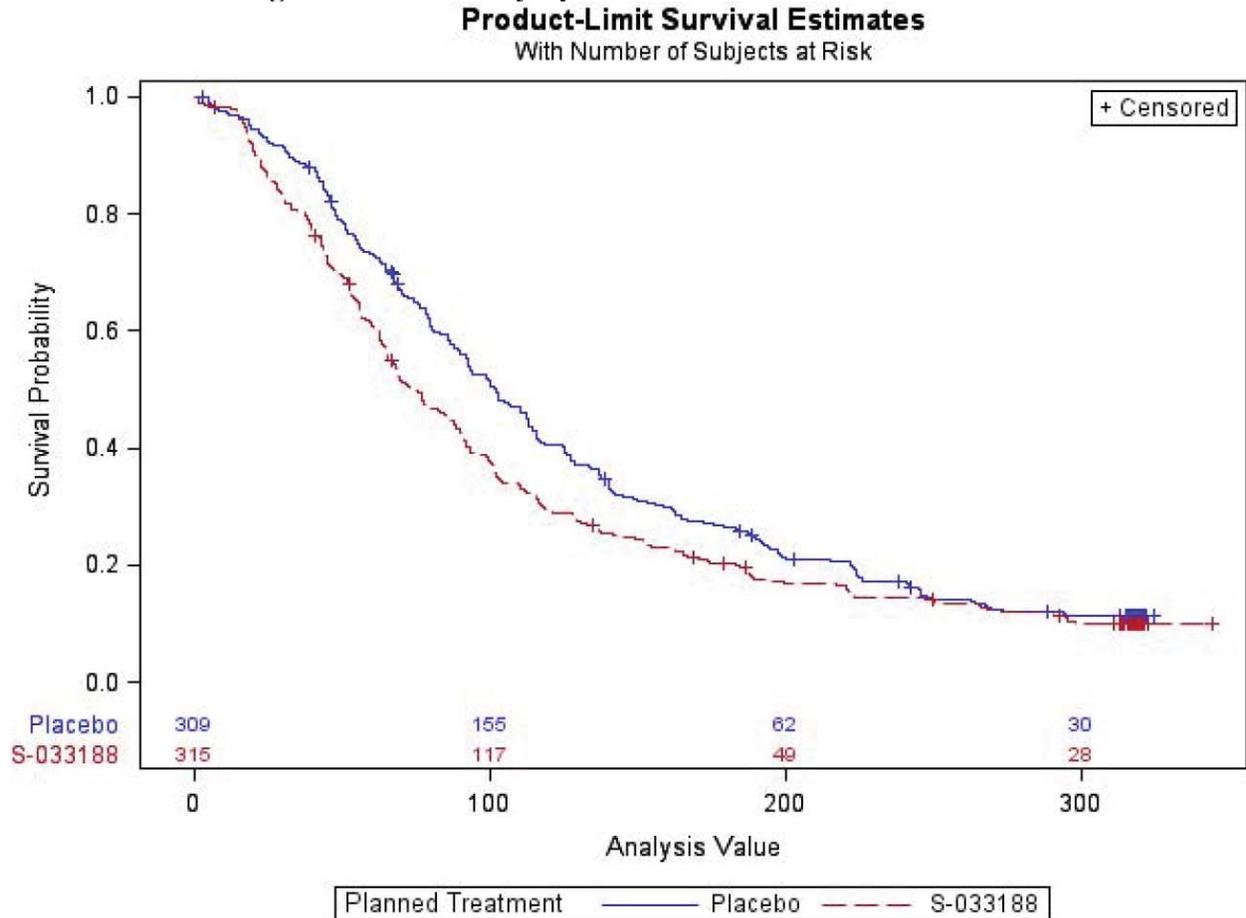


Medians: S-033188= 73 hours, Placebo= 102 hours

Stratified Peto Wilcoxon p-value =0.012

Source: Reviewer's analysis

**Figure 18: Kaplan-Meier plot for the Time to Improvement of Symptoms in subjects without Pre-existing and Worsened Symptoms at Baseline**



Medians: S-033188= 74 hours, Placebo= 102 hours

Stratified Peto Wilcoxon p-value =0.001

Source: Reviewer's analysis

The median difference in TTIS between placebo and baloxavir was 34 hours in favor of baloxavir in subjects with pre-existing and worsened symptoms and 19 hours in favor of baloxavir in subjects without pre-existing and worsened symptoms.

**Table 17: Time to Improvement of Symptoms by Presence of Pre-existing and Worsened Symptoms**

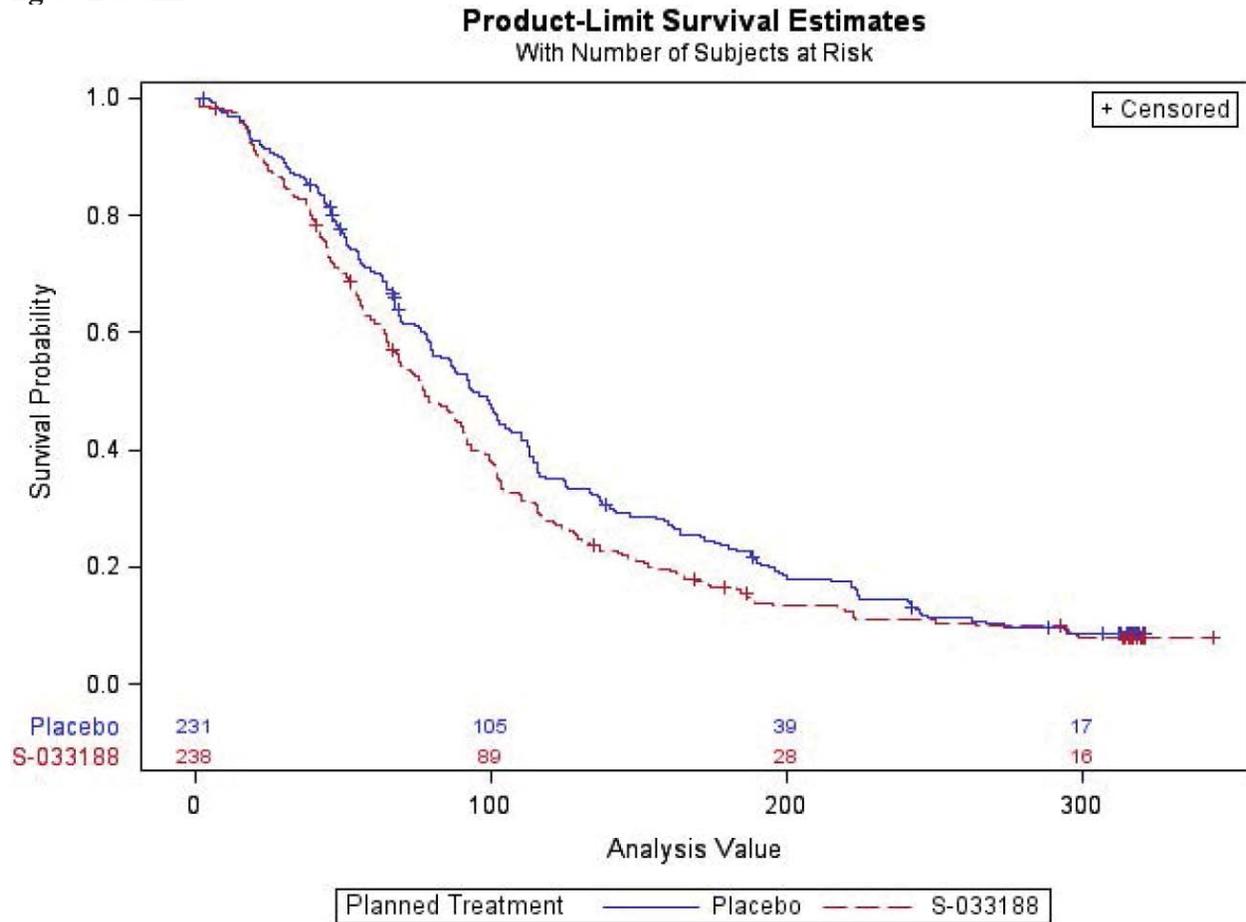
	Baloxavir marboxil	Placebo
<b>Subjects with pre-existing and worsened symptoms</b>	N=70	N=76
Median (95% CI) (hours)	73 (57, 98)	102 (78, 143)
Difference (95% CI)*		34 (6, 61)
<b>Subjects without pre-existing and worsened symptoms</b>	N=315	N=309
Median (95% CI) (hours)	74 (65, 88)	102 (92, 113)
Median Difference (95% CI)*		19 (7, 30)

\* Hodges-Lehmann estimate and asymptotic 95% CI

Source: Reviewer's analysis

In subjects <80 kg at baseline and in subjects who weighted at least 80 kg at baseline, statistically significant differences ( $p=0.035$ ) were observed for time to improvement of symptoms in favor of S-033188 compared to placebo.

**Figure 19: Kaplan-Meier plot for the Time to Improvement of Symptoms in Subjects <80 kg at Baseline**

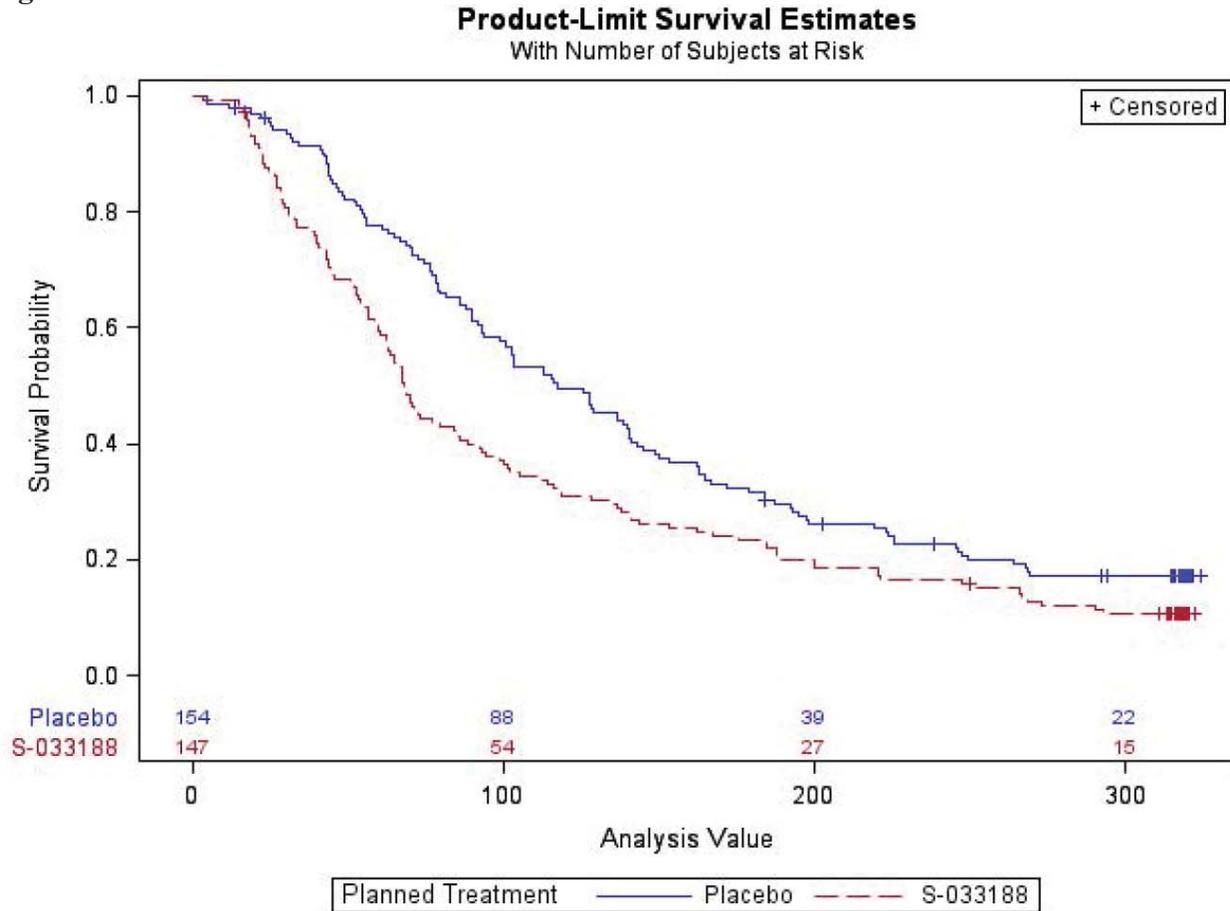


Medians: S-033188=77 hours, Placebo=94 hours

Stratified Peto Wilcoxon  $p$ -value =0.035

Source: Reviewer's analysis

**Figure 20: Kaplan-Meier plot for the Time to Improvement of Symptoms in Subjects  $\geq 80$  kg at Baseline**



Medians: S-033188=68 hours, Placebo=118 hours

Stratified Peto Wilcoxon p-value =0.001

Source: Reviewer's analysis

The median difference in TTIS between placebo and baloxavir was 14 hours in favor of baloxavir in subjects weighing <80 kg at baseline and 33 hours in favor of baloxavir in subjects weighing ≥80 kg at baseline.

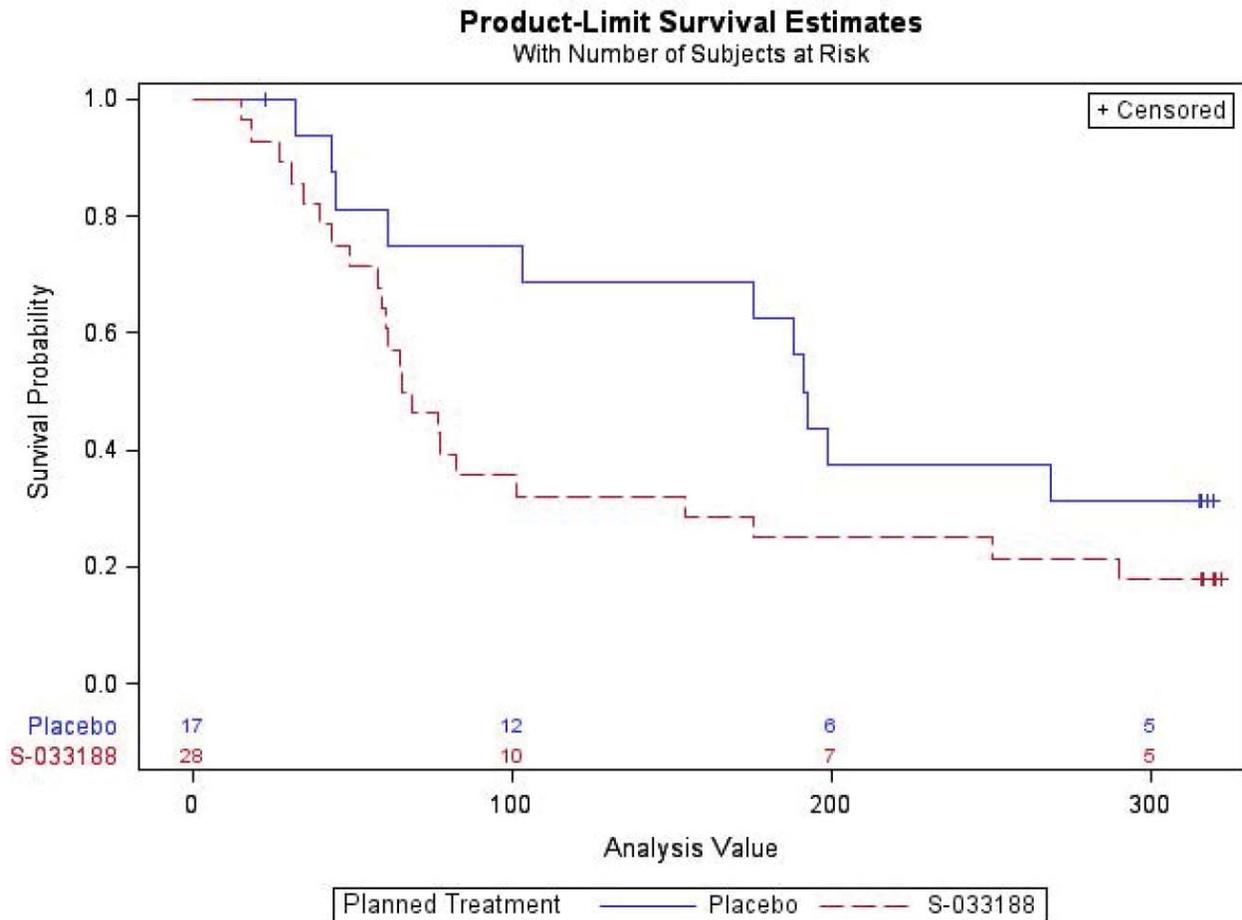
**Table 18: Median Time to Improvement of Symptoms by Body Weight**

	Baloxavir Marboxil	Placebo
<b>&lt; 80 kg</b>	N=238	N=231
Median (95% CI) (hours)	77 (68, 90)	94 (81, 106)
Median Difference (95% CI)*		14 (1, 26)
<b>≥ 80 kg</b>	N=147	N=154
Median (95% CI) (hours)	68 (62, 85)	118 (99, 141)
Median Difference (95% CI)*		33 (15, 52)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

In subjects who were Influenza A subtype H1N1, a non-statistically significant trend ( $p=0.11$ ) was observed for time to improvement of symptoms not in favor of S-033188 compared to placebo.

**Figure 21: Kaplan-Meier plot for the Time to Improvement of Symptoms in Subjects with Influenza Type A/H1N1**



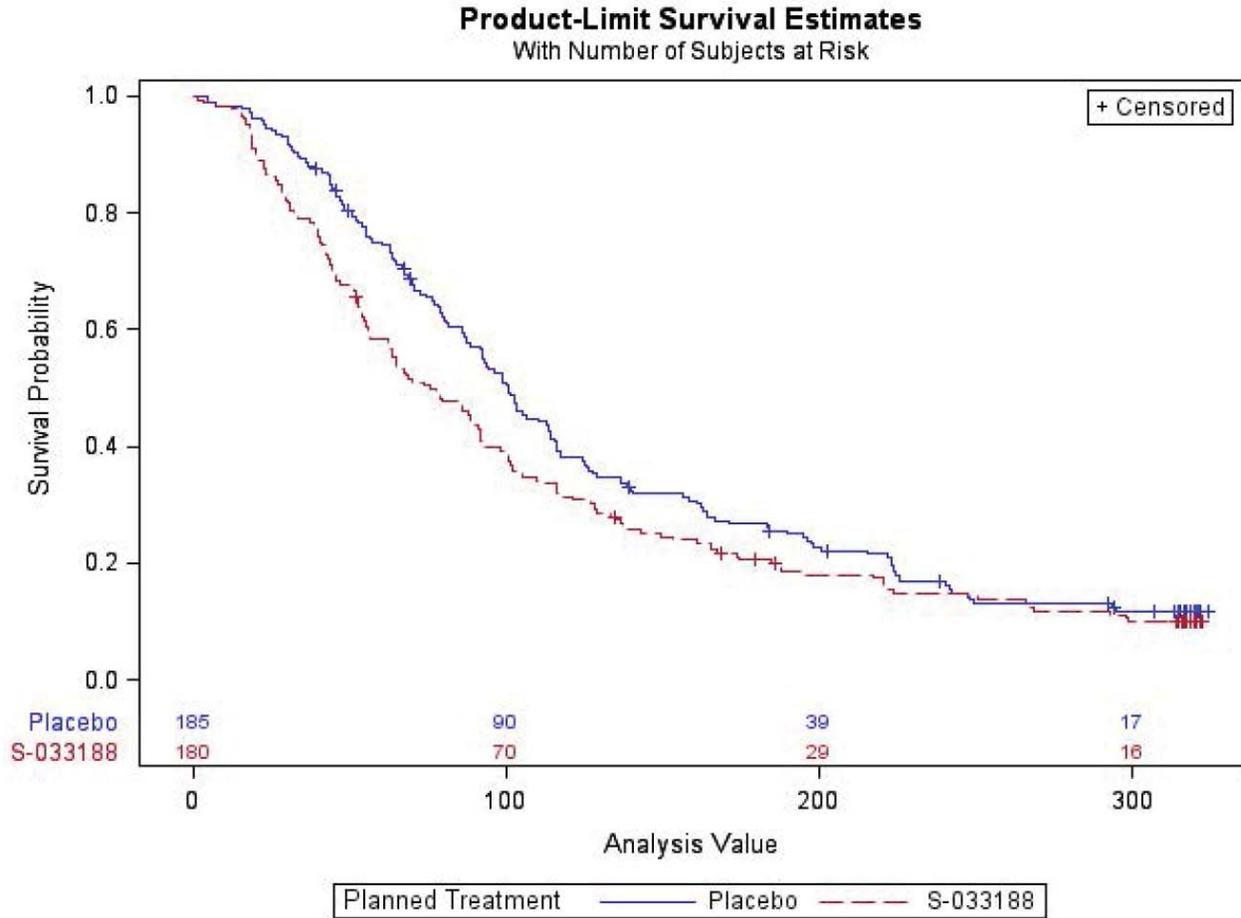
Medians: S-033188=67 hours, Placebo=192 hours

Peto Wilcoxon stratified  $p$ -value = 0.11

Source: Reviewer's analysis

In subjects with Influenza A/H3N2 ( $p=0.014$ ) and Influenza B ( $p=0.014$ ), the TTIS was significantly lower for baloxavir compared to placebo.

**Figure 22: Kaplan-Meier plot for the Time to Improvement of Symptoms in Subjects with Influenza Type A/H3N2**

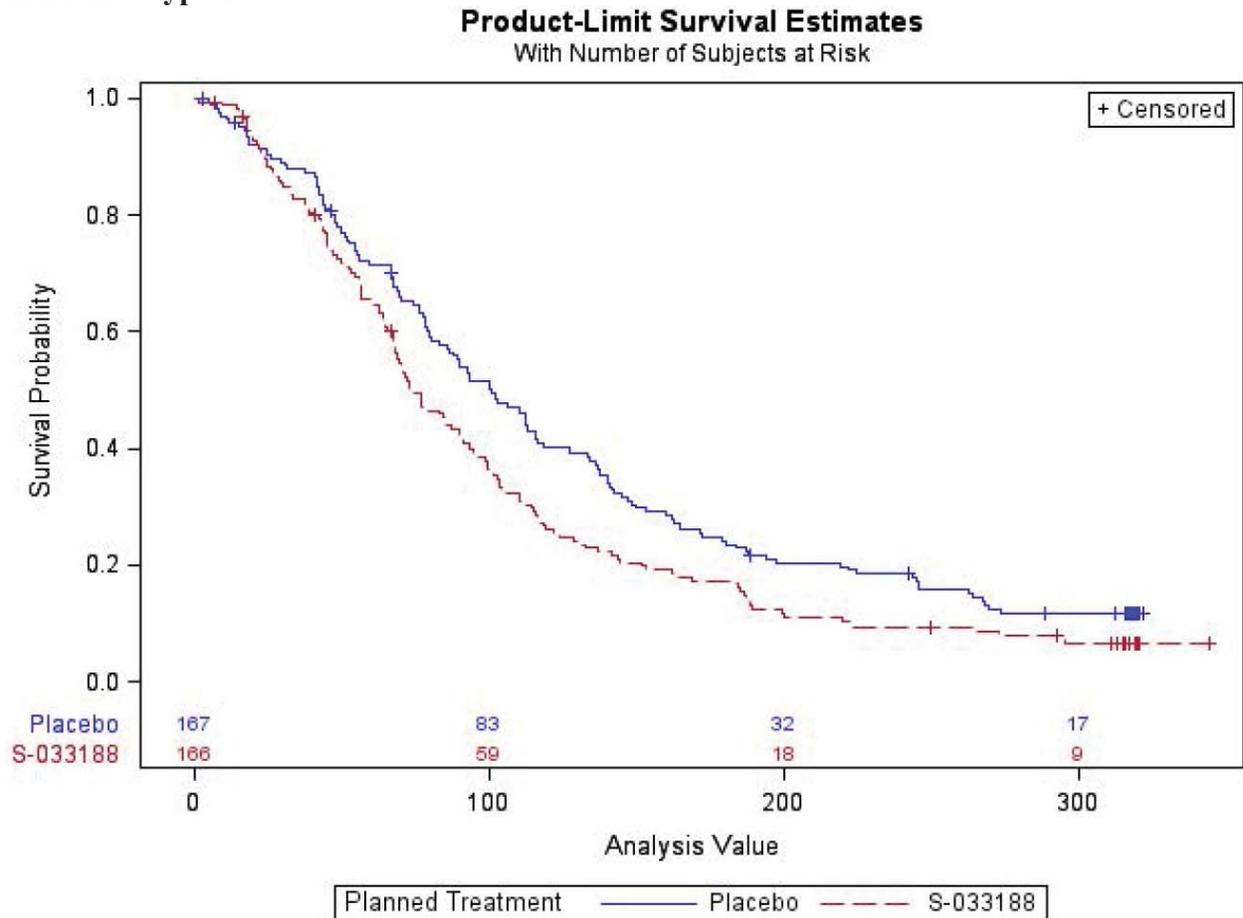


Medians: S-033188=75 hours, Placebo=100 hours

Peto Wilcoxon stratified  $p$ -value = 0.014

Source: Reviewer's analysis

**Figure 23: Kaplan-Meier plot for the Time to Improvement of Symptoms in Subjects with Influenza Type B**



Medians: S-033188=75 hours, Placebo=101 hours

Peto Wilcoxon stratified p-value = 0.014

Source: Reviewer's analysis

Compared to placebo subjects, the median time to improvement of symptoms was 21 and 18 hours longer for baloxavir treatment group in subjects infected with influenza type A/H3N2 and B respectively. The 81-hour median difference in type A/H1N1 subjects had a much wider 95% CI than for other subgroups ranging from 0 to 161 hours, reflecting the large extent of variability that was most likely due to the small sample size.

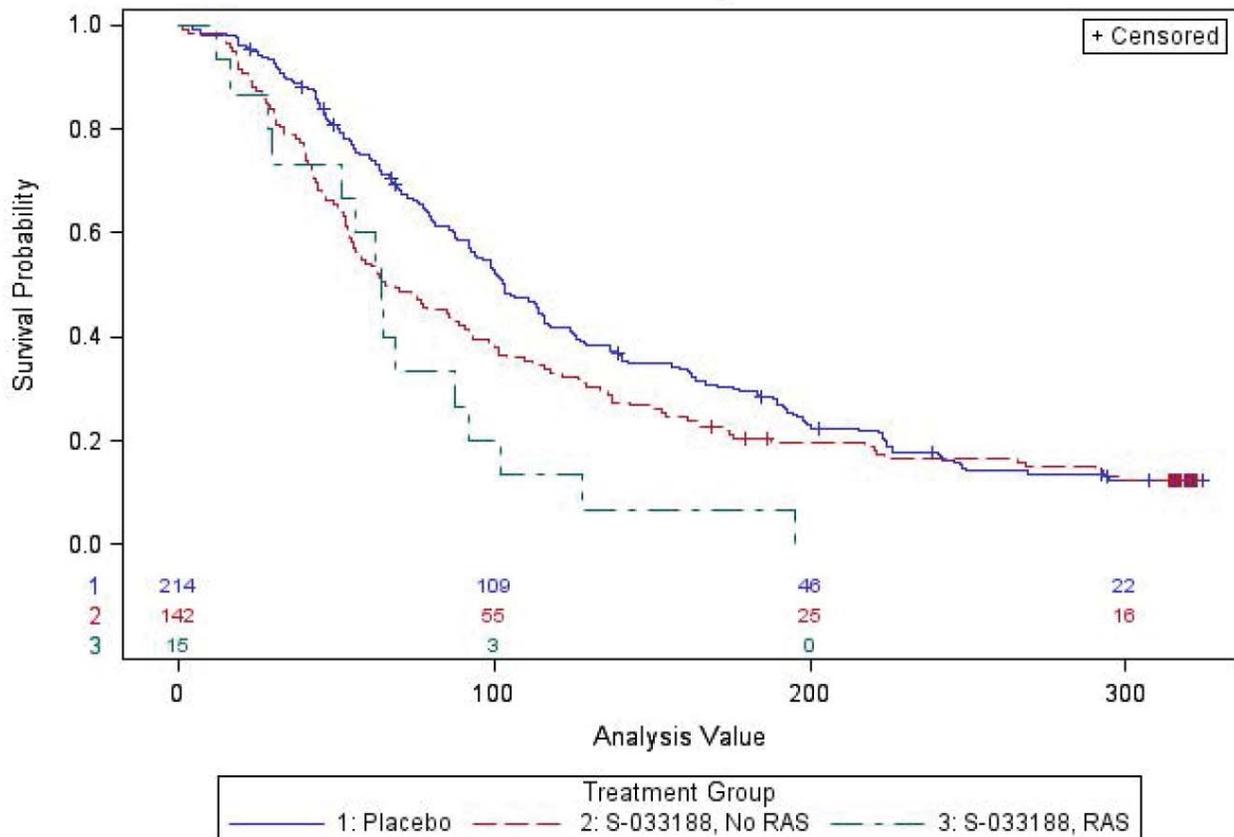
**Table 19: Median Time to Improvement of Symptoms by Influenza Type/Subtype**

	Baloxavir Marboxil	Placebo
<b>A/H1N1</b>	N=28	N=17
Median (95% CI) (hours)	67 (58, 101)	192 (61, --)
Median Difference (95% CI)*		81 (0, 161)
<b>A/H3N2</b>	N=180	N=185
Median (95% CI) (hours)	75 (62, 92)	100 (88, 113)
Median Difference (95% CI)*		21 (6, 36)
<b>B</b>	N=166	N=167
Median (95% CI) (hours)	75 (67, 90)	101 (83, 116)
Median Difference (95% CI)*		18 (2, 35)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

In subjects without the amino acid substitution, there was a statistically significant difference for the time to improvement of symptoms comparison between S-033188 and placebo subjects ( $p=0.01$ ) and for the comparison between S-033188 patients with the amino acid substitution and placebo subjects ( $p=0.03$ ). There was no statistically significant difference between S-033188 subjects with RAS and those with no RAS ( $p=0.50$ )

**Figure 24: Kaplan-Meier plot for the Time to Improvement of Symptoms, RAS vs. No RAS for Subjects with Influenza Type A/H1N1 &/or H3N2, A/Unknown**  
**Product-Limit Survival Estimates**  
 With Number of Subjects at Risk



Medians: S-033188 with RAS=65 hours, S-033188 with no RAS=67 hours, Placebo=103 hours  
 Peto Wilcoxon stratified p-value comparing S-033188 subjects with no RAS to placebo = 0.01  
 Peto Wilcoxon stratified p-value comparing S-033188 subjects with RAS to placebo = 0.03  
 Peto Wilcoxon stratified p-value for S-033188 subjects, comparing RAS vs. No RAS = 0.50  
 Source: Statistics Reviewer's analysis

Compared to placebo subjects, the median difference in TTIS was 45 hours in favor of baloxavir subjects with RAS at baseline and 20 hours in favor of baloxavir subjects who did not have RAS at baseline. The difference between baloxavir subjects with no RAS and baloxavir subjects with RAS was 19 hours, favoring those with RAS. However, the 95% CI was (-13, +51) indicating lack of any statistically significant difference between the median difference in TTIS for subjects in the two groups.

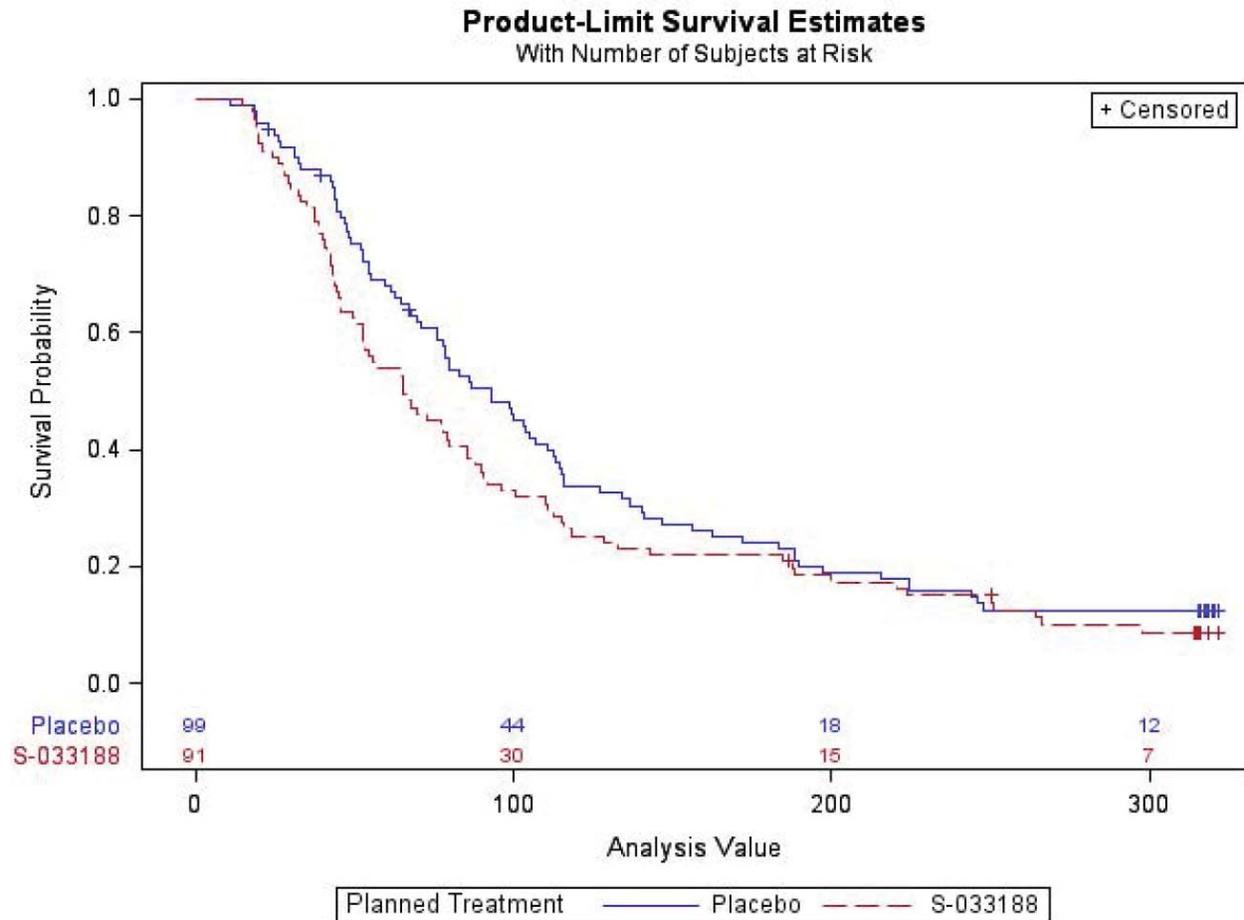
**Table 20: Median Time to Improvement of Symptoms, RAS vs. No RAS in Subjects with Influenza Type A/H1N1 &/or H3N2, A/Unknown**

Baloxavir Marboxil Subgroup	Baloxavir Marboxil	Placebo
<b>Subjects with RAS</b>	N=15	N=214
Median (95% CI) (hours)	65 (28, 88)	103 (93, 116)
Median Difference (95% CI)*		45 (8, 82)
<b>Subjects with no RAS</b>	N=142	N=214
Median (95% CI) (hours)	67 (55, 91)	103
Median Difference (95% CI)*		20 (5, 35)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

Additional Kaplan-Meier analyses were performed for subjects who received influenza vaccination. TTIS was shorter for baloxavir subjects than placebo subjects in both strata, but the difference between treatment groups was not statistically significant at the two-sided 0.05 level in the relatively smaller number of subjects who were vaccinated within 6 months ( $p=0.10$ ).

**Figure 25: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: Influenza Vaccination received within 6 months)**

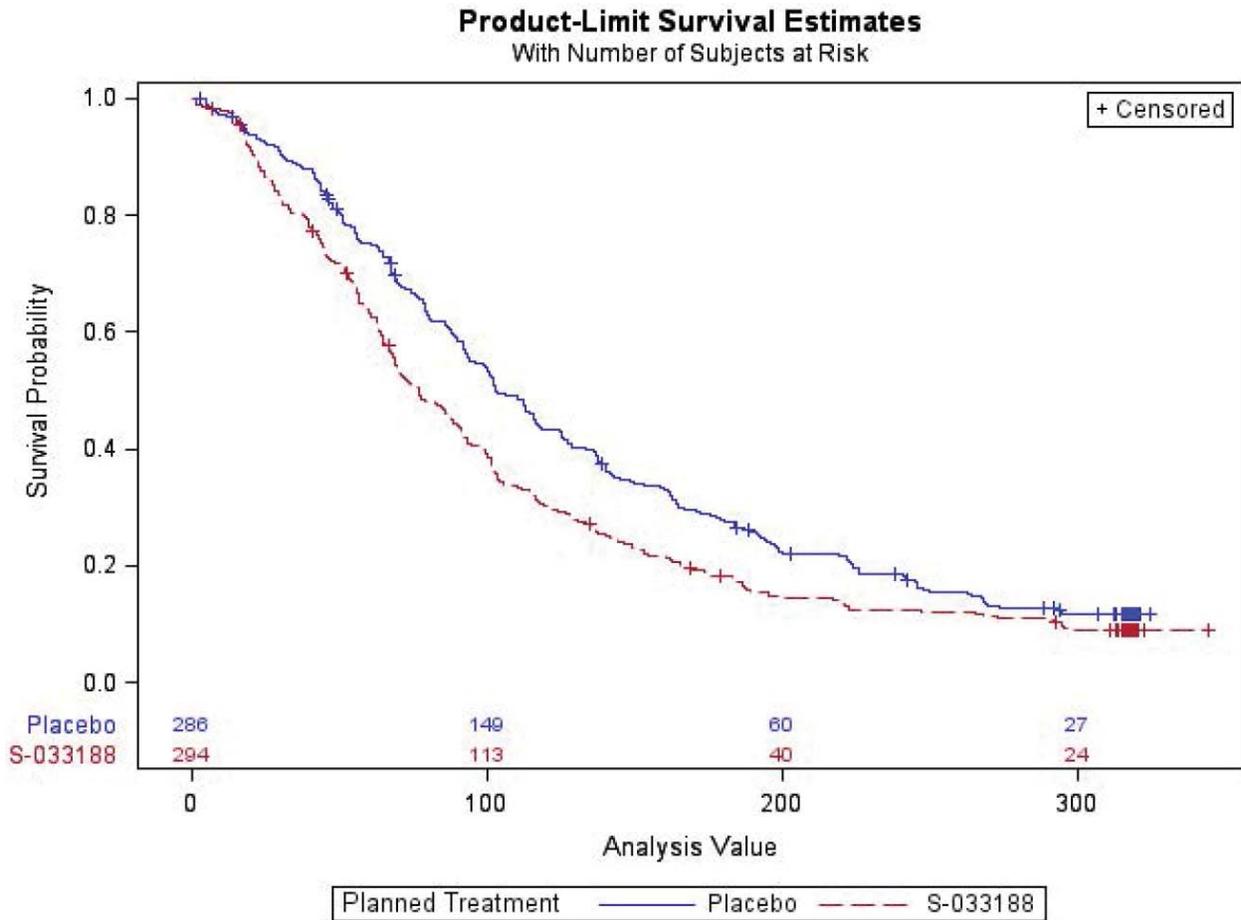


Medians: S-033188=65 hours, Placebo=93 hours

Peto Wilcoxon stratified p-value = 0.10

Source: Reviewer's analysis

**Figure 26: Kaplan-Meier Plot of Time to Improvement of Symptoms (Subgroup: No Influenza Vaccination within 6 months)**



Medians: S-033188=77 hours, Placebo=103 hours

Peto Wilcoxon stratified p-value < 0.001

Source: Reviewer's analysis

The median difference in TTIS between placebo and baloxavir was 18 hours in favor of baloxavir in subjects who received an influenza vaccination within the past 6 months and 23 hours in favor of baloxavir in subjects who were not vaccinated within the past 6 months.

**Table 21: Median Time to Improvement of Symptoms by Influenza Vaccination within the past 6 months**

	Baloxavir Marboxil	Placebo
<b>Influenza vaccine within 6 months</b>	N=91	N=99
Median (95% CI) (hours) Median Difference (95% CI)*	65 (53, 85)	93 (76, 111) 18 (0.4, 36)
<b>Not vaccinated within 6 months</b>	N=294	N=286
Median (95% CIs) (hours) Median Difference (95% CI)*	77 (68, 90)	103 (93, 117) 23 (10, 36)

\* Hodges-Lehmann estimate and asymptotic 95% CI  
Source: Reviewer's analysis

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

The generalized Wilcoxon test is typically used for the primary analysis for acute uncomplicated influenza trials as it puts more weight on earlier events than the log rank test, while the log rank test is more powerful when there are proportional hazards which is not usually the case in these types of trials with self-limiting response after a few days. The proportional hazards assumption does not hold for acute uncomplicated influenza because it is an illness of limited duration and survival plots converge after a few days. Therefore, a version of the generalized Wilcoxon test is frequently used for the primary efficacy analysis for drugs intended to treat uncomplicated influenza. All statistical versions of the generalized Wilcoxon test and the log rank test demonstrated statistically significant results for baloxavir compared to placebo.

The applicant calculated the difference in medians between treatment groups A and B as the difference between the median response of all individuals in group A minus the median responses of all subjects in group B. This calculation considers the difference between the 50<sup>th</sup> percentile of group A and group B. The reviewer also evaluated the Hodges-Lehmann estimate of the median difference comparing the entire distribution of each treatment arm by computing the median of all pairwise differences between patients in group A and patients in group B.

Note that the difference in medians of treatment groups is usually not equal to the median difference between treatment groups in contrast to the mean difference which is equal to the difference in means. For the primary efficacy endpoint of time to improvement of symptoms, the median difference between subjects in S-033188 and placebo subjects was 21 hours while the difference in the median of the S-033188 subjects and the median of placebo subjects was 29 hours.

## **5.2 Collective Evidence**

A statistically significant difference in TTIS was observed between S-033188 and placebo subjects who were infected with the type A/H3N2 and B strains of influenza while there was no statistically significance between the TTIS in S-0331888 and placebo subjects with the type A/H1N1 strain (most likely due to the small number of type A/H1N1 subjects). This finding in subjects with the type B strain of influenza agrees with the findings in the phase 2b trial, in contrast to what was observed in the phase 3 trial in the original NDA where an earlier median TTAS was observed in the placebo subjects than in S-033188 subjects. However due to the small number of subjects with type B influenza in the previous trials, the conflicting results could have been observed by chance.

## **5.3 Conclusions and Recommendations**

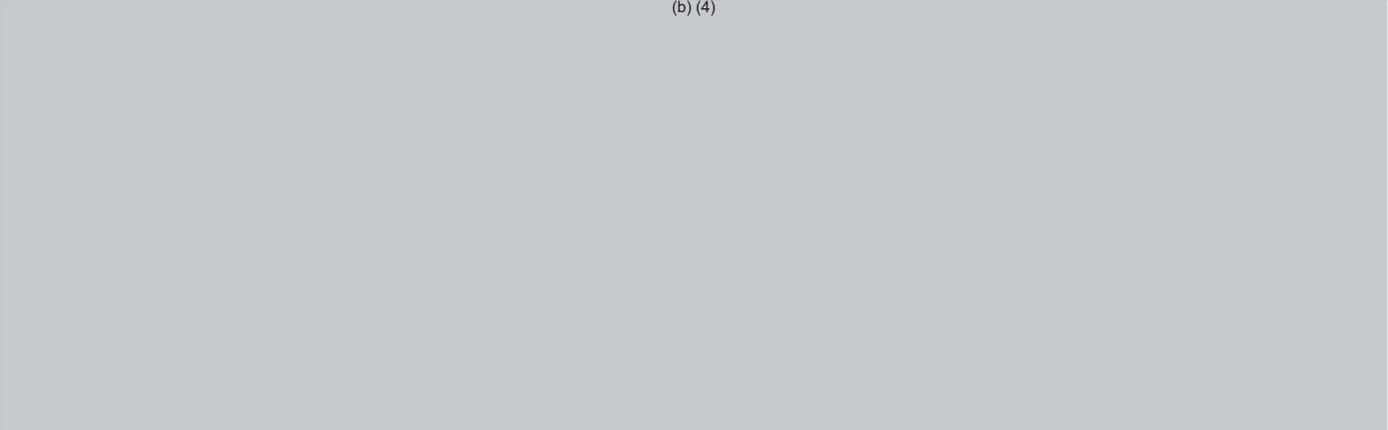
Based on the evidence presented, the majority of subjects in the trial were infected with type A/H3N2 and B strains of the influenza virus and there was clear evidence of a treatment effect for S-033188. There were far fewer subjects with the type A/H1N1 strain and the efficacy of S-033188 compared to placebo appeared to be less evident in these subjects. There were statistically significant results in favor of S-033188 over placebo in the subjects with the type A/H1N1 strain in the phase 2b trial. There was also a non-statistically significant trend in the first phase 3 trial which had an even smaller of subjects infected with type A/H1N1 influenza than the current trial (n=7 in the placebo and n=7 in the S-033188 arm). In addition, unlike the first phase 3 trial, the efficacy of S-033188 over placebo was also confirmed in the current trial for subjects with the type B strain of influenza.

#### **5.4 Labeling Recommendations (as applicable)**

The additional paragraphs in Section 8.4 of the proposed label summarizing results from this study read as follows:

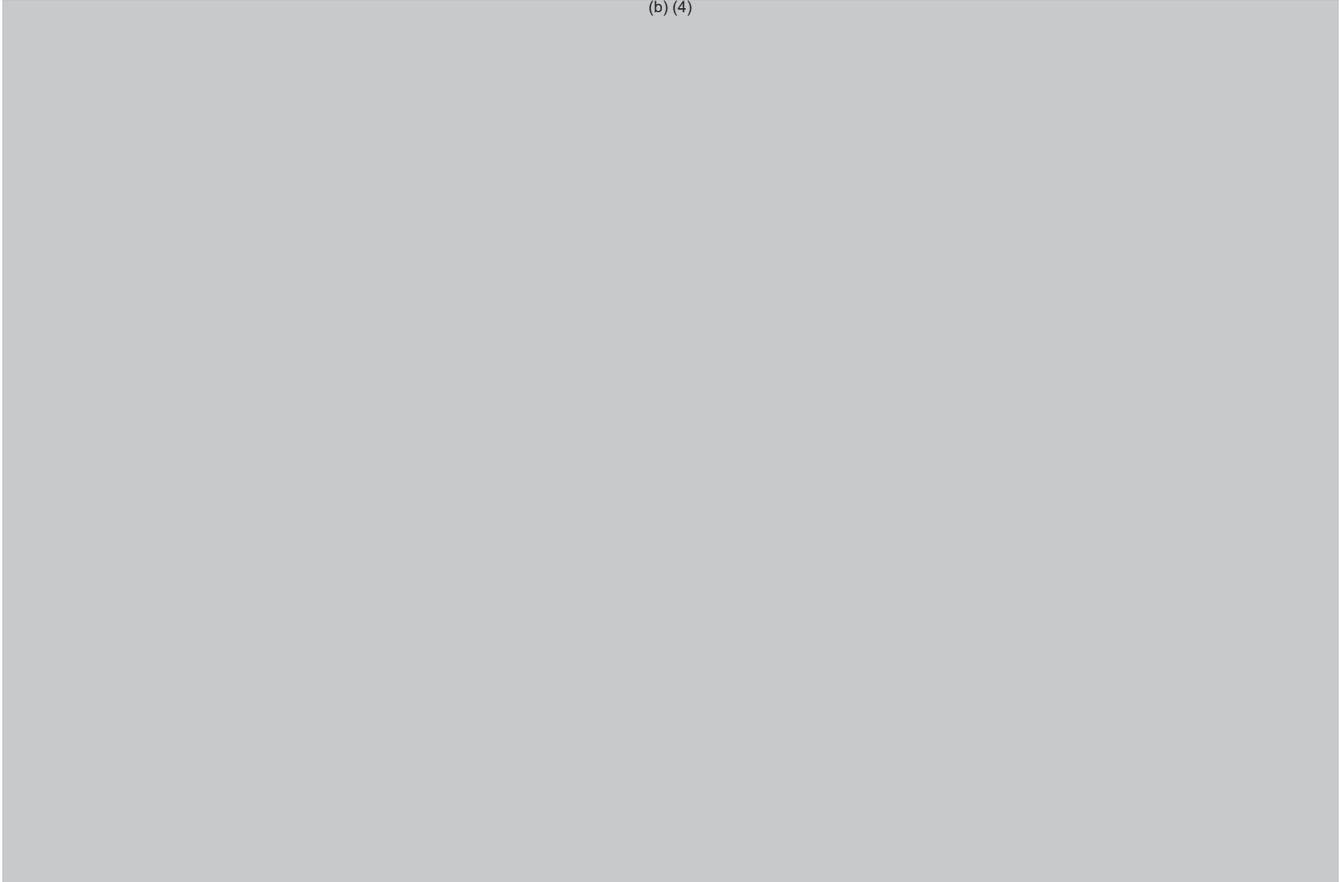
#### **8.4 Pediatric Use**

(b) (4)



Section 14.2 of the proposed label reads as follows:

(b) (4)



*Reviewer's comments:* The applicant proposed using differences in medians=<sup>(b)</sup><sub>(4)</sub> hours in Table 7 of the label instead of the median difference of <sup>(b)</sup><sub>(4)</sub> hours. Since labels for other drugs in adult trials used differences between medians the reviewer did not propose using a different method for this label. However, the reviewer has suggested removing the column for differences between the two treatment arms. This is similar to what was done for the peramivir pediatric sNDA where only medians for each treatment arm were provided. For the original baloxavir NDA submission (Section 14.1 of the label), the medical division allowed the applicant to keep the p-value as a footnote for the table and included in a footnote stating what the test was (i.e., Gehan-Breslow's generalized Wilcoxon test for Table 5 and the Peto-Prentice generalized Wilcoxon test for Table 6) because the p-value was not a test of the differences between the two medians.

Similarly, the reviewer also suggested removing the estimated difference of (b) (4) hours for the paragraph describing efficacy results for subjects infected with type B virus since the Hodges-Lehmann estimate was only (b) (4) hours. The reviewer also proposed removing the associated 95% CI and the p-value for this subgroup of subjects since the applicant did not pre-specify how to control the type I error rate for subgroup comparisons. The reviewer also recommended removing (b) (4)

## APPENDIX 1: Additional Details about Statistical Methods

The following SAS code was used by the reviewer for the comparison between the S-033188 group and the placebo group for the primary efficacy analysis:

```
proc lifetest data = analysisdata plots= (s (test atrisk(atrisktickonly)=0 50 100 200 300));  
where (TRTPN=1 or TRTPN=2);  
    {e.g., for a comparison of S-033188 and placebo}  
time AVAL * CNSR (1);  
strata TSSGR BLALLTYP REGION / group = TRTP test = (logrank wilcoxon peto modpeto);  
run;
```

- TRTP: Treatment group
- AVAL: Time to improvement of symptoms
- CNSR: =1 if censored, 0 otherwise
- TSSGR: Category of baseline composite symptom score ( $\leq 14$  or  $\geq 15$ )
- BLALLTYP: Pre-existing and worsened symptoms (Yes/No)
- REGION: Category of region (Japan/Asia, USA/Europe or Southern Hemisphere)

Similar code was used for Kaplan-Meier plots and with the exception of the strata statement which was

```
strata TRTP / test = (logrank WILCOXON peto modpeto);
```

Subjects in the primary efficacy analysis were selected using the parameter code (paramcd)='ALLIEDES'.

The following data step was required for the Hodges-Lehmann estimates to be computed:

```

data bal vs pl;
**** select only baloxavir and placebo subjects;   *** for use in proc npar1way;
set analysisdata;
if trtpn=1 or trtpn=2;
    *** censoring variable consistent with both trials;
    if cnsr>. then cnsr2=cnsr;
    *** set censored values to maximum follow-up time of 14 weeks;
    if cnsr2=1 then aval=max(aval,14*24);
run;

```

- TRTPN: Numeric treatment group

Hodges-Lehmann estimates and associated 95% CIs were computed using the following SAS code and a dataset that selected the two treatment groups for the comparison of interest:

```

proc npar1way data=bal_vs_pl hl;
class trtp;
var aval;
run;

```

The 10,000 bootstrap samples were generated by the following SAS code. A random seed of 16010831 and 16010832 was used for comparisons between the S-033188 and the Placebo or Oseltamivir, respectively. Then, the treatment group difference in median time was calculated by each bootstrapped sample and its 95% CI was constructed using percentiles of the bootstrap distribution.

```

proc surveysselect data = analysisdata seed = 16010831 out = boot01 method = urs
rate = 1.0 rep = 10000 outhits;
strata TRTPN;
run;

```

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/s/  
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FRASER B SMITH  
08/12/2019 03:29:47 PM

THAMBAN I VALAPPIL  
08/12/2019 04:25:12 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**CLINICAL MICROBIOLOGY/VIROLOGY**  
**REVIEW(S)**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA: 210854 SDN: 145 (Addendum to supplemental NDA review S00-1) DATE REVIEWED: 9/20/2019**

**Reviewer:** William Ince, Ph.D.

SDN NDA	Date Submitted	Date Received	Date Assigned
145	9/18/2019	9/18/2019	9/19/2019

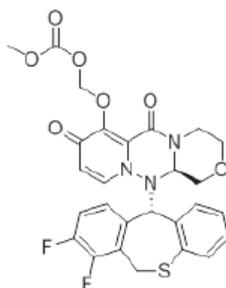
**Other submissions referenced:**

SDN NDA	Date Submitted	Date Received	Date Assigned
077	1/4/2019	1/4/2019	1/4/2019
120	6/03/2019	6/03/2019	6/04/2019

Sponsor	Contact
Genentech, Inc. 1 DNA Way MS-355G South San Francisco, CA 94080-4990	Roberto Barrozo, PhD Associate Regulatory Program Director Regulatory Program Management  Phone : (650) 784-2357 Fax: (650) 467-3198 Email: barrozo.roberto@gene.com

**Product Names:** S-033188 (prodrug) (active metabolite S-033447 or RSC-033447) **XOFLUZA®**  
**Chemical Names:** ((12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl)oxy)methyl methyl carbonate

**Structure:**



**S-033188**

**Molecular formula:** C<sub>27</sub>H<sub>23</sub>F<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S

**Molecular weight:** 571.55 (active metabolite S-033447, ~482)

**Drug category:** Antiviral

**Indication:** Treatment (b) (4) influenza (b) (4).

**Dosage Form/Route of administration:** Tablet/oral

**Abbreviations:** CSR, clinical study report; HA, hemagglutinin; HHC, household contact; mITT, modified intent-to-treat; NA, neuraminidase; NAI, neuraminidase inhibitor; PEP, post-exposure prophylaxis; POC, point of care; RIDT, rapid influenza diagnostic test; sNDA, supplemental New Drug Application; TTAS, time to alleviation of symptoms.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA: 210854 SDN: 145 (Addendum to supplemental NDA review S00-1) DATE REVIEWED: 9/20/2019**

**BACKGROUND and SUMMARY**

Baloxavir marboxil ([XOFLUZA®](#)), a polymerase acidic (PA) endonuclease inhibitor, was approved 10/24/2018 in the U.S. for the treatment of acute, uncomplicated influenza (b) (4) in subjects 12 years of age and older ([N210854.000](#)) with a pending approval for inclusion of subjects at high risk for influenza complications ([N210854.SE-001.077](#)).

This submission contains:

- Updated cell culture susceptibility data for potential resistance-associated substitutions.
- Sponsor's response to a request for concurrence on a Virology PMR sent 9/13/2019 in reference to the pending approval of NDA 210854 supplement 1 ([N210854.SE-001.077](#)).

**Proposed PMR:** Evaluate the impact of the following substitutions on susceptibility to baloxavir of cloned virus in cell culture: type A/H1N1 PA substitutions I38N, Q365R, and E397G; type A/H3N2 PA substitutions L71M+K158R and F191L; and type B PA substitutions S328G, A365S, and T619I.

Substitutions were identified that could be associated with reduced efficacy, but further evaluation may be required. I38N, F191L, S328G, Q365R (A/H1N1), A365S (B), E397G, and T619I were all treatment-emergent in only one case, but were selected because they were treatment-emergent substitutions associated with virus rebound or were treatment-emergent at amino acid positions previously associated with reduced susceptibility. L71M and K158R are polymorphisms that were identified in a baseline isolate with reduced susceptibility (see APPENDIX 6 in [N210854.SE-001.077](#)).

**Sponsor's response** (Times New Roman font):

The Sponsor has evaluated the impact of the PA substitutions A/H1N1 I38N and E397G, and A/H3N2 L71M using cloned virus in the plaque reduction assay, and results are shown in the table below. The A/H3N2 recombinant virus with PA/F191L could not be recovered after transfection of the plasmids likely due to a growth defect (Roche report no. 1094819)

Type/Subtype	Strain	Mean EC <sub>50</sub> value (nM)	SD	FC
A/H1N1	A/WSN/33	0.36	0.03	N/A
A/H1N1	A/WSN/33-PA/I38N	8.52	2.87	23.66
A/H1N1	A/WSN/33-PA/E397G	0.33	0.08	0.92
A/H3N2	A/Victoria/3/75	0.73	0.41	N/A
A/H3N2	A/Victoria/3/75-PA/L71M	0.46	0.08	0.64

Fold-change (FC) was calculated as relative EC<sub>50</sub> value of each tested virus to that of the cognate wild-type virus.

Based on this data (sic), we plan to include the I38N mutation into the updated USPI since it is associated with reduced susceptibility to baloxavir, but do not plan to include L71M, F191L, and E397 (sic) as they do not impact baloxavir susceptibility. With regard to the other listed substitutions (Q365R, L71M+K158R, S328G, A365S and T619I) the Sponsor has currently not planned to evaluate these mutations in the cell assay, because they are not expected to have significant impact on susceptibility to baloxavir and do not meet our following criteria for mutations to be generated by reverse genetics and assessed in cell culture:

- Treatment-emergent amino acid changes in PA N-terminal domain (1-200 aa)
- Amino acid changes which were detected in combination with I38x
- Treatment-emergent amino acid changes which were detected in more than one subject including past studies
- Amino acid substitutions that require >1 nucleotide change (even if detected in only one patient)

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA: 210854 SDN: 145 (Addendum to supplemental NDA review S00-1) DATE REVIEWED: 9/20/2019**

In detail, A/H1N1 PA/Q365R was detected in only one patient and not located in the PA-N terminus (1-200aa). For A/H3N2 PA/L71M+K158R, K158R was not a specific treatment-emergent substitution, but was found to be a polymorphic amino acid present at baseline in many patients. L71M was shown not to impact susceptibility to baloxavir. B/S328G, A365S and T619I are located outside of the PA-N terminal domain.

The sponsor would like to ask if the Division agrees with our assessment that the substitutions Q365R, L71M+K158R, S328G, A365S and T619I are unlikely to have an impact on susceptibility to baloxavir and therefore do not need to be generated by reverse genetics and evaluated in the plaque reduction assay.

**Reviewer note:** Study report 1094819 (S-033188-EB-335) was submitted in SDN 120, and I38N was included in labeling. Data from SDN 120 were reviewed and included in APPENDIX 13 of the Virology NDA review ([N210854.SE-001.077](#)); however, the sponsor did not identify the I38N, R356K, or E397G variants in the data table included in their “response” document. Thus, these substitutions were not noted as having been evaluated.

The table below serves to correct the records for the A/WSN/33 variants evaluated in study report S-33188-EB-335, associated with the respective mean EC<sub>50</sub> values and fold changes, reproduced in Table 2 of APPENDIX 13 of the Virology NDA review ([N210854.SE-001.077](#)).

Type/subtype	Strains	Mean EC <sub>50</sub> (nM)	SD	Fold-change	Study ID
A/H1N1	rgA/WSN/33 (H1N1)	0.36	0.03	N/A	<a href="#">S-033188-EB-335-N</a>
A/H1N1	rgA/WSN/33-PA/I38T (H1N1)*	6.90	2.94	19.16	<a href="#">S-033188-EB-335-N</a>
A/H1N1	rgA/WSN/33-PA/I38N (H1N1)	8.52	2.87	23.66	<a href="#">S-033188-EB-335-N</a>
A/H1N1	rgA/WSN/33-PA/R356K (H1N1)	0.38	0.07	1.07	<a href="#">S-033188-EB-335-N</a>
A/H1N1	rgA/WSN/33-PA/E397G (H1N1)	0.33	0.08	0.92	<a href="#">S-033188-EB-335-N</a>

\*rgA/WSN/33-PA/I38T (H1N1) was employed as an assay control.

**Virology follow-up response:** We appreciate your directing us to the data regarding I38N and E397G and agree with your assessment regarding these substitutions; these variants were not correctly labeled in the “response” document (SN 118 6/3/19) summary table and thus were not initially captured as having been evaluated.

The criteria we use for proposing that substitutions be evaluated include treatment-emergent and associated with reduced response or virus rebound (S328G in combination with A365S) or treatment-emergent in more than one subject, including different substitutions at the same position or structurally analogous positions in other types/subtypes (Q365R, see type B Y361H in trial T0831; T619I, see A/H3N2 E623G/K in multiple trials).

We acknowledge that S328G and A365S, detected at Day 4, were not temporally associated with the rebound event on Day 8, and that there were discordant results between the viral RNA at Day 8 (<LOD) and infectivity (5.2 log<sub>10</sub> TCID<sub>50</sub>/mL). We also acknowledge that for Q365R and T619I, the confidence in their structural equivalence to treatment-emergent substitutions identified in other virus types is low, and the substitutions identified in other types (Y361H and E623G/K) were evaluated and shown to not significantly affect susceptibility. We accept your conclusion that these do not need to be evaluated at this time.

With regard to L71M+K158R, we acknowledge that L71M alone did not appear to impact susceptibility, and that K158R was identified as a baseline polymorphism in isolates from more than one subject and

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA:** 210854 **SDN:** 145 (Addendum to supplemental NDA review S00-1) **DATE REVIEWED:** 9/20/2019

was not consistently associated with reduced susceptibility; however, the unique combination of L71M and K158R was associated with an otherwise unaccounted for reduction in susceptibility of a baseline isolate, and thus it is possible that this combination may contribute to reduced susceptibility.

Given that you have evaluated I38N and E397G, the primary concerns of the PMR, and that the data are equivocal with respect to whether the other proposed substitution meet our criteria for further evaluation, we will defer issuing a PMR to evaluate the proposed substitutions until more data become available or circumstances warrant. In any case, we encourage you to include these substitutions in future cell culture evaluations of susceptibility in your continuing effort to assess the scope of potential resistance pathways to baloxavir.

**CONCLUSIONS:**

The sponsor provided rationale for rejecting the proposed PMR. We have accepted their rationale on the basis that they had submitted data for the substitutions of greatest concern and that the data are equivocal with respect to whether other substitutions meet the criteria for cell culture evolution.

---

**William Ince Ph.D.**  
**Clinical Virology Reviewer**

**CONCURRENCES**

\_\_\_\_\_ Date: \_\_\_\_\_  
HFD-530/Clin Virology TL/J O'Rear

cc:

HFD-530/IND 126653  
HFD-530/Division File  
HFD-530/RPM/Kim

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**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.**  
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/s/  
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WILLIAM L INCE  
10/07/2019 11:15:54 AM

JULIAN J O REAR  
10/07/2019 11:49:12 AM

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019**

**Virology Reviewer: William Ince, Ph.D.**

<b>Sponsor</b>	<b>Contact</b>
Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990	Roberto Barrozo, Ph.D. Regulatory Program Management (650) 784-2357 barrozo.roberto@gene.com

<b>Reviewer</b>
William Ince, Ph.D.

<b>New Drug Application #</b>	<b>Supporting Document Number</b>	<b>Sequence Number (eCTD)</b>
210854 S-001	077	<a href="#">0066</a>

<b>CDER Receipt Date</b>	<b>Assigned Date</b>	<b>Review Complete Date</b>	<b>PDUFA Date</b>
<b>1/4/2019</b>	<b>1/4/2019</b>	<b>8/13/2019</b>	<b>11/4/19</b>

**Amendments:** None

**Additional Submissions Reviewed**

SDN	eCTD (SN)	Received	Assigned	Description <sup>a</sup>	Appendix <sup>b</sup>
079	0076	1/15/2019	1/24/2019	Cross-reference to IND 126653	NA
097	0095	3/13/2019	3/14/2019	Response to IR: References to applicable study reports previously submitted to the NDA.	NA
113	0112	5/3/2019	5/3/2019	120-Day Safety Update	NA
115	0115	5/14/2019	5/14/2019	Annotation update to revised labeling	NA
120	0118	6/3/2019	6/4/2019	Response to IR: Updated antiviral activity and phenotypic resistance analyses	13
128	0127	7/24/2019	7/25/2019	Revised draft labeling	NA
131	0130	8/2/2019	8/2/2019	Response to IR: Safety	NA
132	0131	8/9/2019	8/9/2019	Response to IR: Safety	NA

a. IR: Information request

b. Appendices include correspondence regarding the submission and additional actions taken. NA – Not applicable (material was reviewed and relevant information was incorporated into the NDA body).

**Related/Supporting Documents:** IND 126653

**Product Name(s):**

**Proprietary Name:** XOFLUZA®

**Non-Proprietary/USAN:** baloxavir marboxil (active metabolite: baloxavir)

**Code Name/Number:** S-033188 (prodrug), (active metabolite: S-033447 or RSC-033447)

**Chemical Name:** ({(12aR)-12-[(11S)-7,8-difluoro-6,11-dihydrodibenzo[b,e]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1H-[1,4]oxazino[3,4-c]pyrido[2,1-f][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate

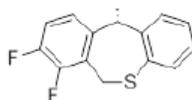
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

Structural formula:



**S-033188**

**Molecular Formula:** C<sub>27</sub>H<sub>23</sub>F<sub>2</sub>N<sub>3</sub>O<sub>7</sub>S

**Molecular Weight:** 571.55 Da (482 Da, active metabolite S-033447).

**Drug category:** Antiviral

**Dosage Form(s):** Tablets: 20 mg and 40 mg

**Route(s) of Administration:** Oral

**Indication(s):** Treatment of acute uncomplicated influenza in patients 12 years of age and older

**Dispensed:** Rx  OTC

**Abbreviations:** BID, twice daily; CPE, cytopathic effect; CSR, clinical study report; EC, effective concentration; HA, hemagglutinin; IC, inhibitory concentration; ITTI, intent-to-treat-infected; IV, intravenous; MDCK, Madin-Darby canine kidney; MOI, multiplicity of infection; NA, neuraminidase; NAI, neuraminidase inhibitor; OSE, oseltamivir; PBO, placebo; PER, peramivir; PK, pharmacokinetics ; PPV, positive predictive value; QD, once daily; RAT, rapid antigen test; RIDT, rapid influenza diagnostic test; RSV, respiratory syncytial virus; RT-PCR, reverse transcription-polymerase chain reaction; SOP, standard operating procedure; TCID<sub>50</sub>, 50% tissue culture infectious dose; TTAS, time to alleviation of symptoms; USPI, United States Prescribing Information; ZAN, zanamivir.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

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DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

**EXECUTIVE SUMMARY**

**1 RECOMMENDATIONS**

**1.1 Recommendation and Conclusion on Approvability**

This supplemental NDA for baloxavir marboxil is approvable from a Clinical Virology perspective for “the treatment of acute uncomplicated influenza (b) (4) in patients 12 years of age and older and *who are at high risk of developing influenza-related complications.*” Treatment with baloxavir marboxil resulted in statistically significant reductions in virus and viral RNA shedding in nasopharyngeal swabs for both type A and type B influenza virus infections, although as with previous trials, the magnitude of the effect on influenza B virus shedding was reduced compared to influenza A virus. Of note, equivalent and statistically significant clinical activity was apparent for baloxavir marboxil against both influenza A and influenza B virus infections, in contrast to pivotal trial data supporting the original NDA, which demonstrated a reduced clinical effect of treatment against influenza B virus infections across pivotal trials. Of the 290 subjects in the ITTI set (300 subjects were evaluated), 16 (5.5%) exhibited treatment-emergent resistance. Similar to previous trials, the highest frequency of treatment-emergent resistance was observed in A/H3N2 virus (9.6%), followed by A/H1N1 (5%); treatment-emergent resistance remains rare in type B virus (0.7%). Subjects with treatment-emergent resistant virus, while exhibiting virus rebound and prolonged virus shedding, also exhibited similar clinical responses to treatment compared to those without treatment-emergent resistance, in contrast to pivotal trial data supporting the original NDA. Taken together, the clinical trial data reviewed to date indicate that the clinical response in subjects with virus with reduced susceptibility (either influenza B virus in general, or treatment-emergent virus with reduced susceptibility) is variable; however, reduced virologic responses and prolonged virus shedding have remained consistently correlated with reduced susceptibility across trials.

**1.2 Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management:**

(b) (4)

**2. SUMMARY OF OND VIROLOGY ASSESSMENT**

Refer to the original NDA Clinical Virology Review ([N210854.000](#)) for information regarding non-clinical virology and pivotal clinical efficacy results and resistance evaluations for registrational studies.

**2.1 Clinical Virology**

With this supplemental NDA, the sponsor is seeking to add a new population to the indication: Treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours, *and are at high risk of developing influenza-related complications.* To support the new indication, the sponsor submitted results from trial T0832 ([NCT02949011](#)): *A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Subjects with Influenza at High Risk for Influenza Complications (CAPSTONE-2) (CSR 1602T0832).*

*Trial T0832*

Key inclusion criteria included subjects who had clinical signs and symptoms of influenza virus infection, were at high risk of complications due to influenza virus infection, and were rapid diagnostic test-positive or who had contact with a confirmed influenza case within 7 days (implemented at US sites during the second season of the trial). The primary endpoint was time to improvement of symptoms, and key secondary endpoints included virus and viral RNA shedding and resistance analyses.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#))

DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

A total of 1163 subjects were included in the intent-to-treat-infected (ITTI) population (primary analysis set, based on central-lab-confirmation of influenza virus infection by RT-PCR) and were randomized 1:1:1 to receive baloxavir marboxil, oseltamivir, or placebo. Influenza A/H1N1, A/H3N2, and type B virus infections comprised approximately 7%, 48%, and 42% of infections, respectively (approximately 3% were infected with an unknown type A subtype or were co-infected with multiple types/subtypes).

Baloxavir marboxil treatment significantly reduced the time to improvement of symptoms (TTIS) in trial T0832 (-29.1 median hours [-28%] vs. placebo). In a subset analysis based on virus type and subtype, baloxavir marboxil treatment was similarly effective compared to placebo across A/H1N1, A/H3N2, and type B virus subsets (differences in medians of -125 [-65%], -25 [-25%], and -26 [-26%] hours, respectively). These results differed from the previous phase 3 trial (T0831), carried out in subjects without risk of complications (and based on a different endpoint of time to *alleviation* of symptoms), in which the impact of treatment on clinical outcomes was reduced for type B virus infections compared to type A virus infections.

The treatment effect of baloxavir marboxil based on virologic endpoints was greater for type A virus infections compared to type B virus infection, with median Day 2 reductions of approximately -2.5 log<sub>10</sub> TCID<sub>50</sub>/mL vs -2 log<sub>10</sub> TCID<sub>50</sub>/mL, respectively. Likewise, the proportion of baloxavir marboxil-treated subjects who were positive for virus at each time point was reduced for type A virus infections compared to type B virus infections. Virologic responses were similar between A/H3N2 and A/H1N1 type A subtype subsets. These results are consistent with the reduced cell culture susceptibility of type B viruses measured at baseline in this trial and in trials evaluated to date (see below). The impact of treatment on viral RNA shedding was less apparent compared to the impact on virus shedding. Overall, virologic endpoint results were consistent with those observed in the previous phase 3 clinical trial (T0831).

Baseline viruses evaluated in trial T0832 exhibited susceptibilities to baloxavir in cell culture within the range measured historically for each virus type/subtype; median EC<sub>50</sub> values were 6.00 nM (1.79 - 20.67, n=80), 4.74 (0.05 - 199.9, n=498), and 48.45 (4.61 - 148.9, n=452) for A/H1N1, A/H3N2, and type B virus, respectively, with one clear outlier observed among A/H3N2 isolates (which was identified for follow-up genotypic and phenotypic analysis). Other than influenza virus type, there were no baseline genotypic markers identified that clearly associated with virologic or clinical response to baloxavir marboxil treatment.

Treatment-emergent resistance was observed in 5.3% (16/300; 5.5% [16/290] of subjects in the ITTI population) of subjects who were treated and evaluated for resistance overall and in 5% (1/20), 9.6% (14/146), and 0.7% (1/134) of subjects infected with A/H1N1, A/H3N2, and type B viruses, respectively. The differences in the frequencies of treatment-emergent resistance observed in trial T0832 across virus type/subtypes are consistent with what has been observed in trials to date; while the dominant virus types/subtypes in most trials, A/H3N2 virus infections have exhibited the highest rate of treatment-emergent resistance, and type B virus infections the lowest. These results are also consistent with recent cumulative surveillance reports in regions with significant baloxavir marboxil usage ([Japan, National Institute of Infectious Diseases surveillance report 7/16/2019](#)). One new treatment-emergent, resistance-associated substitution was identified in trial T0832, I38N, at a position at which the most frequent treatment-emergent resistance-associated substitutions have been identified to date. Treatment-emergent resistance in trial T0832 was associated with virus rebound and prolonged virus shedding (there was not a clear association between treatment-emergent resistance and viral RNA rebound or prolonged shedding), consistent with previous phase 3 trial (T0831) results; however, in contrast to the previous phase 3 trial, treatment-emergent resistance was not associated with a reduced impact of treatment on the primary clinical endpoint.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

**3. ADMINISTRATIVE**

**3.1 Reviewers' Signatures**

\_\_\_\_\_  
William L. Ince, Ph.D.  
Virologist, HFD-530

**3.2 Concurrence**

\_\_\_\_\_ Date \_\_\_\_\_  
HFD-530/J. O'Rear /TL Micro

cc:

HFD-530/NDA  
HFD-530/Division File  
HFD-530/RPM/Kim

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

**OND VIROLOGY REVIEW**

**1. INTRODUCTION AND BACKGROUND**

Baloxavir marboxil ([XOFLUZA®](#)) was approved 10/24/2018 in the U.S. for the treatment of acute, uncomplicated influenza (b) (4) in subjects 12 years of age and older ([N210854.000](#)). Baloxavir has been approved in Japan since February 2018. With this supplemental NDA, the sponsor is seeking to include in the indication a new population: "Treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours, and are at *high risk of developing influenza-related complications*." The sponsor has provided the results of 1 clinical trial (T0832) to support this new indication. The sponsor also proposes to update Section 12.4, *Antiviral Activity and Cross-Resistance* and has included non-clinical study reports evaluating the antiviral activity of baloxavir against additional temporally and geographically distinct isolates and neuraminidase inhibitor-resistant viruses.

The median cell culture EC<sub>50</sub> values of baloxavir reported in current labeling are 0.73 nM (n=19; range: 0.20-1.85 nM) for subtype A/H1N1 virus strains, 0.68 nM (n=19; range: 0.35-1.87 nM) for subtype A/H3N2 virus strains, and 5.28 nM (n=21; range: 3.33-13.00 nM) for type B virus strains ([XOFLUZA®](#)). Antiviral and clinical activity of baloxavir marboxil against influenza type B virus infections was reduced compared to influenza A virus infections in pivotal trials. Treatment-emergent resistance was observed in approximately 3-11% of adult/adolescent subjects (trials T0821 and T0831 [[N210854.000](#)]) and 23-26% of pediatric subjects (trials T0822 [[N210854.000](#)] and T0833 [[I126653.128](#)]).

**1.2 Methodology**

Methodologies for virologic assays used for trial T0832 were the same as those used in phase 3 trial T0831 supporting the original NDA and are described in the Clinical Virology Review ([N210854.000](#)). Key features of virologic assays are summarized below. The turn-around time for sample processing was collected, and in their analyses, the sponsor censored data from any sample that was not processed within 96 hours of acquisition, which affected 1.4% of all samples in trial T0832 and may have resulted in a reduction in infectivity.

**1.2.1: Virus quantitation**

Virus was quantified from respiratory specimens using a TCID<sub>50</sub> assay carried out by (b) (4). The LLOQ/LOD for the infectivity (virus) assay was 0.7 log<sub>10</sub> TCID<sub>50</sub>/mL ([CF-120-N](#)).

**1.2.2: Viral RNA quantitation**

Viral RNA quantitation in respiratory samples was carried out by (b) (4). Two quantitative (real time) RT-PCR assays, each specific for type A or B influenza virus were used on RNA extracted from each sample. The LLOQ and LOD for the assay were 2.18 and 2.05 log<sub>10</sub> copies["virus particles"]/mL, respectively, for type A virus, and 2.93 and 2.83 log<sub>10</sub> copies/mL, respectively, for type B virus ([RPT-VAL-INFA/8-FAST-FNL](#)). Note that RT-PCR values are reported in the CSR as "vp" [virus particle equivalent units]/mL, but are referred to as "copies/mL" throughout this review.

**1.2.3: Viral RNA sequencing**

Sequencing of the PA gene segment for trial T0832 was carried out by (b) (4) (procedure and validation reports [RPT-VAL039-FNL](#) and [RPT-VAL065-FNL](#)) as described in [N210854.000](#). Briefly, RNA was extracted from clinical specimens and three overlapping amplicons were generated for PA by generating cDNA in an RT reaction followed by nested PCR reactions (RT-PCR and sequencing primers listed in [N210854.000](#) APPENDIX E). The limit of detection of the sequencing assay was reported to be 3.99 log<sub>10</sub> "virus particles" [copies]/mL and 4.33 "virus particles" [copies]/mL for type A and B viruses, respectively.

**1.2.4: EC<sub>50</sub> value determination of baseline isolates**

Baseline EC<sub>50</sub> values for baloxavir were evaluated using the Virospot assay performed by (b) (4) (validation report: [EF-230-N](#); study data collection: [CB-247-N](#)). Note that EC<sub>50</sub> values

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obtained with the Virospot assay can range between 2-fold and 15-fold greater than EC<sub>50</sub> values obtained with a standard plaque reduction assay for the same virus or virus types (based on the data from study reports [EB-235-N](#), [EB-276-N](#), and [EB-290-N](#), which evaluated susceptibility of cloned wild-type virus and variants with resistance-associated substitutions using a plaque reduction assay). Baseline IC<sub>50</sub> values for oseltamivir carboxylate were evaluated by (b) (4) on virus isolated in cell culture from clinical specimens using the [NA-Star™](#) assay ([Buxton et al., 2000](#)).

### 1.3 Prior FDA virology reviews

The original NDA submission, NDA 210854, for baloxavir marboxil was reviewed by William L. Ince, Ph.D and Michael Thomson, Ph.D. ([N210854.000](#)). Pre-IND submissions were initially reviewed by Takashi Komatsu, Ph.D.; the original IND and subsequent submissions were reviewed by William L. Ince, Ph.D.

### 1.4 Major virology issues that arose during product development

Key concerns that arose in the course of the original NDA review for baloxavir marboxil included the observed reduced antiviral and clinical activity of baloxavir marboxil against type B influenza virus, which was consistent with a 5-10-fold greater EC<sub>50</sub> value against type B virus compared to type A viruses. In a pooled analysis of data from pivotal trials T0821 and T0831, the primary endpoint of time to alleviation of symptoms was not statistically significantly different between baloxavir marboxil treatment vs placebo in the type B virus subset. The median times to alleviation of symptoms in baloxavir and placebo arms were 65.4 (n=106) and 81.6 (n=43) hours (p = 0.1057), respectively, in the type B virus subset, vs. 51.3 (n=627) and 79.9 (n=277) hours (p <0.0001), respectively, in the type A virus subset, and 53.1 (n=753) and 79.9 (n=330) hours overall (p <0.0001). The impacts of treatment on virus and viral RNA shedding were consistent with the differences observed for the clinical endpoints between virus type subsets in trials T0821 and T0831. Approved labeling does not specify influenza type, and a Limitations of Use statement alludes to the variable impact of baloxavir marboxil across virus types ([XOFLUZA®](#); [N210854.000](#)). Data from trial T0832 submitted to support this supplement provide additional data on the antiviral activity of baloxavir marboxil against type B virus.

Treatment-emergent resistance arose in 2.7% to 11% of adults and adolescents, and 25.6% of pediatric subjects, in previous trials and appeared to have an impact on virologic and clinical endpoints, although subjects with treatment-emergent resistance generally derived a clinical benefit from treatment ([N210854.000](#)).

### 1.5 State of antivirals used for the indication sought

Refer to the original NDA Clinical Virology Review ([N210854.000](#)) for detailed background on influenza antivirals. There are currently no antivirals specifically indicated for the treatment of patients “at high risk of developing influenza-related complications”, as is being sought with this supplemental application.

## 2. NONCLINICAL VIROLOGY

### 2.1 Mechanism of action

Baloxavir marboxil (S-033188) is a prodrug that is hydrolyzed to the active compound, baloxavir, which selectively inhibits the endonuclease activity of the influenza virus PA polymerase complex subunit. Hence, the virus is prevented from generating the 5' 7-methylguanosine (m<sup>7</sup>G) cap-containing oligomers from host mRNA that are required for viral gene expression ([Krug et al., 1976](#)). Evidence supporting the mechanism of action includes inhibition of PA endonuclease activity in influenza virus ribonucleoprotein complexes, lack of specific activity against RNA-dependent RNA polymerase primer extension activity, and the mapping of determinants of resistance to the endonucleolytic site of the PA protein ([N210854.000](#)).

### 2.2 Cell culture studies

#### 2.2.1 Antiviral activity in cell culture

The sponsor evaluated the susceptibility of additional globally representative strains of influenza A and B virus ([S-033188-EB-318-N](#)), as well as viruses with substitutions conferring reduced susceptibility to oseltamivir

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(H275Y [A/H1N1], E119V, [H3N2], R292K [A/H3N2], and R152K [B]; [S-033188-EB-312-N](#)), in a plaque reduction assay. MDCK-SIAT1 or MDCK cells were infected with virus dilutions targeted to yield 50 plaques/well of a 12-well plate. After a 1 hour infection period, virus was removed, and cells were overlaid with plaque assay medium containing one of 6, 5-fold serial dilutions of drug (0.08-250 nM).

The evaluations of globally circulating strains submitted with this supplemental NDA included 7 A/H1N1 strains collected between 1999-2014, 12 A/H3N2 strains collected between 1999-2017 (including one strain with an I38M substitution), and 7 type B strains collected between 2003-2012 ([S-033188-EB-318-N](#)). Median EC<sub>50</sub> values for strains without known resistance-associated substitutions were 0.54 nM (range: 0.34-1.34 nM, n=7) of A/H1N1, 1.04 nM (range: 0.58-2.12 nM, n=11) for A/H3N2 (the EC<sub>50</sub> value of the I38M variant was 11.2 nM), and 9.91 nM (range: 5.5-14.2, n=7) for type B viruses.

Baloxavir was similarly active against stains with and without neuraminidase inhibitor resistance substitutions ([S-033188-EB-312-N](#)). The EC<sub>50</sub> value ranges for A/H1N1 (3 NA H275Y and 2 wild-type strains), A/H3N2 (1 NA E119V, 1 NA R292K, and 1 wild-type strain), and type B (1 NA R152K and 1 wild-type) were 0.60-1.19 nM, 1.35-2.63 nM, and 2.67-5.07 nM, respectively.

Given that the assay used provided consistent results across studies, the sponsor pooled EC<sub>50</sub> values from both of the above studies with data submitted to the original NDA (see Appendix13) and recalculated the summary statistics under section 12.4 *Antiviral Activity*. EC<sub>50</sub> values for pooled data (FDA analysis) were 0.73 nM (n=31; range: 0.20-1.85 nM) for A/H1N1 strains, 0.83 nM (n=33; range: 0.35-2.63 nM) for A/H3N2 strains, and 5.97 nM (n=30; range: 2.67-14.23 nM) for type B strains, identical to the summary statistics reported by the sponsor in proposed labeling (Review Section 6).

### 3 CLINICAL VIROLOGY REVIEW OF EFFICACY

#### 3.1 Trial T0832 ([NCT02949011](#))

##### 3.1.1 Trial overview

**Title:** A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Subjects with Influenza at High Risk for Influenza Complications (CAPSTONE-2) ([CSR 1602T0832](#); protocol reviewed in [I126653.022](#); [I126653.058](#); [I126653.102](#))

##### Protocol summary

**Primary endpoint:** The time to improvement of influenza symptoms (with modification for preexisting symptoms), defined as the time from the start of study treatment to the improvement of influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). The improvement of influenza symptoms was defined as the time when all of a patient's influenza symptoms had been alleviated, maintained, or improved for a duration of at least 21.5 hours (24 hours – 10%).

##### Secondary endpoints relevant to Virology:

- Proportion of patients positive for virus titer at each time point.
- Proportion of patients positive by RT-PCR at each time point.
- Change from baseline in virus titer and viral RNA at each time point.
- AUC adjusted by baseline in virus titer and viral RNA.
- Time to cessation of virus and viral RNA shedding.
- Time to resolution of fever.
- Time to improvement of each influenza symptom.
- Time to return to pre-influenza health status.
- Requirement for systemic antibiotics for infections secondary to influenza infection.
- Intrahousehold infection rate (for Japan only).

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- Serum influenza antibody titer.
- Polymorphic and treatment-emergent amino acid substitutions in the PA gene.
- Drug susceptibility in patients with evaluable virus.

#### Inclusion criteria relevant to Virology:

- Male or female patients  $\geq 12$  years at the time of signing the informed consent form.
- Patients with a diagnosis of influenza virus infection confirmed by all of the following:
  - a. Fever  $\geq 38^{\circ}\text{C}$  (axillary) during the pre-dose examinations or  $> 4$  hours after dosing of antipyretics if they were taken.
  - b. At least 1 each of the following general and respiratory symptoms associated with influenza (excluding those that are chronic and existed in the 30 days prior to the influenza episode) is present with a severity of moderate or greater:
    - General symptoms (headache, feverishness or chills, muscle or joint pain, or fatigue)
    - Respiratory symptoms (cough, sore throat, or nasal congestion).
  - c. (*US sites only, implemented 8/29/2017*) A positive rapid influenza diagnostic test (RIDT) result OR  
A patient with a negative RIDT may be enrolled if the patient reports contact with a known case of influenza within the prior 7 days and all other inclusion criteria are met. Inclusion in the ITTI population required central-lab confirmation of infection by RT-PCR.

**Note:** All subjects deemed eligible by criteria a and b were given an RIDT (provided by the sponsor or investigator). Per protocol, the subject was informed of the RIDT result, and if the result was negative, “the investigator will explain the low and unpredictable sensitivity of the RIDT and will confirm with the patient that they wish to continue in the study”, and the decision was recorded. Informing the subject of the test result and prompting a decision as to whether they want to continue may result in RIDT-dependent exclusion of some subjects ([1126653.033](#); [1126653.058](#)).

- The time interval between the onset of symptoms and the pre-dose examinations (Screening) is 48 hours or less. The onset of symptoms is defined as either:
  - a. Time of the first increase in body temperature (an increase of at least  $1^{\circ}\text{C}$  from normal body temperature)
  - b. Time when the patient experiences at least 1 new general or respiratory symptom.
- Patients will be considered at high risk of influenza complications if they meet the criteria outlined in the definition of high risk adapted from [CDC criteria](#).

#### Exclusion criteria relevant to Virology:

- Patients with severe influenza virus infection requiring inpatient treatment.
- Patients with known allergy to oseltamivir (Tamiflu®).
- Patients unable to swallow tablets or capsules.
- Patients who have previously received S-033188.
- Patients weighing  $< 40$  kg.
- Patients who have been exposed to an investigational drug within 30 days prior to the pre-dose examinations.
- Patients with concurrent infections at the pre-dose examinations requiring systemic antimicrobial therapy.
- Patients with liver disease associated with hepatic impairment.
- Patients with cancer within the last 5 years (unless non-melanoma skin cancer).
- Patients with untreated HIV infection or treated HIV infection with a  $\text{CD4}^+$  T cell count  $< 350$  cells/ $\mu\text{L}$  in the last 6 months.

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- Patients with immunosuppression following organ or bone marrow transplants.
- Patients exceeding 20 mg of prednisolone or equivalent dose of chronic systemic corticosteroids.
- Patients who have received peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the pre-dose examinations.
- Patients who have received an investigational monoclonal antibody for a viral disease in the last year.

### Design overview

A total 2182 subjects (2178 in the safety population, and **1163** in the ITTI population [see below]) were randomized 1:1:1 to receive one of 3 treatments: Baloxavir marboxil (a single dose on study day 1 of 40 mg for subjects <80 kg and 80 mg for subjects ≥80 kg), oseltamivir (75 mg BID for 5 consecutive days) or placebo. Subjects were enrolled between 1/11/2017 and 4/20/2018.

### 3.1.2 Virologic assessments

Two nasopharyngeal swabs (not specified whether it was one from each nostril) were collected pre-dose at Visit 1 (Day 1, at the same time as the rapid influenza diagnostic test [RIDT]), Visit 2 (Day 2), Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 9). Nasopharyngeal swabs were the preferred method of virologic sample collection, but pharyngeal swabs were acceptable when nasopharyngeal swabs could not be performed (sample types were not distinguished in patient-level data). If circumstances permitted, specimens were also to have been collected at Optional Visit 1 (Day 4) and Optional Visit 2 (Day 6). If the investigator or sub-investigator determined that influenza symptoms were ongoing, specimens were also to have been collected at Visit 6 (Day 15) and Visit 7 (Day 22) (or at early termination).

### 3.1.3 Baseline characteristics

A total of 2182 subjects were randomized (2 subjects were each assigned 2 subjects IDs; 1 patient was initially assigned ID (b) (6) [baloxavir marboxil group] and was re-assigned ID (b) (6) [oseltamivir group] before dosing and 1 patient was initially assigned ID (b) (6) [placebo group] and was re-assigned ID (b) (6) [oseltamivir group] before dosing) and of these, 1163 subjects were included in the ITTI set based on central-lab RT-PCR confirmation (Note: 1196 subjects were RT-PCR-positive for influenza virus at baseline; however, 32 of these subjects were excluded from the ITTI set based on enrolment at a non-GCP-compliant site [6 in placebo, 12 in oseltamivir, and 14 in the baloxavir marboxil arms] and one subject was not treated).

Overall, the numbers of subjects in the ITTI population infected with influenza virus types A/H1N1, A/H3N2, and B were 80 (6.9%), 557 (47.9%), and 484 (41.6%), respectively; of the 42 additional subjects, 28 subjects (2.4%) were infected with an unknown type A subtype virus, 2 subjects (0.2%) were infected with both A/H1N1 and A/H3N2 viruses, and 12 subjects (1%) were infected with both type A and B viruses (Table 3.1.3.1). The representation of influenza virus types/subtypes in the trial are consistent with global representations of circulating type/subtypes during the period of the trial (64.2% type A [69.4% A/H3N2 and 30.6% A/H1N1], and 35.8% type B; [WHO FluNet database \[flumart\]](#)).

Of the 2182 subjects randomized, 2181 had baseline RIDT results reported, and of these subjects, 852 (39%) were negative. The overall positive and negative predictive values of RIDTs based on central-lab RT-PCR confirmatory testing (n=2155) were 77.5% and 79.1%, respectively (FDA analysis). The most common test was the Clearview Exact test ([K1030610](#); [I26653.022](#)), used for 69% of subjects evaluated, which exhibited positive and negative predictive values of 62.5% and 79.5%, respectively. RIDT performance in general was consistent across influenza virus type. Among subjects confirmed to be infected with type A influenza virus, 16.9% were RIDT-negative, whereas among subjects infected with type B virus, 11.5% were RIDT-negative. RIDT performance in subjects ≥75 years of age was similar to that observed overall (positive and negative predictive values were 74% and 78%, respectively).

Baseline characteristics of the ITTI set were generally evenly distributed across treatment arms (Table 3.1.3.1); however, females were slightly under-represented in the baloxavir marboxil treatment arm compared to

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placebo (50% vs 53%), and a slightly lower proportion of subjects who were within 12 hours of symptoms onset were randomized to baloxavir marboxil.

**Table 3.1.3.1: Baseline characteristics of the ITTI set.**

Characteristic	Statistic/subset	Baloxavir marboxil	Oseltamivir	Placebo
Age (years) <sup>a</sup>	n	388	389	386
	Mean	52.3	51.1	51.9
	SD	16.8	17.0	16.7
	Min	12	12	12
	Median	55.0	53.0	53.0
	Max	84	89	86
		% (n)	% (n)	% (n)
	12 to 19	4.9 (19)	5.7 (22)	4.4 (17)
	20 to 29	7.5 (29)	6.9 (27)	5.7 (22)
	30 to 39	10.8 (42)	11.3 (44)	15 (58)
	40 to 49	16.2 (63)	19.3 (75)	14.2 (55)
	50 to 59	21.4 (83)	21.3 (83)	26.2 (101)
	60 to 64	10.1 (39)	9 (35)	7.8 (30)
	65 to 74	21.9 (85)	20.1 (78)	19.7 (76)
	≥ 75	7.2 (28)	6.4 (25)	7 (27)
	< 80	61.6 (239)	59.9 (233)	60.1 (232)
≥ 80	38.4 (149)	40.1 (156)	39.9 (154)	
Sex <sup>a</sup>	Male	49.7 (193)	49.1 (191)	46.6 (180)
	Female	50.3 (195)	50.9 (198)	53.4 (206)
Region <sup>a</sup>	Asia	41 (159)	39.1 (152)	39.1 (151)
	North America/Europe	54.6 (212)	56.6 (220)	56 (216)
	Southern Hemisphere	4.4 (17)	4.4 (17)	4.9 (19)
Race <sup>a</sup>	American Indian or Alaska Native	0.3 (1)	0.8 (3)	0.5 (2)
	Asian	43 (167)	41.9 (163)	40.7 (157)
	Black or African American	10.1 (39)	7.5 (29)	7.8 (30)
	White	45.9 (178)	48.3 (188)	50.3 (194)
	Other	0.8 (3)	1.5 (6)	0.8 (3)
Smoking habits <sup>a</sup>	Yes	15.2 (59)	17 (66)	15 (58)
	No	84.8 (329)	83 (323)	85 (328)
Composite symptom scores at baseline <sup>a</sup>	n	388	389	386
	Mean	14.3	14.2	14.4
	SD	3.7	3.5	3.6
	Min	5	5	4
	Median	15.0	14.0	15.0
	Max	21	21	21
		% (n)	% (n)	% (n)
	≤ 14	48.5 (188)	51.7 (201)	48.7 (188)
≥ 15	51.5 (200)	48.3 (188)	51.3 (198)	
Time to treatment from influenza symptoms onset (hours) <sup>a</sup>	≥ 0 to ≤ 12	7 (27)	9.5 (37)	10.9 (42)
	> 12 to ≤ 24	38.9 (151)	30.6 (119)	38.9 (150)
	> 24 to ≤ 36	29.4 (114)	36.2 (141)	31.1 (120)
	> 36 to ≤ 48	24.5 (95)	23.7 (92)	19.2 (74)
	Missing	0.3 (1)	0 (0)	0 (0)
Influenza virus subtype based on RT-PCR <sup>b</sup>	A/H1N1	7.2 (28)	9.0 (35)	4.4 (17)
	A/H3N2	46.9 (182)	48.8 (190)	47.9 (185)
	A/Unknown	1.8 (7)	2.6 (10)	2.9 (11)
	A/H1N1 and A/H3N2	0 (0)	0.3 (1)	0.3 (1)
	A/H3N2 and B	0.3 (1)	0.5 (2)	0.8 (3)
	A/H1N1 and B	0.3 (1)	0 (0)	0.3 (1)
	A/Unk and B	0.5 (2)	0.5 (2)	0 (0)
	B	43.0 (167)	38.3 (149)	43.5 (168)
	RT-PCR positive non-GCP site (not included in ITTI) n	14	12	6
Influenza vaccination <sup>a, c</sup>	Yes	91 (23.5)	104 (26.7)	99 (25.6)
	No	297 (76.5)	285 (73.3)	287 (74.4)
	n	378	380	377
	Mean	4.96	5.25	5.27

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Influenza virus titer at baseline log <sub>10</sub> (TCID <sub>50</sub> /mL) <sup>a</sup>	SD	2.28	2.27	2.39
	Min	0.7	0.7	0.7
	Median	5.20	5.70	6.00
	Max	10.0	9.7	9.5
Influenza virus titer at baseline log <sub>10</sub> (TCID <sub>50</sub> /mL) <sup>b</sup>	Type/subtype	Median (n)		
	A/H1N1	4.95 (28)	6.35 (34)	5.7 (17)
	A/H3N2	5 (178)	5.2 (186)	5 (183)
	B	5.5 (165)	6 (147)	6.8 (167)
Viral RNA at baseline log <sub>10</sub> copies/mL <sup>a</sup>	n	385	387	378
	Mean	6.72	6.81	6.87
	SD	1.43	1.37	1.54
	Min	2.2	2.2	2.2
	Median	7.00	7.00	7.30
	max	9	9.3	9.7
Viral RNA at baseline log <sub>10</sub> copies/mL by virus type/subtype <sup>b</sup>	Type/subtype	Median (n)		
	A/H1N1	6.2 (28)	6.78 (35)	6.5 (17)
	A/H3N2	7.04 (182)	7.015 (190)	7.05 (185)
	B	7.22 (167)	7.26 (149)	7.59 (166)

a. Sponsor analyses derived from CSR Table 11-2.

b. FDA analysis of data derived from datasets ADSL and ADLB1.

c. Influenza vaccination within 6 months prior to enrollment.

### 3.1.4 Primary endpoint analysis summary

The overall impact of baloxavir marboxil treatment on the time to improvement of symptoms (TTIS) in trial T0832 (-29.1 median hours [-28%] vs. placebo) (Table 3.1.4.1) was similar to the overall impact on time to alleviation of symptoms (a similar endpoint) observed in otherwise healthy subjects (-26.8 median hours [-33.5%] vs placebo; Integrated Summary of Efficacy [studies T0821 and T0831; Table 2.1.1.1; SDN 000 see also [N210854.000](#)]).

In a subset analysis based on virus type and subtype, baloxavir marboxil treatment was similarly effective compared to placebo across A/H1N1, A/H3N2, and type B virus subsets (differences in medians of -125 [-65%], 25 [-25%], and -26 [-26%] hours, respectively); the large effect observed in A/H1N1 subset appears to have been driven by a disproportionately long TTIS in the placebo arm (Table 3.1.4.1).

With respect to type B infections, the results are in contrast to those observed in both trials in otherwise healthy subjects, where the overall median difference vs placebo in the type B subset ranged from -6.5 to -14.0 hours (Hodges-Lehmann estimate), nearly half the magnitude of the response observed in type A infections in otherwise healthy subjects overall ([N210854.000](#)). It should be noted that the single-arm pediatric trials evaluated to date (T0822 [[N210854.000](#)] and T0833 [[I126653.128](#)]), baloxavir marboxil treatment clinical responses were similar between type A and type B virus infections.

Taken together, among the trials evaluated to date, there is a high degree of variability in the clinical treatment response among type B virus infections relative to responses in type A virus infections. An independent analysis of the data generally confirmed the sponsor's results.

**Table 3.1.4.1 (sponsor analysis): Time to improvement of symptoms by influenza virus type/subtype, ITTI.**

Summary statistic <sup>a</sup>	Treatment arm		
	Baloxavir marboxil	Oseltamivir	Placebo
<b>Overall</b>			
N	385	388	385
Median (hours)	73.2	81	102.3
95% CI (hours)	67.2, 85.1	69.4, 91.5	92.7, 113.1
Difference vs placebo <sup>b</sup>	-29.1		
P value vs placebo <sup>c</sup>	0.0008		

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**NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019**

**Virology Reviewer: William Ince, Ph.D.**

P value vs oseltamivir <sup>c</sup>	0.8449		
<b>A/H1N1</b>			
N	28	35	17
Median (hours)	67	56.9	192.1
95% CI (hours)	58.3, 101.4	32.2, 72.5	61.3, ---
Difference vs placebo <sup>b</sup>	-125.1		
P value vs placebo <sup>c</sup>	0.1079		
P value vs oseltamivir <sup>c</sup>	0.0697		
<b>A/H3N2</b>			
N	180	190	185
Median (hours)	75.4	68.2	100.4
95% CI (hours)	62.4, 91.6	53.9, 81	88.4, 113.4
Difference vs placebo <sup>b</sup>	-25.0		
P value vs placebo <sup>c</sup>	0.0141		
P value vs oseltamivir <sup>c</sup>	0.1433		
<b>B</b>			
N	166	148	167
Median (hours)	74.6	101.6	100.6
95% CI (hours)	67.4, 90.2	90.5, 114.9	82.8, 115.8
Difference vs placebo <sup>b</sup>	-26.0		
P value vs placebo <sup>c</sup>	0.0138		
P value vs oseltamivir <sup>c</sup>	0.0251		

Source: Derived from CSR Tables 11-5 and 11-8.

a. Subjects who did not experience improvement of symptoms were treated as censored at the last observation time point.

b. Difference between medians.

c. Long-rank test stratified by region, composite symptom scores at baseline, and preexisting and worsened symptom.

### **3.1.5 Virologic response**

#### *Time to virus negativity*

A total of 98 samples of the 6855 collected (1.4%) for virus titer evaluation were processed later than 96 hours after collection, which may have affected the reliability of infectivity measurements of the virus in the sample (influenza virus infectivity degrades at or above room temperature and with each freeze/thaw cycle; see Appendix 1), and therefore were censored in the sponsor's analysis. These samples were generally proportionally distributed across treatment arms and subgroups, and inclusion of these samples had a negligible impact on virus shedding endpoints (FDA analyses, not shown).

The sponsor reported time to virus negativity for each subject, defined as the time between the initiation of treatment and the first time point that virus is undetectable. This endpoint does not account for virus rebound. Overall, median times to cessation of virus shedding were 48, 96, and 96 hours in the baloxavir, oseltamivir, and placebo treatment arms, respectively, based on the sponsor's Kaplan-Meier estimates (Table 3.1.5.1). The treatment effect compared to placebo was primarily driven by type A virus infections, which had a median time to negativity of 24 hours, compared to 72 hours for type B virus. The sponsor's analysis results were consistent with an independent FDA analysis of uncensored data based on the proportion virus positive at each analysis day (Appendix 2). Treatment did not appear to significantly affect time to viral RNA negativity relative to placebo, based on the proportion positive at each study day (Appendix 3); only at Day 3 was the percent viral-RNA-positive statistically significantly reduced in the baloxavir marboxil arm compared to placebo (92.3% vs 97.8%, respectively), but only slightly in magnitude and only in the A/H3N2 subset.

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**Table 3.1.5.1 (sponsor analysis): Time to cessation of virus shedding (first negative time point) (ITTI).**

Summary statistic <sup>a</sup>	Treatment arm		
	Baloxavir marboxil	Oseltamivir	Placebo
<b>Overall</b>			
N	352	356	352
Median (hours)	48	96	96
Difference vs placebo <sup>b</sup>	-48		
P value vs placebo <sup>c</sup>	<0.0001		
P value vs oseltamivir <sup>c</sup>	<0.0001		
<b>A/H1N1</b>			
N	28	33	17
Median (hours)	24	72	72
Difference vs placebo <sup>b</sup>	-48		
P value vs placebo <sup>c</sup>	0.0027		
P value vs oseltamivir <sup>c</sup>	<0.0001		
<b>A/H3N2</b>			
N	169	177	169
Median (hours)	24	72	96
Difference vs placebo <sup>b</sup>	-72.0		
P value vs placebo <sup>c</sup>	<0.0001		
P value vs oseltamivir <sup>c</sup>	<0.0001		
<b>B</b>			
N	151	138	158
Median (hours)	72	96	96
Difference vs placebo <sup>b</sup>	-24		
P value vs placebo <sup>c</sup>	<0.0001		
P value vs oseltamivir <sup>c</sup>	<0.0001		

Source: Derived from CSR Tables 14.2.1.1.1 and 14.2.1.6.7.

- a. Subjects who did not achieve negativity were treated as censored at the last observation time point.
- b. Difference between medians.
- c. Generalized Wilcoxon test stratified by region, composite symptom scores at baseline, and preexisting and worsened symptom.

**Change from baseline in virus and viral RNA shedding (FDA analysis)**

Virus shedding was statistically significantly reduced compared to placebo in both the oseltamivir and baloxavir marboxil treatment arms at Day 2 (treatment initiated on Day 1) (Figure 3.1.5.1); however, the treatment effect was greater for type A virus infections compared to type B virus infection, with median Day 2 reductions of approximately -2.5 log<sub>10</sub> TCID<sub>50</sub>/mL vs -2 log<sub>10</sub> TCID<sub>50</sub>/mL, respectively. The differences in the treatment effect as measured by this endpoint between type A and type B viruses were not as great as observed in trials T0821 and T0831 (median Day 2 reductions in virus shedding of pooled data were approximately -3 log<sub>10</sub> and -2 log<sub>10</sub> relative to placebo for type A and type B virus infections, respectively). Of note, oseltamivir reduced virus shedding by approximately 1 log<sub>10</sub> TCID<sub>50</sub>/mL at Day 2 for type A virus but appeared to have no impact on type B virus shedding.

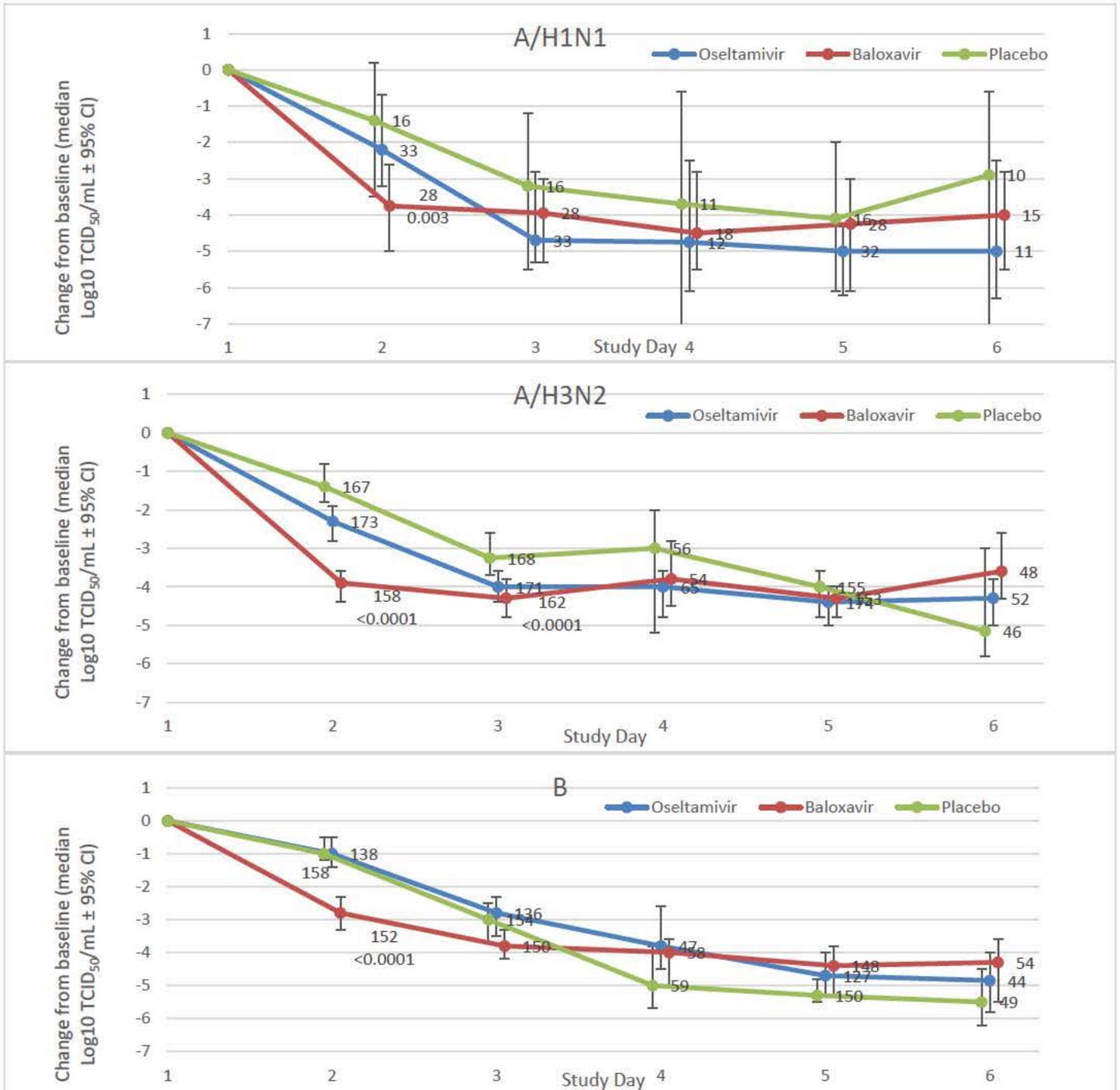
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**Figure 3.1.5.1 (FDA analysis):** Virus shedding change from baseline. Analyses included all data from subjects who were included in the ITTI set (which excludes subjects who were RT-PCR positive but enrolled at sites censored for non-GCP compliance); data were not censored based on the 96 hour turn-around time for sample processing. Study Days include the following analysis days (days relative to treatment initiation on day 1): Day 1: days -3 to 1; Day 2: day 2; Day 3: days 3-4; Day 4: day 4; Day 5: days 5 and 6; Day 6: day 6; Day 9: days 7 to 11. Data labels indicate number of subjects included in the analysis (top) and P values (bottom) <0.05 based on a Mann-Whitney test compared to placebo.



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Baloxavir treatment statistically significantly reduced viral RNA shedding by approximately -0.5 and -0.3 log<sub>10</sub> copies/mL compared to placebo at Day 2 in the type A and type B virus subsets, respectively (Appendix 4), consistent with the limited impact of baloxavir marboxil treatment on viral RNA shedding relative to virus shedding observed in previous trials.

In summary, baloxavir marboxil treatment had impacts on virus and viral RNA shedding across influenza virus type/subtype subsets consistent with what has been observed in previous trials. Baloxavir marboxil continues to appear less active against type B virus as measured by virologic endpoints, but the virologic response was less predictive of the clinical response in this trial.

#### 3.1.6 Ratio of post-baseline to baseline influenza antibody titer.

Post-baseline to baseline serum influenza virus antibody titer ratios measured by hemagglutination inhibition were generally similar between treatment arms (Appendix 14). Median ratios were the same for placebo and baloxavir marboxil arms across A/H1N1, A/H3N2, and type B virus-infected subjects; however, the distribution was shifted slightly lower in the baloxavir marboxil arm compared to placebo for titers against the Yamagata strain in subjects infected with type B virus (P=0.041). These results are consistent with trends observed for previous trials ([N210854.000](#)). The shift was only observed in one virus type subgroup analysis, and the clinical consequence of these slight but apparent perturbations in post-infection antibody titers is not known. Labeling currently makes no representation as to the impact of baloxavir marboxil treatment on the immune response to influenza virus infection.

#### 3.1.7 Intra-household infection rate.

The sponsor reported results from an exploratory analysis of the rate of intra-household transmission in households of study subjects. Subjects at study centers in Japan were interviewed about household cases of influenza at baseline and at Days 1 to Day 15. The percentage of household members reported by the subject to have been diagnosed with influenza during the observation period were reported. The intra-household infection rate of influenza between Days 1 and 15 were 10.7%, 12.4%, and 9.5% in the baloxavir marboxil, oseltamivir, and placebo arms, respectively; differences were not statistically significant (p >0.5 Poisson regression model; CSR table 14.2.27.1). Similar trends were observed in virus type/subtype subsets.

## 4. RESISTANCE

### 4.1 Baseline resistance (FDA analysis)

#### *Phenotypic:*

Baseline isolate EC<sub>50</sub> value fold changes were derived relative to a reference according to virus type/subtype. The distributions of such normalized values within type/subtype were very similar to the distribution of absolute values in trial T0832, which show that the median absolute EC<sub>50</sub> value for type B viruses was approximately 8- to 10- fold higher than for type A viruses (Table 4.1.1). Median baseline EC<sub>50</sub> values of for each virus type/subtype in trial T0832 were similar to those reported for trial T0831, in which the same assay was used (2.3-fold lower for A/H1N1 virus and within 1.1-fold for A/H3N2 and type B virus [N210854.000](#)). All but one subject had baseline fold changes from reference that were <3-fold the median fold-change (Table 4.1.1), and overall, there was no correlation between baseline EC<sub>50</sub> fold change value relative to the median and virologic response as measured by change from baseline at study Day 2 (24 hours post treatment initiation) (Appendix 9). Baseline virus (A/H3N2) from subject (b) (6) exhibited an EC<sub>50</sub> value 40-fold over reference (42.5-fold over the median EC<sub>50</sub> value for A/H3N2 baseline isolates); however, this subject, treated with baloxavir, was virus-negative by 24 hours post treatment, and had improved symptoms at 18 hours post treatment. The baseline virus from subject (b) (6) contained two PA polymorphisms: K158R and L71M, but only L71M was unique to this subject and thus to the significantly elevated fold change in EC<sub>50</sub> value. Neither of these polymorphisms has been observed in previous studies. L71M is at a highly conserved position (M was found in 0.007% of NCBI database sequences) and resides in a flexible structure distant from the baloxavir binding pocket, so it is unclear how it may influence susceptibility ([Kowalinski et al., 2012](#)). K158R is observed in 2.3% of NCBI database sequences. L71M was evaluated for its impact on susceptibility in cloned virus (A/Victoria/3/75-

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PA/L71M) in a standard plaque reduction assay (as previously described for evaluations of cloned virus [N210854.000](#)) and did not reduce susceptibility; the EC<sub>50</sub> value fold-change from the WT parent strain was reported as 0.64 (study report [S-033188-EB-335-N](#), SDN 120; see Appendix 13). The sponsor should evaluate L71M in combination with K158R, although this substitution also resides outside of the binding pocket and is not in close proximity to L71M ([Kowalinski et al., 2012](#)).

**Table 4.1.1 (FDA analysis): Summary of baseline EC<sub>50</sub> values across virus type/subtypes**

Study	T0832 <sup>a</sup>		
Type/subtype <sup>b</sup>	A/H1N1	A/H3N2	B
Reference EC <sub>50</sub> median (range, n) <sup>c</sup>	7.65 nM (5.63-13.7 nM, 10)	5.56 nM (2.56-5.95 nM, 9)	18.36 nM (16.11-47.51 nM, 6)
Subjects isolate EC <sub>50</sub> median (range, n)	6.00 nM (1.79 - 20.67, 80)	4.74 (0.05 - 199.9, 498)	48.45 (4.61 - 148.9, 452)
EC <sub>50</sub> value of isolate / EC <sub>50</sub> value of appropriate reference			
N	80	498	452
Median	1.28	0.89	2.54
Mean	1.57	0.91	2.39
Minimum	0.32	0.01	0.29
Maximum	4.14	40.06	8.27
90th percentile value	3.05	1.343	3.534

a. Virospot assay; reference strain EC<sub>50</sub> values derived from dataset ADVR and are also reported in [CB-249-N](#).

b. Mixed infections were excluded

c. A/H1N1 and A/H3N2: A/Victoria/361/2011; type B: B/Wisconsin/1/2010.

Source: ADVR

**Baseline polymorphisms**

The association of baseline genotype with the following parameters was evaluated: baseline isolate EC<sub>50</sub> values, baseline virus shedding, C<sub>24</sub> values (as a potential confounder for treatment outcomes), time to virus negativity (TTVN), and time to improvement of symptoms (TTIS) (Table 4.1.2). Polymorphisms represented by 3 or more subjects (including subjects with mixed infections, although these subjects were excluded from the association analysis) were evaluated and included a total of 29 positions (3 in A/H1N1, 9 in A/H3N2, and 17 in type B infections). Overall, 5 polymorphisms (listed as substitutions relative to the consensus sequence: K142E [A/H1N1; 0.9% of database sequences], A20T [A/H3N2; 2% of database sequences], F105Y [A/H3N2; 0.02% of database sequences], D529N [B; 0.8% of database sequences], and G713E [B; 0.02% of database sequences]) were associated with notable trends based on non-overlapping confidence intervals among the parameters evaluated; however, the numbers of sequences were generally too small, and p-values too large (i.e. >0.0017, accounting for the number of tests) to draw strong conclusions. K142E (A/H1N1), F105Y (A/H3N2), and G713E (B) trended toward associations with elevated EC<sub>50</sub> value fold changes, although only the difference between K142E and wild type fold changes (median = 3.1-fold vs 1.3-fold, respectively) appeared to be plausibly biologically meaningful. Baseline virus shedding was significantly lower for A/H3N2 virus with the A20T polymorphism compared to wild type (2.5 vs 5.2 log<sub>10</sub> TCID<sub>50</sub>/mL) and was higher for virus with the F105Y polymorphism compared to wild type (7.3 vs 5.0 log<sub>10</sub> TCID<sub>50</sub>/mL), and in both of these cases, consequently, these differences correlated with median changes from baseline at 24 hours post treatment initiation (Day 2). It should be noted that plasma baloxavir C<sub>24</sub> was correlated with greater reductions in virus shedding at Day 2, which may have confounded the associations of A20T and F105Y polymorphisms with this endpoint (Table 4.1.2). D529N was associated with a trend toward longer time to improvement of symptoms.

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**Table 4.1.2 (FDA analysis): Association of baseline genotype with selected baseline parameters and endpoints. P-values determined by Mann-Whitney (Prism 7.0, Graphpad Software Inc., San Diego, CA). Virus data included samples processed ≥96 weeks after collection (excluded from sponsor's endpoint analyses). Yellow highlights indicate parameter comparisons between polymorphic variants and the dominant strain with non-overlapping confidence intervals. Orange highlights indicate polymorphisms in type B virus PA that were not present in sequences from trial T0831.**

Strain	Baseline EC <sub>50</sub> /EC <sub>90</sub> reference value of isolate (nM) Plasma C <sub>50</sub> (μg/ml)				Baseline virus shedding (log <sub>10</sub> TCID <sub>50</sub> /ml)				Change from baseline virus (log <sub>10</sub> TCID <sub>50</sub> /ml)				Time to first virus negative visit (hours)				Time to improvement of symptoms (hours)								
	PA	AA	N	P value	Median	Min	Max	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	P value	Median	Min	Max	Upper CI	Lower CI	Upper CI	Lower CI	Upper CI	P value			
A/H1N1 K42E	2	1.3	2.5	3.1	2.5	3.6	0.0912	26	55.3	19.0	98.5	37.5	63.8	26	24	24	192	24	48	26	67.0	18.1	320.6	58.3	154.5
A/H1N1 K43E	24	1.4	0.9	3.6	1.3	2.8	0.037	26	51.8	19.0	98.5	36.4	58.2	26	3.1	-3.0	-0.8	-0.8	-0.8	26	77.4	15.0	322.3	15.0	322.3
A/H1N1 A343	3	1.3	1.3	1.4	1.3	1.4	0.037	3	80.8	63.8	80.9	63.8	80.9	3	6.8	4.7	7.5	4.7	7.5	3	61.0	49.4	68.6	49.4	68.6
A/H1N1 V407	24	1.4	1.0	3.6	1.3	2.8	0.037	26	56.5	19.0	98.5	44.8	65.5	26	3.8	-6.8	-0.5	-0.5	-0.5	26	67.0	15.0	322.3	49.4	154.5
A/H1N1 V407	3	1.0	0.9	1.3	0.9	1.3	0.095	3	31.5	28.1	37.5	28.1	37.5	3	1.8	-5.3	1.2	-5.3	1.2	3	82.4	65.2	175.9	65.2	175.9
A/H3 A20	1	1.0	1.0	1.0	1.0	1.0	0.433	175	44.2	10.4	134.0	41.0	50.3	175	5.2	0.7	8.2	4.7	5.7	175	69.2	1.4	322.3	56.8	88.7
A/H3 A20	169	44.2	10.4	112.0	40.6	50.0	0.433	174	52.0	0.7	8.2	4.7	5.7	169	3.8	-7.5	2.5	-4.3	-3.6	169	68.6	1.4	322.3	56.8	88.2
A/H3 V61	6	0.7	0.1	1.4	0.1	1.4	0.037	6	64.8	38.7	134.0	38.7	134.0	6	3.5	7.5	1.5	-7.5	-1.5	6	102.1	18.9	316.6	18.9	316.6
A/H3 G101	173	44.8	10.4	134.0	40.9	50.1	0.433	177	50.0	0.7	8.2	4.7	5.5	173	3.8	-7.5	2.5	-4.3	-3.5	173	68.6	1.4	322.3	56.8	88.7
A/H3 G101	4	0.7	0.1	1.3	0.1	1.3	0.037	4	42.0	28.4	53.7	28.4	53.7	4	5.1	-6.0	-2.0	-6.0	-2.0	4	72.2	12.1	223.5	12.1	223.5
A/H3 F155	173	44.2	10.4	134.0	40.8	50.0	0.433	177	50.0	0.7	8.2	4.7	5.5	173	3.8	-7.5	2.5	-4.3	-3.5	173	68.6	1.4	322.3	56.8	88.7
A/H3 F155	5	1.2	1.0	2.1	1.0	2.1	0.0781	4	72.1	44.6	78.2	44.6	79.2	4	4.2	-7.5	4.8	-7.5	4.8	4	62.4	29.2	195.6	29.2	195.6
A/H3 I129M	5	1.0	0.3	1.2	0.3	1.2	0.037	171	44.6	10.4	134.0	41.0	50.0	171	5.0	0.7	8.2	4.7	5.5	171	66.7	1.4	322.3	56.4	90.9
A/H3 K158	154	1.0	0.0	4.1	0.8	1.0	0.037	144	43.2	10.4	134.0	39.0	49.5	144	5.9	3.5	7.0	3.5	7.0	144	74.6	1.4	322.3	56.8	88.7
A/H3 K158R	33	1.0	0.1	4.1	0.5	1.1	0.037	33	50.3	17.2	112.0	40.8	60.7	33	6.5	0.7	8.2	4.7	7.2	33	48.2	24.0	24.0	24.0	24.0
A/H3 S388	150	1.0	0.0	4.1	0.8	1.0	0.037	169	44.2	10.4	134.0	40.6	50.0	172	5.0	0.7	8.2	4.7	5.5	172	66.7	1.4	322.3	56.4	90.9
A/H3 S388R	8	0.7	0.1	1.3	0.1	1.3	0.037	7	52.5	24.6	112.0	24.6	112.0	8	7.2	3.0	8.2	3.0	8.2	8	60.0	24.0	24.0	24.0	24.0
A/H3 K492	153	1.0	0.0	4.1	0.8	1.0	0.037	170	44.6	10.4	134.0	40.8	50.0	174	5.1	0.7	8.2	4.7	5.5	174	66.7	1.4	322.3	56.4	90.9
A/H3 K492R	6	0.4	0.1	1.0	0.1	1.0	0.037	7	44.2	32.5	68.6	32.5	68.6	7	5.2	0.7	8.2	4.7	5.5	7	62.4	24.0	24.0	24.0	24.0
A/H3 G668	155	1.0	0.0	4.1	0.8	1.0	0.037	172	44.2	10.4	134.0	40.8	50.0	176	5.2	0.7	8.2	4.7	5.5	176	66.2	1.4	322.3	56.8	88.3
A/H3 G668R	4	0.2	0.1	1.0	0.1	1.0	0.037	5	95.7	40.6	98.8	40.6	98.8	5	4.5	0.7	7.2	0.7	7.2	5	24.2	24.0	24.0	24.0	24.0
B T6	139	2.9	1.2	4.2	2.5	3.2	0.037	149	49.9	6.6	164.0	46.7	54.5	148	5.6	0.7	10.0	5.0	6.2	143	73.1	1.6	344.4	66.5	91.0
B T6A	7	3.0	1.2	3.9	1.2	3.9	0.037	6	89.7	46.8	134.0	46.8	134.0	7	6.8	4.0	8.2	4.0	8.2	6	96.2	24.0	24.0	24.0	24.0
B T6B	139	3.1	0.9	4.2	2.5	3.2	0.037	148	51.3	6.6	164.0	47.9	55.8	148	5.7	0.7	10.0	5.0	6.2	142	72.2	24.0	24.0	24.0	24.0
B R203K	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B S238N	140	2.9	1.0	4.2	2.4	3.2	0.037	149	49.9	6.6	164.0	47.5	54.5	148	5.5	0.7	10.0	5.0	6.0	143	72.2	24.0	24.0	24.0	24.0
B S238N	6	3.5	1.5	3.6	1.5	3.6	0.037	6	55.2	48.1	71.8	40.1	71.8	6	4.4	-4.7	0.0	-4.7	0.0	6	120.4	68.8	168.8	68.8	168.8
B K258	138	3.0	0.9	4.2	2.5	3.2	0.037	147	50.9	6.6	164.0	47.9	55.5	147	5.7	0.7	10.0	5.0	6.2	143	72.2	24.0	24.0	24.0	24.0
B K258T	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B N271	138	3.0	0.9	4.2	2.5	3.2	0.037	147	51.6	6.6	164.0	47.9	55.8	147	5.7	0.7	10.0	5.0	6.2	143	72.2	24.0	24.0	24.0	24.0
B N271D	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B E273	138	3.1	0.7	4.2	2.5	3.2	0.037	148	50.8	6.6	164.0	46.7	55.5	148	5.0	0.7	10.0	5.0	6.2	145	2.8	-7.5	2.6	-3.4	-2.3
B E273D	8	1.8	1.0	3.9	1.0	3.9	0.037	7	48.9	30.8	109.0	30.8	109.0	7	6.8	5.2	8.2	5.2	8.2	6	96.4	21.6	48.4	21.6	96.4
B V326M	119	3.1	0.9	4.2	2.5	3.2	0.037	126	50.8	6.6	164.0	46.8	57.0	126	5.7	0.7	10.0	5.0	6.2	124	2.8	-7.5	2.6	-3.3	-2.3
B V326M	2	4.0	2.7	3.9	1.2	3.2	0.037	29	49.9	15.7	91.5	32.0	55.8	27	2.6	-7.3	-1.7	-7.3	-1.7	28	60.0	24.0	24.0	24.0	24.0
B M352A	139	3.1	0.9	4.2	2.5	3.2	0.037	148	51.3	6.6	164.0	47.9	55.8	148	5.7	0.7	10.0	5.0	6.2	144	2.8	-7.5	2.6	-3.3	-2.3
B M352A	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B V428I	139	3.1	0.9	4.2	2.5	3.2	0.037	148	51.3	6.6	164.0	47.9	55.8	148	5.7	0.7	10.0	5.0	6.2	144	2.8	-7.5	2.6	-3.3	-2.3
B V428I	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B I485V	139	3.1	0.9	4.2	2.5	3.2	0.037	148	51.3	6.6	164.0	47.9	55.8	148	5.7	0.7	10.0	5.0	6.2	144	2.8	-7.5	2.6	-3.3	-2.3
B I485V	7	1.1	0.7	3.4	0.7	3.4	0.037	7	26.8	15.7	68.8	15.7	68.8	7	6.0	2.5	7.2	2.5	7.2	7	48.4	19.2	48.4	19.2	48.4
B D529N	143	2.9	1.7	4.2	2.5	3.2	0.037	151	50.7	6.6	164.0	47.5	55.5	151	5.7	0.7	10.0	5.0	6.2	147	2.8	-7.5	2.6	-3.3	-2.3
B D529N	3	2.2	1.1	3.5	1.1	3.5	0.037	4	40.4	35.2	92.8	35.2	92.8	4	0.9	-3.4	1.5	-3.4	1.5	3	72.2	24.0	24.0	24.0	24.0
B G547Z	136	3.1	0.9	4.2	2.5	3.2	0.037	144	51.3	6.6	164.0	47.8	56.6	144	5.7	0.7	10.0	5.0	6.2	142	2.8	-7.5	2.6	-3.3	-2.3
B G547Z	10	2.5	0.7	3.4	0.9	3.4	0.037	11	26.1	15.7	68.8	18.4	59.0	11	2.6	-5.7	0.0	-5.7	0.0	10	48.4	19.2	48.4	19.2	48.4
B I594V	107	2.0	0.7	3.2	2.4	3.2	0.037	113	50.7	6.6	164.0	46.7	55.5	113	5.7	0.7	10.0	5.0	6.2	109	2.8	-7.5	2.6	-3.3	-2.3
B I594V	39	2.0	0.7	3.2	2.4	3.2	0.037																		

#### 4.2 Treatment-emergent substitutions (FDA analysis)

Overall, paired baseline and post baseline PA sequence data were obtained for 300 subjects (of 402 treated subjects positive for viral RNA at baseline, including subjects excluded from the ITTI set based on enrollment at sites what were designated as non-GCP compliant). Treatment-emergent substitutions were identified between 1 and 7 days post-treatment initiation in a total of 55 subjects (Table 4.2.1). Resistance-associated substitutions (RASs) (substitutions included in current labeling based on analyses carried out on data submitted to the original NDA [[N210854.000](#)] and new substitutions at amino acid positions previously associated with reduced susceptibility) were identified between 3 and 6 days post-treatment initiation (day 0) in 16 subjects (5.3%). As with previous trials ([\[N210854.000\]](#)), the highest frequency of treatment-emergent RASs was observed in A/H3N2 virus (9.6%), followed by A/H1N1 (5%); treatment-emergent RASs remain rare in type B virus (0.7%) (Table 4.2.1). The overall frequencies of treatment-emergent RASs in clinical trials evaluated to date are 4.4%, 13.2%, and 0.9% for A/H1N1, A/H3N2, and type B virus infections, respectively. While frequencies varied between trials, relative frequencies trended similarly between virus type/subtype subsets (Appendix 5).

In trial T0832, a subset of treatment-emergent substitutions arose in more than one subject at amino acid positions not previously associated with reduced susceptibility, including distinct substitutions at the same amino acid position, and were identified as potential RAS (Table 4.2.1). It should be noted, however, that substitutions identified at the same amino acid position in an alignment but in different influenza virus types (Q365R, S395N, and T619I) may not necessarily be structurally analogous, and the plurality of such substitutions should be interpreted with caution. All potential RASs were located outside of the PA N-terminal domain, which contains the endonuclease drug target ([Kowalinski et al., 2012](#)), and the mechanistic consequence of these substitutions is not apparent based on structure. Some potential RASs could not be structurally mapped because they are located in protein regions that are not included in currently available structures. Substitutions at two positions (E333G and Q365R) were not represented among sequences queried in the NCBI database (Appendix 6). Potential RAS (PA) S395N (A/H3N2), E397K (A/H3N2), D201E (type B), D201G (type B), E333G (type B), S415N (type B), and S415G (type B) were evaluated for their impact on baloxavir susceptibility in cloned virus and did not confer a fold change in EC<sub>50</sub> value >2 (Appendix 13). Q365R (A/H1N1), E397G (A/H1N1), and T619I (type B) have not been evaluated; these substitutions should be evaluated for their impact on baloxavir susceptibility in cell culture.

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**Table 4.2.1 (FDA analysis): Summary treatment-emergent PA substitutions.**

Subtype	# of subjects with paired PA sequence data <sup>a</sup> (subjects in the ITTI set)	# of subjects with any treatment-emergent substitution <sup>a</sup> (subjects in the ITTI set)	% subjects with a RAS <sup>b</sup> % (substitution, n) <sup>a</sup>	Number and identity of potential RAS <sup>b</sup> substitutions identified in more than one subject (substitution identified in another trial) <sup>c</sup>
H1N1	20 (18)	7 (6)	5% (I38N, 1)	1 Q365R (Y361H <sup>d</sup> , B T0831), 1 E397G
H3N2	146 (141)	31 (31)	9.6% (E23K, 1; I38T, 12; I38M, 1)	1 S395N <sup>d,e</sup> (S395N <sup>d</sup> , A/H3N2, T0831), 1 E397K <sup>d</sup>
B	134 (131)	17 (17)	0.7% (I38T, 1)	1 D201G <sup>d,e</sup> , 1 D201E <sup>d,e</sup> , 1 E333G <sup>d</sup> (E333K <sup>d</sup> , B, T0831), 1 S415N <sup>f,d</sup> , 1 S415G <sup>d,f</sup> , 1 T619I (E623K <sup>d</sup> , A/H3N2, T0822; E623G <sup>d</sup> , A/H3N2, T0831) <sup>g</sup>
<b>Total<sup>h</sup></b>	<b>300 (290)</b>	<b>55 (54)</b>	<b>5.3%<sup>i</sup> (16)</b>	

a. Includes analysis of 10 subjects who were excluded from the ITTI on the basis of being enrolled at non-GCP-compliant sites. These subjects were not included in primary and secondary endpoint analyses but are included in analyses of the impact of treatment-emergent resistance on selected outcomes. None of the subjects who were excluded from the ITTI set were identified with a treatment-emergent RAS.

b. RAS: resistance-associated substitution defined as associated with reduced susceptibility to baloxavir (>2-fold). Listed amino acid numbering is type/subtype-specific. All RASs were identified in subjects included in the ITTI set.

c. Substitutions at amino acid positions where variability was observed as treatment-emergent in another subject in T0832 or in trials evaluated to date (T0821, T0822, T0831 [N210854.000] T0833 [I126653.128], and T0832). Includes substitutions observed at aligned amino acid positions in other virus type/subtypes (alignment based on dominant strains in trial T0832 using MUSCLE [Multiple Sequence Comparison by Log-Expectation]). These substitutions have not been evaluated for their impact on susceptibility to baloxavir. Listed amino acid numbering is type/subtype-specific.

d. Evaluated in molecular clone for impact on susceptibility (conferred EC<sub>50</sub> value fold changes were <2, see Appendix 13).

e. Occur outside of the solved PA structure (Kowalinski et al., 2012).

f. Occur in linear/flexible regions of the PA protein structure (Kowalinski et al., 2012).

g. E623G and E623K were evaluated in molecular clone-derived A/H3N2 virus and found to confer 1.0- and 1.2-fold increases, respectively, in baloxavir EC<sub>50</sub> values (N210854.000).

h. Includes 5 co-infected subjects, but only one virus was sequenced at baseline and post baseline for each subject: (b) (6) A/H1N1+A/H3N2, A/H1N1 sequenced; (b) (6) A/H1N1+B, A/H1N1 and B sequenced at baseline, only A/H1N1 sequenced post baseline; (b) (6) A/H3N2+B, A/H3N2 sequenced; (b) (6) A/Unk+B, B sequenced; (b) (6) A/Unk+B, B sequenced.

i. Observed in 5.5% (16/290) subjects in the ITTI set.

*Association of treatment-emergent substitutions with clinical and virologic endpoints (FDA analysis)*

Treatment-emergent RASs were statistically significantly associated with virus rebound (67%), compared to virus without treatment-emergent RAS (14%) or with non-RAS treatment-emergent variants (11%) (Figure 4.2.1). Virus rebound typically occurred between 3 and 6 days post treatment initiation, coincident with the detection of RASs. Non-RAS treatment-emergent substitutions F191L and G344E in influenza A virus, and D201G, S328G, E333G, A365S, and S415G in influenza B virus, were identified in subjects with virus rebound; however, only the substitutions identified in type A virus were associated with the rebound event (see Appendices 6 and 7).

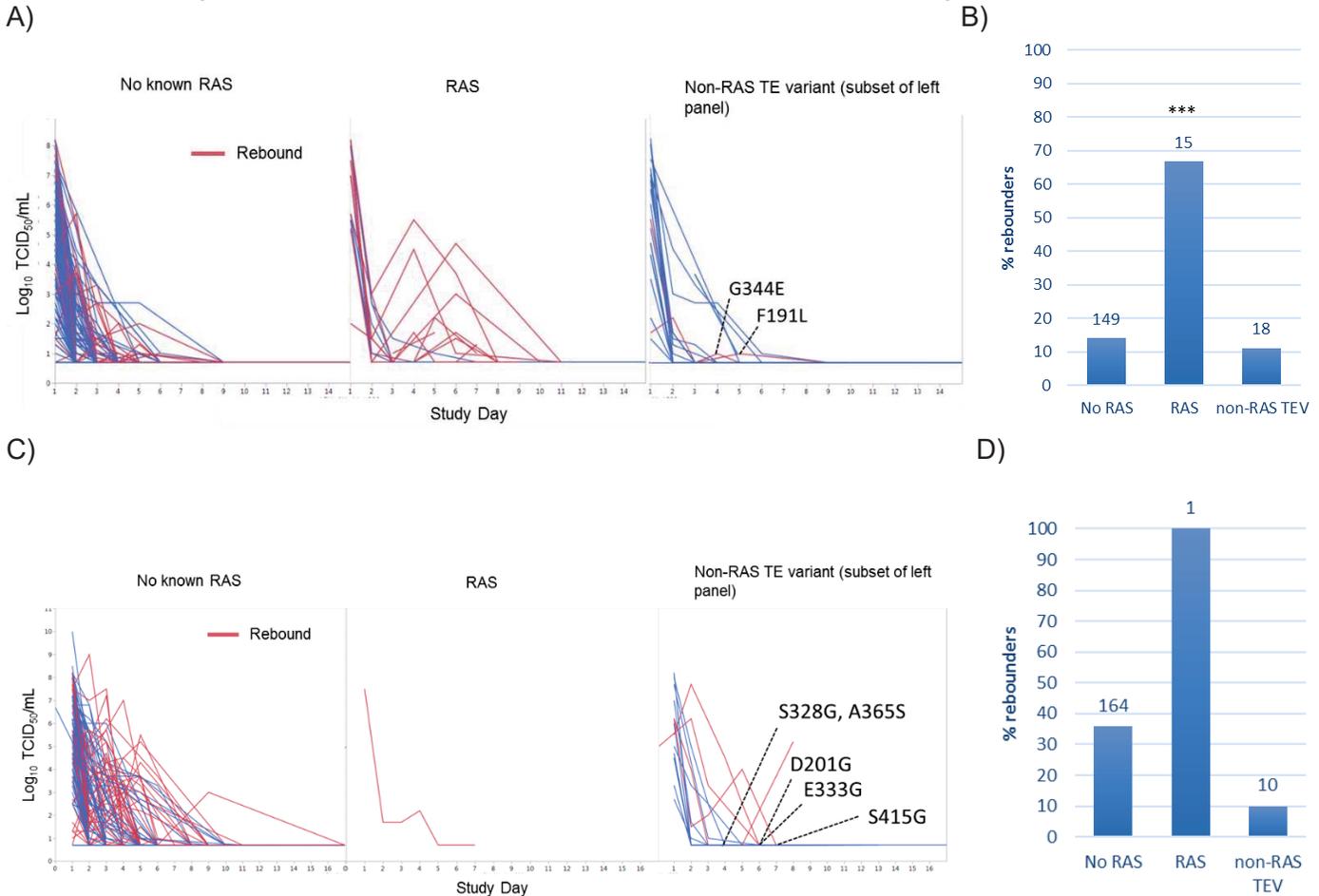
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**Figure 4.2.1** (FDA analysis): Association of RASs with virus rebound. Influenza A (A and B) and influenza B (C and D) virus shedding kinetics (A and C) and the associations of RAS with virus rebound (B and D). Includes all subjects evaluated for baseline and post-baseline PA substitutions. All samples evaluated for infectivity were included. \*\*\* P<0.0001 (Fisher's exact). Data labels in B and D represent the number of subjects. RAS: treatment-emergent resistance-associated substitution; TEV treatment-emergent variant.



In an analysis of the association of treatment-emergent substitutions with clinical and virologic responses to baloxavir marboxil among type A virus infections, treatment-emergent RASs were statistically significantly associated with increased duration of virus shedding (Figure 4.2.2). The time to sustained virus negativity was longer in baloxavir marboxil-treated subjects with treatment-emergent RASs compared to placebo subjects ( $p = 0.0082$ , Mann Whitney test; Figure 4.2.2). The difference in virus shedding did not correlate with the clinical response to treatment; the time to improvement of symptoms was nearly identical for subjects with and without treatment-emergent RASs (Figure 4.2.2).

In type A virus-infected subjects who were vaccinated within 6 months prior to enrollment, the frequency of treatment-emergent RAS was 7% (3/44), compared to 11% (12/105) in subjects who were not vaccinated within 6 months; this difference in frequencies was not statistically significant ( $p = 0.5543$ , Fisher's exact test). Baseline titers against the reference strain matching the infecting strain were not associated with treatment-emergent resistance (data not shown).

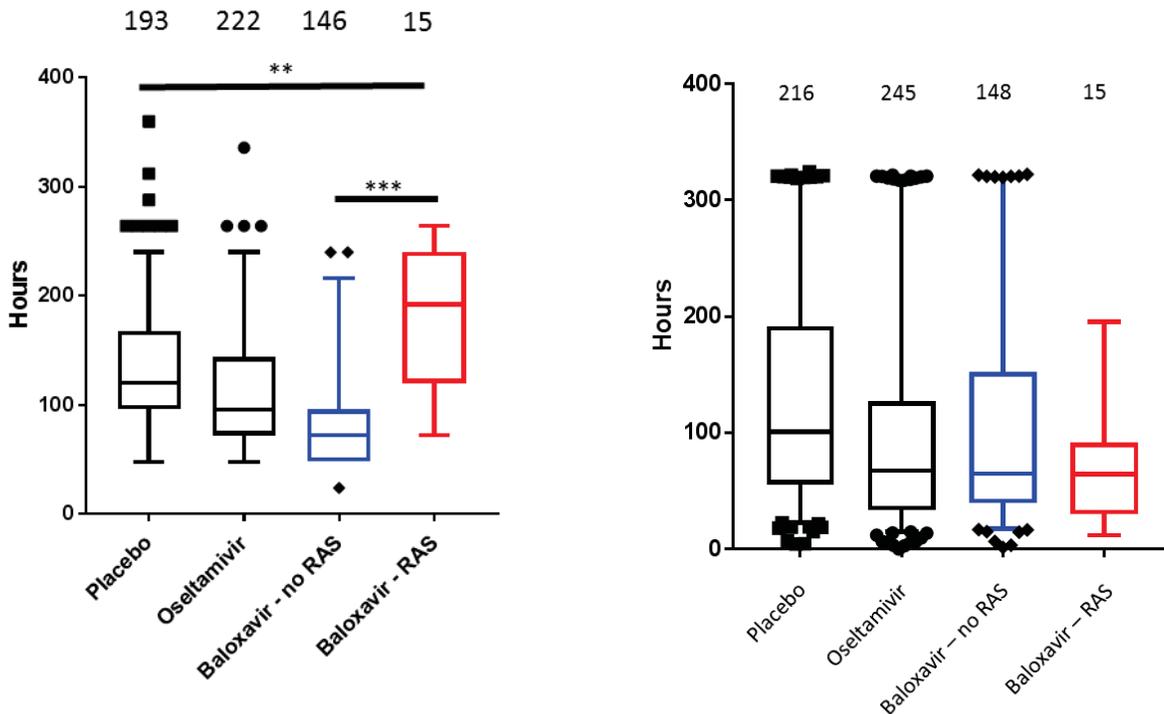
Substitutions designated as potential RASs did not exhibit a clear association with virus rebound (Appendices 6 and 7) or with prolonged time to improvement of symptoms (potential RAS vs no substitution in treated

subjects infected with type A virus (n=4): median, 58.7 hours vs 65 hours, respectively; range, 55.0-101.4 hours vs 1.4-322.3 hours, respectively).

**Figure 4.2.2** (FDA analysis): Association of treatment-emergent resistance (RAS) with duration of type A virus shedding (A), and time to improvement of symptoms in type A virus-infected subjects (B). Time to sustained virus negativity is defined as the first negative time point after which no positive time points were reported; data were included for all subjects evaluated for virus shedding at Day 5 or later, and subjects positive at the last time point were given an imputed value of 240 hrs. Time to improvement of symptoms is the primary endpoint of trial T0832. All type A virus-infected subjects identified by a treatment arm were included, and all samples were included regardless of processing turn-around time. \*\* p <0.01; \*\*\* p<0.0001, Mann Whitney test (Prism 7.0, Graphpad Software Inc., San Diego, CA).

A) Time to sustained virus negativity

B) Time to improvement of symptoms



*Association of baseline PA genotype and treatment-emergent resistance (FDA analysis):*

All baseline polymorphisms (defined as any differences at baseline from the PA consensus for each virus type/subtype) were evaluated for their association with treatment-emergent RASs (Table 4.2.2).

Polymorphisms were flagged for imbalance if the frequency of treatment-emergent RASs exceeded by  $\geq 50\%$  the frequency observed overall in each type/subtype. There were 8 polymorphic amino acid positions among A/H1N1, A/H3N2, and type B virus sequences that were associated with an imbalance in treatment-emergent RASs. Three polymorphisms, Y305C in A/H1N1, F105Y in A/H3N2 and N416D in type B, were associated with treatment-emergent resistance based on a P value <0.05, although none of the associations met a Bonferroni-corrected  $\alpha$  of <0.00119 (based on 42 polymorphisms represented by more than 1 sequence), and none of the potential associations were reproduced in pooled data for studies T0821, T0822, and T0831 (analysis not shown). Nevertheless, these polymorphisms should be noted for future analysis with additional data, as they may contribute to permissiveness of acquiring RASs.

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**Table 4.2.2 (FDA analysis): Association of baseline polymorphisms with treatment-emergent RASs**

Type/subtype	Amino acid position (type/subtype-specific)	Type/subtype alignment numbering <sup>a</sup>	Consensus amino acid (type/subtype-specific) <sup>b</sup>	Baseline amino acid	No TE RAS (n)	TE RAS (n)	% treatment-emergent RAS	P value <sup>c</sup>	RAS
A/H1N1	305	319	Y	Y	19	0	0.0		
A/H1N1	305	319	Y	C	0	1	100.0	0.05	I38N
A/H1N1	407	424	V	V	18	0	0.0		
A/H1N1	407	424	V	I	1	1	50.0	0.1	I38N
A/H3N2	62	63	V	V	127	13	9.3		E23K, I38M, I38T
A/H3N2	62	63	V	I	5	1	16.7	0.4599	I38T
A/H3N2	101	102	G	G	129	13	9.2		E23K, I38T
A/H3N2	101	102	G	E	3	1	25.0	0.3348	I38M
A/H3N2	105	106	F	F	130	11	7.8		E23K, I38M, I38T
A/H3N2	105	106	F	Y	2	3	60.0	0.0064	I38T
A/H3N2	129	130	I	I	129	13	9.2		E23K, I38M, I38T
A/H3N2	129	130	I	M	3	1	25.0	0.3348	I38T
A/H3N2	581	598	M	M	132	13	9.0		E23K, I38M, I38T
A/H3N2	581	598	M	V	0	1	100.0	0.0959	I38T
B	395	416	N	N	133	0	0.0		
B	395	416	N	D	0	1	100.0	0.0075	I38T
B	594	619	I	I	98	0	0.0		
B	594	619	I	V	36	1	2.7	0.2741	I38T

TE RAS: Treatment-emergent resistance-associated substitution.

- Alignment of baseline consensus amino acid sequences for each type/subtype in trial T0832 implemented using MUSCLE (Multiple Sequence Comparison by Log-Expectation).
- Consensus based on all baseline sequences within each type/subtype.
- Fisher's exact test (Prism 7.0, Graphpad Software Inc., San Diego, CA). Note values are not corrected for multiple tests.

**5 CONCLUSIONS**

Overall, the data submitted with this supplement support the proposed amendments to labeling pertinent to Virology. The effect of treatment observed in trial T0832 of “high-risk” subjects was similar to what was observed in otherwise healthy populations; however, in contrast to previous trial results, baloxavir marboxil had a similar and statistically significant impact on type B virus infections compared to type A virus infections, as measured by time to improvement of symptoms. The effect of baloxavir marboxil treatment on type B virus infections was still reduced compared to type A virus infections based on virologic endpoints. Similarly, treatment-emergent resistance, which resulted in virus rebound and prolonged shedding, did not appear to impact the outcome of time to improvement of symptoms. Together, these data indicate that the association between clinical and virologic endpoints is variable between studies.

It should be noted that the inconsistent clinical response to treatment observed for type B virus could be a result of season-to-season strain variation. Type B virus is comprised of two lineages, Yamagata and Victoria, defined by their HA sequences, which are estimated to have diverged around 1983. The proportions of the dominant Yamagata virus have ranged between 52% and 82% across seasons in which trials have been

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performed. However, while PB1 and PB2 appear to co-segregate with the HA (and thus may be lineage-specific), all other viral genes, including PA, appear to be derived from one lineage: All recently circulating PA, NP, NA, and M genes segments appear to be from the Yamagata lineage and the NS gene is from the Victoria lineage ([Dudas et al., 2015](#)), and there was no signal among type B virus sequences for an impact of PA genotype on clinical or virologic responses, although strain variation in other genes may play a role in the clinical response to treatment.

Treatment-emergent resistance remains a concern with baloxavir marboxil; however, the frequencies observed in T0832 were within the range for each virus type/subtype observed in previous trials of baloxavir marboxil (approximately 1-12% in adults and adolescents; Appendix 5) and overlap with the range of frequencies observed in clinical studies of neuraminidase inhibitors; in clinical studies evaluating oseltamivir, treatment-emergent resistance has ranged from approximately 1-5% in otherwise healthy adults (reviewed in [N210854.000](#)). Resistance analysis results in clinical studies of baloxavir marboxil conducted to date are consistent with recent cumulative surveillance reports in regions with significant baloxavir marboxil usage ([Japan, National Institute of Infectious Diseases surveillance report 7/16/2019](#)), where higher rates of resistance have been reported in A/H3N2 virus infections compared to A/H1N1 and type B virus infections. In some cases, baloxavir-resistant variants have been detected in patients who have not been treated with baloxavir marboxil, possibly indicating transmission of resistant virus. A planned trial evaluating the impact of baloxavir marboxil treatment on transmission of virus to household contacts will also evaluate the potential for transmission of baloxavir-resistant virus. There was one novel RAS, I38N, observed in trial T0832, which will be proposed for inclusion in labeling (see Review Section 6).

**6. PACKAGE INSERT**

Sponsors proposed edits are in red

Virology proposed edits are in green

(b) (4)

**12.4 Microbiology**Mechanism of Action

Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza virus activity. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription, resulting in inhibition of influenza virus replication. The 50% inhibitory concentration (IC<sub>50</sub>) of baloxavir was 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 in a PA endonuclease assay. Viruses with reduced susceptibility to baloxavir have amino acid substitutions in the PA protein.

Antiviral Activity

The antiviral activity of baloxavir against laboratory strains and clinical isolates of influenza A and B viruses was determined in an MDCK-cell-based plaque reduction assay. The median 50% effective concentration (EC<sub>50</sub>) values of baloxavir were 0.73 nM (n=~~19~~ 31; range: 0.20-1.85 nM) for subtype A/H1N1 strains, ~~0.68~~ 0.83 nM (n=~~19~~ 33; range: 0.35-~~1.87~~ 2.63 nM) for subtype A/H3N2 strains, and ~~5.28~~ 5.97 nM (n=~~21~~ 30; range: ~~3.33-13.00~~ 2.67-14.23 nM) for type B strains. In an MDCK-cell-based virus titer reduction assay, the 90% effective concentration (EC<sub>90</sub>) values of baloxavir against avian subtypes A/H5N1 and A/H7N9 were ~~1.64 and 0.80 nM, respectively~~ in the range of 0.80 to 3.16 nM. The relationship between antiviral activity in cell culture and clinical response to treatment in humans has not been established.

Resistance

Cell culture: Influenza A virus isolates with reduced susceptibility to baloxavir were selected by serial passage of virus in cell culture in the presence of increasing concentrations of baloxavir. Reduced susceptibility of influenza A virus to baloxavir was conferred by amino acid substitutions I38T (A/H1N1 and A/H3N2) and E199G (A/H3N2) in the PA protein of the viral RNA polymerase complex.

Clinical studies: Influenza A and B viruses with treatment-emergent amino acid substitutions at positions associated with reduced susceptibility to baloxavir in cell culture were observed in clinical studies (Table 4). The overall ~~incidence-frequencies~~ of treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir in Trials ~~1 and 2 was 2.7% (5/182) and 11% (39/370), respectively.~~ 1, 2 and 3 [~~see Clinical Studies-(14)-14.1 and 14.2~~] were ~~was~~ 2.7% (5/182), 11% (39/370) and 5.25% (156/290), respectively.

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[Comment to Applicant: We included the following substitutions identified in the listed subjects:

USUBJID	TRTA	ITTIFL	STYPPCRD	PA substitution
(b) (6)	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H1N1pdm	I38N
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	B	I38T
	S-033188	Y	A/H3	I38M
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	E23K
	S-033188	Y	A/H3	I38T
	S-033188	Y	A/H3	I38T

Table 4 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/N/T	E23G/K, A37T, I38M/T, E199G	I38T

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. Strains containing substitutions known to be associated with reduced susceptibility to baloxavir were identified in approximately 0.05% of PA sequences in the National Center for Biotechnology Information/GenBank database (queried August 2018).

Prescribers should consider currently available surveillance information on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use XOFLUZA.

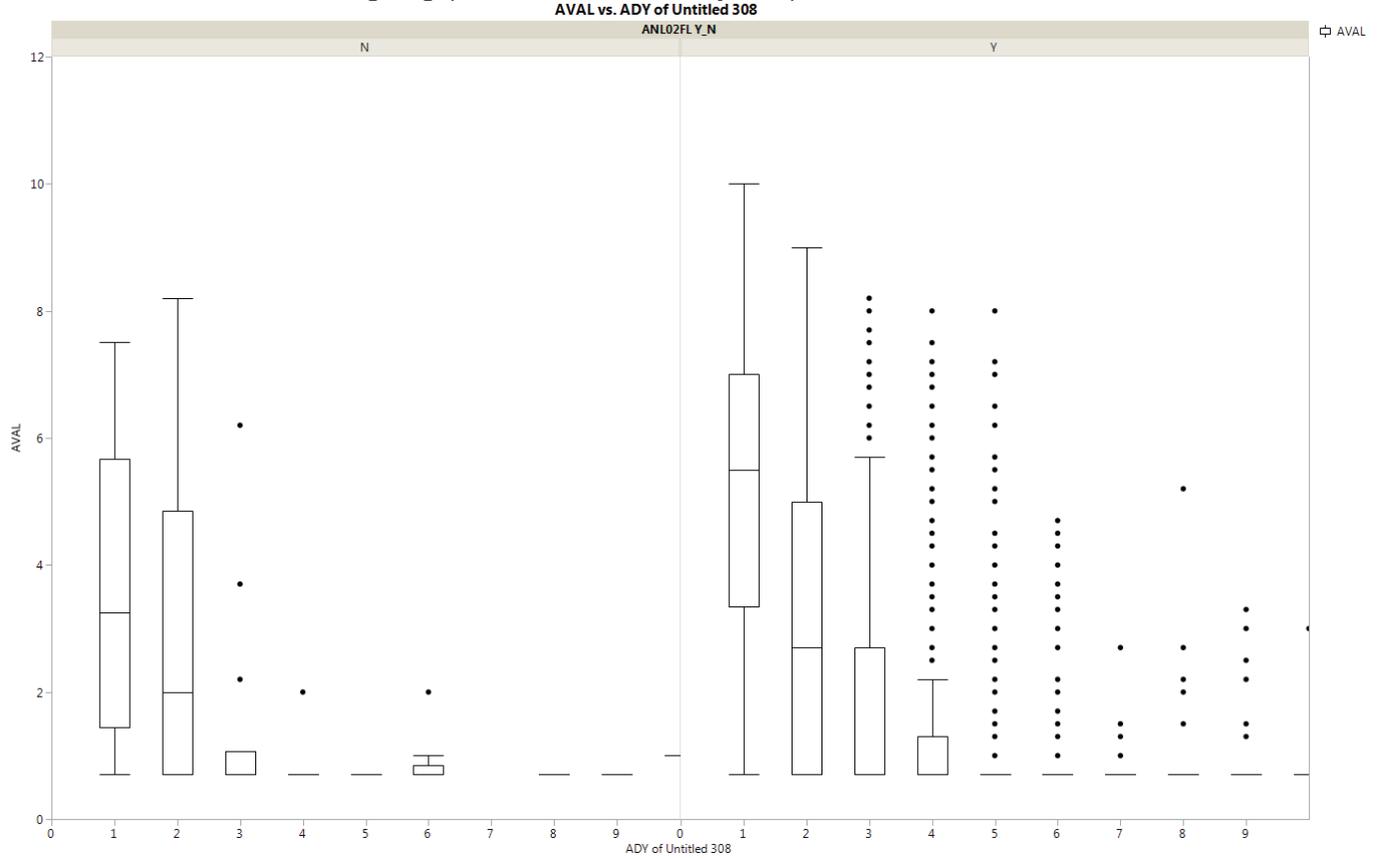
Cross-Resistance

Cross-resistance between baloxavir and neuraminidase (NA) inhibitors, or between baloxavir and M2 proton pump inhibitors (adamantanes), is not expected, because these drugs target different viral proteins. Baloxavir is active against NA inhibitor-resistant strains, including A/H1N1 and A/H5N1 viruses with the NA substitution H275Y (A/H1N1 numbering), A/H3N2 virus with the NA substitution E119V and R292K, A/H7N9 virus with the NA substitution R292K (A/H3N2 numbering), and type B virus with the NA substitution R152K and D198E (A/H3N2 numbering). The NA inhibitor oseltamivir is active against viruses with reduced susceptibility to baloxavir, including A/H1N1 virus with PA substitutions E23K or I38F/T, A/H3N2 virus with PA substitutions E23G/K, A37T, I38M/T, or E199G, and type B virus with the PA substitution I38T. Influenza virus may carry amino acid substitutions in PA that reduce susceptibility to baloxavir and at the same time carry resistance-associated substitutions for NA inhibitors and M2 proton pump inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

7. APPENDICES

APPENDIX 1:

FDA analyses: Clinical sample virus titers with ≤96 hour turn-around time (Y) or >96 hour turn-around time (N), based on ANL02FL censoring flag (JMP 12.1, SAS, Cary, NC).



DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

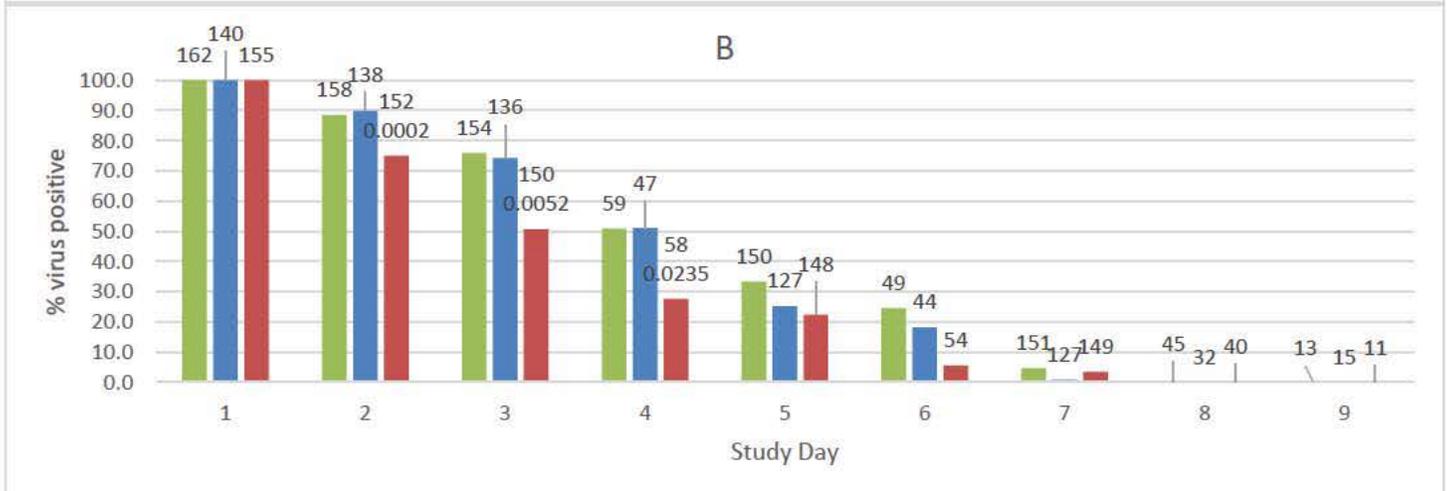
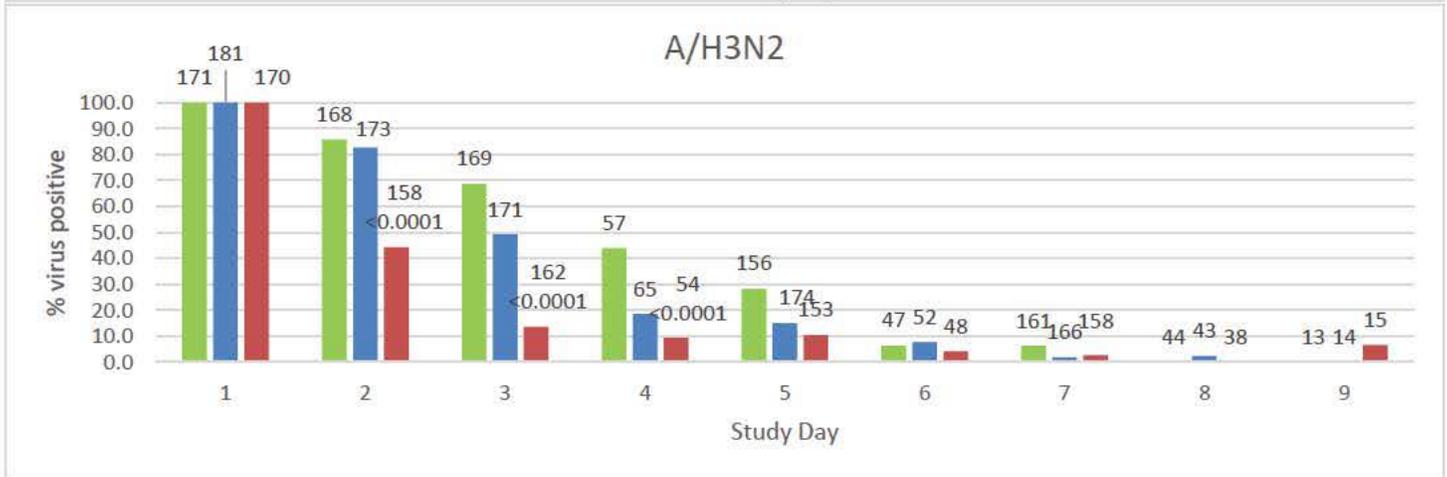
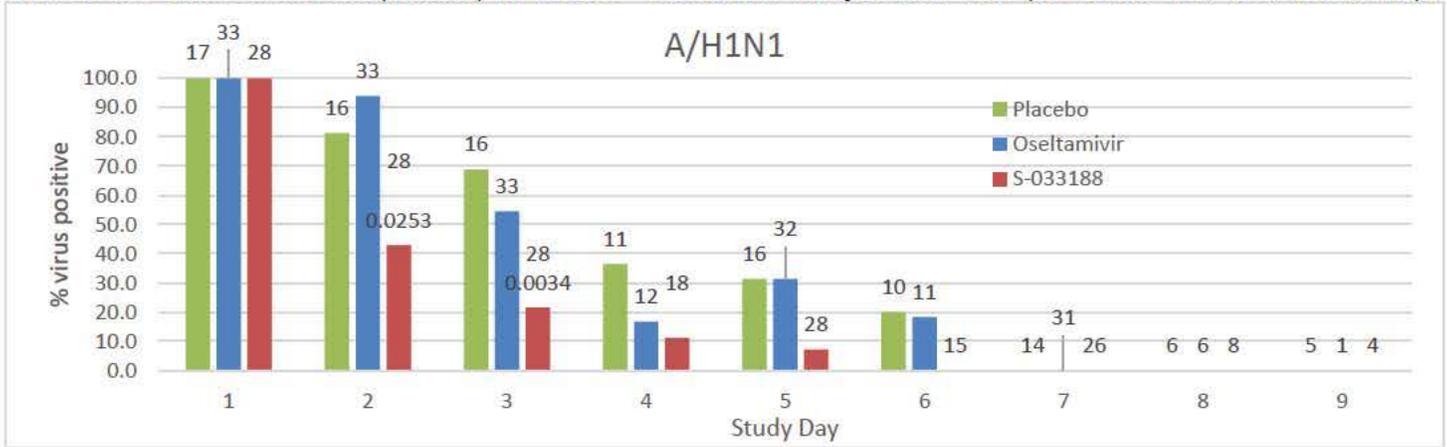
NDA: 210854 S-001 SDN: 077 (SN 0066)

DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 2:

FDA analyses: Proportion virus positive at each study Day by virus type/subtype. Analyses included all data from subjects who were included in the ITTI set; data were not censored based on the 96 hour turn-around time for sample processing (excluded subjects who were RT-PCR positive but enrolled at sites censored for non-GCP compliance). Study Days include the following analysis days (days relative to treatment initiation on day 1): Day 1: days -3 to 1; Day 2: day 2; Day 3: days 3-4; Day 4: day 4; Day 5: days 5 and 6; Day 6: day 6; Day 9: days 7 to 11. Data labels indicate number of subjects included in the analysis (top) and P values <0.05 based on Fisher's exact test (bottom) for values <0.05. Data analyzed in Excel (Microsoft Inc., Redmond, WA).



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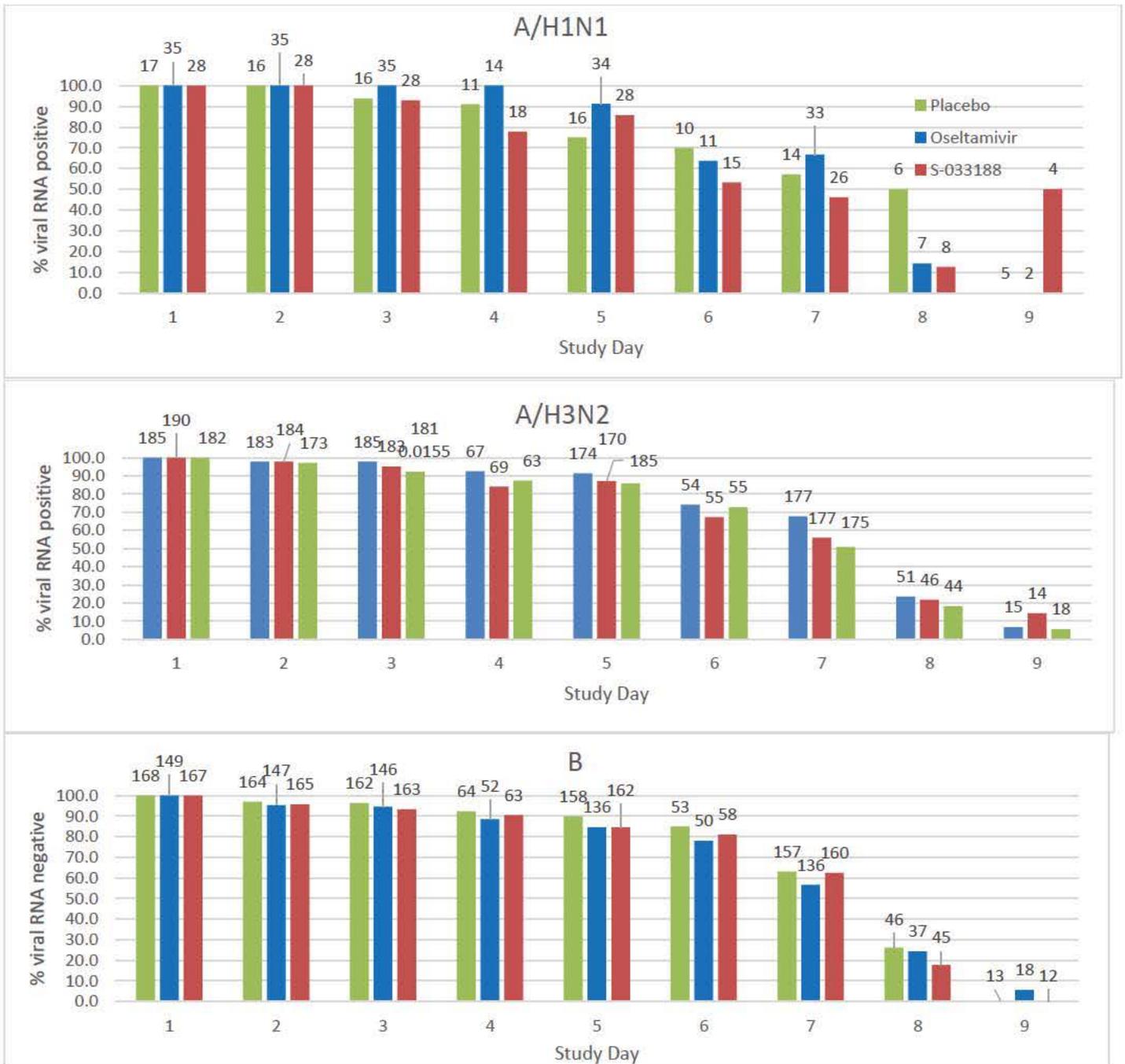
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 3:

FDA analyses: Proportion viral RNA positive at each study Day by virus type/subtype. Analyses included all data from subjects who were included in the ITTI set (excludes subjects who were RT-PCR-positive but enrolled at sites censored for non-GCP compliance); data were not censored based on the 96 hour turn-around time for sample processing. Samples with viral RNA >LOD were considered positive, including sample <LLoQ (See Methods). Study Days include the following analysis days (days relative to treatment initiation on day 1): Day 1: days -3 to 1; Day 2: day 2; Day 3: days 3 and 4; Day 4: day 4; Day 5: days 5 and 6; Day 6: day 6; Day 9: days 7 to 11. Data labels indicate number of subjects included in the analysis (top) and P values <0.05 based on Fisher's exact test (bottom) for values <0.05. Data analyzed in Excel (Microsoft Inc., Redmond, WA).



DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

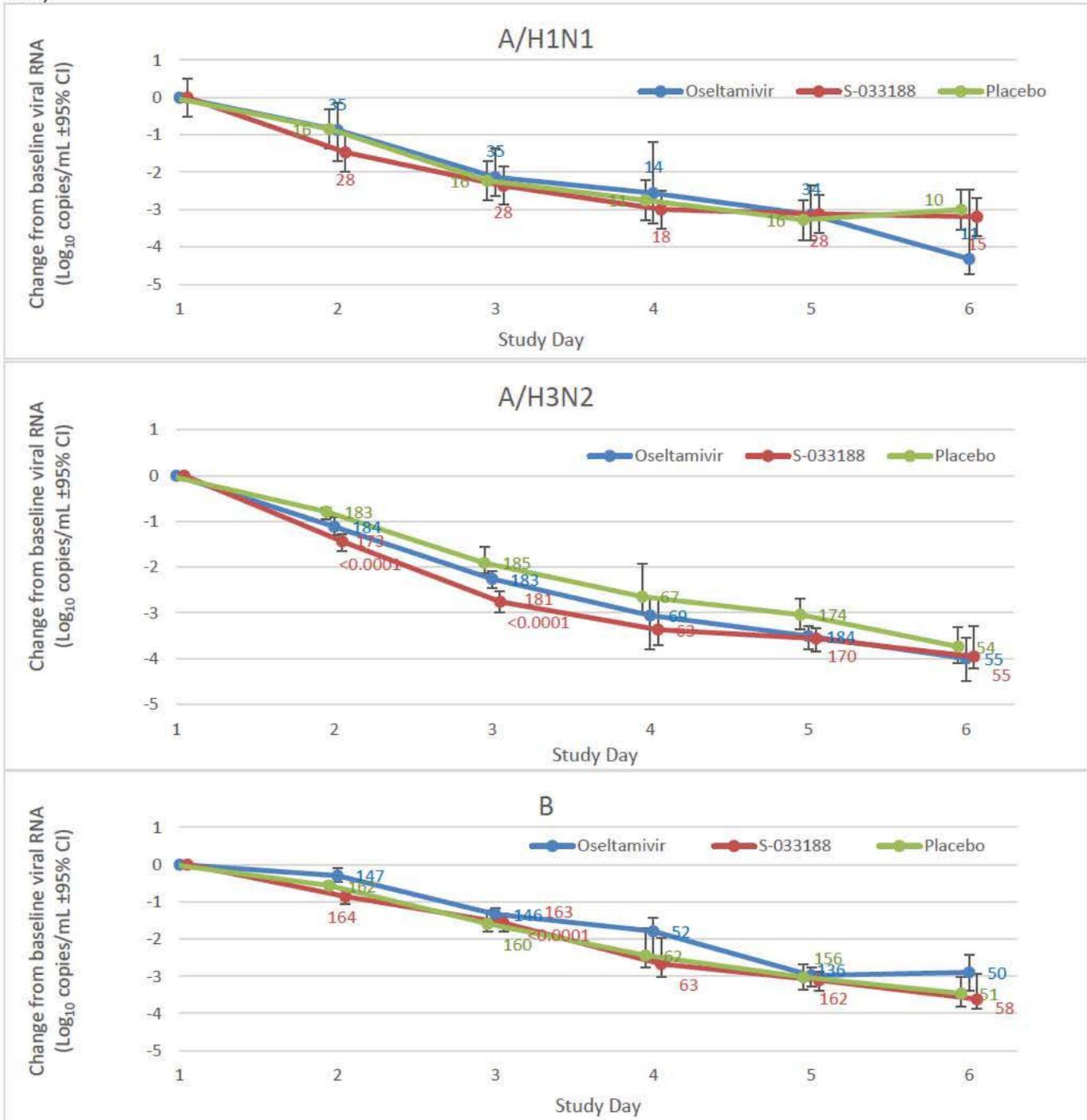
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 4:

FDA analysis: Viral RNA shedding change from baseline by virus type/subtype. Analyses included all data from subjects who were included in the ITTI set (which excludes subjects who were RT-PCR positive but enrolled at sites censored for non-GCP compliance); data were not censored based on the 96 hour turn-around time for sample processing. Study Days include the following analysis days (days relative to treatment initiation on day 1): Day 1: days -3 to 1; Day 2: day 2; Day 3: days 3-4; Day 4: day 4; Day 5: days 5 and 6; Day 6: day 6; Day 9: days 7 to 11. Data labels indicate number of subjects included in the analysis (top) and P values (bottom) <0.05 based on a Mann-Whitney test compared to placebo. Data analyzed in Excel (Microsoft Inc., Redmond, WA).



**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

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**APPENDIX 5:**

FDA analysis: Treatment-emergent resistance across studies (see [N210854.000](#)).

Subtype	Trial	Number of subjects with paired PA sequence data	Percent of subjects with RAS (n)	RAS
H1N1	T0821	112	4.4% (5)	E23K, I38F/T
	T0831	4	0 % (0)	--
	T0832	20	0.5% (1)	I38N
	T0822	2	0% (0)	--
	Total	138	4.4 (6)	
H3N2	T0821	14	0% (0)	--
	T0831	330	12% (40)	E23G/K, A37T, I38M/T,
	T0832	146	9.6% (14)	E23K, I38T, I38M
	T0822	70	29% (20)	A37T, I38M/T, E199G,
	Total	560	13.2 (74)	
B	T0821	56	0% (0)	--
	T0831	37	2.7% (1)	I38T
	T0832	134	0.7% (1)	I38T
	T0822	8	0% (0)	--
	Total	235	0.9 (2)	

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**APPENDIX 6:**

FDA analysis: T0832 treatment-emergent substitutions and their attributes listed by subject.

Subject	PA Type/subtype	Substitution	Day of detection (treatment initiated on day 1)	A/B alignment #	T0832 baseline consensus	Number of subjects with substitution (any substitution at the same position)	Amino acid position of treatment-emergent variability in other trials (type/subtype, trial)	RAS	Potential RAS	Rebound subject	# of database sequences queried	Frequency of TE substitution among database sequences	Proposed for further evaluation <sup>a</sup>
(b) (6)	A/H1N1	I38N	4	38	I	1 (15)		Y			12027	0.000	Y
	A/H1N1	P274H	2	281	P						12040	0.008	
	A/H1N1	K328E	3	345	K						12056	0.017	
	A/H1N1	G344E	4	361	E					Y	12056	99.967	Y
	A/H1N1	Q365R	2	382	Q	1 (2)	361 (B, T0831)		Y		12057	0.000	Y
	A/H1N1	P/L376P	6	393	P						12057	99.992	
	A/H1N1	E397G	3	414	E	1 (2)			Y		12057	0.025	Y
	A/H1N1	R401K	6	418	R						12057	0.299	
	A/H1N1	Y445N	6	462	Y						12057	0.000	
	A/H3N2	E23K	5	23	E	3 (5)	23 (A/H1N1, A/H3N2; T0821, T0831)	Y			15180	0.000	
	A/H3N2	L28V	8	28	L						15203	0.000	
	A/H3N2	K34E	3	34	K						15207	0.000	
	A/H3N2	I38M	7	38	I	1 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	5	38	I	13 (15)		Y			15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y			15213	0.000	
	A/H3N2	I38T	7	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	7	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	5	38	I	13 (15)		Y			15213	0.000	
	A/H3N2	I38T	6	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	I38T	5	38	I	13 (15)		Y		Y	15213	0.000	
	A/H3N2	P68L	3	69	P						15220	0.000	
	A/H3N2	V90A	3	91	V						15229	0.053	
	A/H3N2	N98T	3	99	T						15234	99.947	
	A/H3N2	D160G	3	161	D						15252	0.000	
	A/H3N2	F191L	5	192	F					Y	15256	0.007	Y

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(b) (6)

A/H3N2	H/R192H	3	193	R					15256	0.007	
A/H3N2	E203K	4	204	E					15257	0.000	
A/H3N2	P221L	3	224	P					15257	0.007	
A/H3N2	D294N	3	308	D					15263	99.928	
A/H3N2	P295L	2	309	P					15263	0.007	
A/H3N2	K/R309R	3	323	K					15240	0.046	
A/H3N2	F315I	3	329	F					15240	0.000	
A/H3N2	S395N	3	412	S	2 (2)	395 (A/H3N2, T0831)		Y	15241	0.013	NC
A/H3N2	E397K	2	414	E	1 (2)			Y	15241	0.039	NC
A/H3N2	L417P	3	434	L					15241	0.000	
A/H3N2	K/E610E	6	627	E					15225	99.869	
A/H3N2	I/V628V	2	649	V					15225	99.882	
B	R7K	4	7	R					8853	0.203	
B	S25G	2	25	S					8853	0.011	
B	I38T	7	38	I	13(15)			Y	8853	0.000	
B	T62K	5	62	T					8853	0.011	
B	D201E	5	207	D	1 (2)			Y	8853	0.068	NC
B	D201G	6	207	D	1 (2)			Y	8853	0.068	NC
B	L289V	2	304	L					8853	0.000	
B	V326A	3	341	V					8853	0.011	
B	S328G	4	343	S				Y	8853	0.000	Y
B	E329K	4	344	E					8853	0.158	
B	N332K	3	348	N					8853	0.000	
B	E333G	6	349	E	1 (2)	333 (B, T0831)		Y	8853	0.000	NC
B	A365S	4	386	A				Y	8853	0.000	Y
B	T/I412T	2	433	T					8853	99.853	
B	S415G	7	436	S	1(2)			Y	8853	1.050	NC
B	S415N	5	436	S	1(2)			Y	8853	1.050	NC
B	E445G	5	466	E					8853	0.000	
B	V454I	3	475	V					8853	99.435	
B	T619I	3	644	T	1 (3)	623 (A/H3N2; T0822, T0831)		Y	8853	0.090	Y
B	K715Q	2	740	K					8853	0.000	

<sup>a</sup> Y = Requires further evaluation; NC = evaluated for impact on susceptibility in cell culture and no significant fold-change was detected, see Appendix 13.

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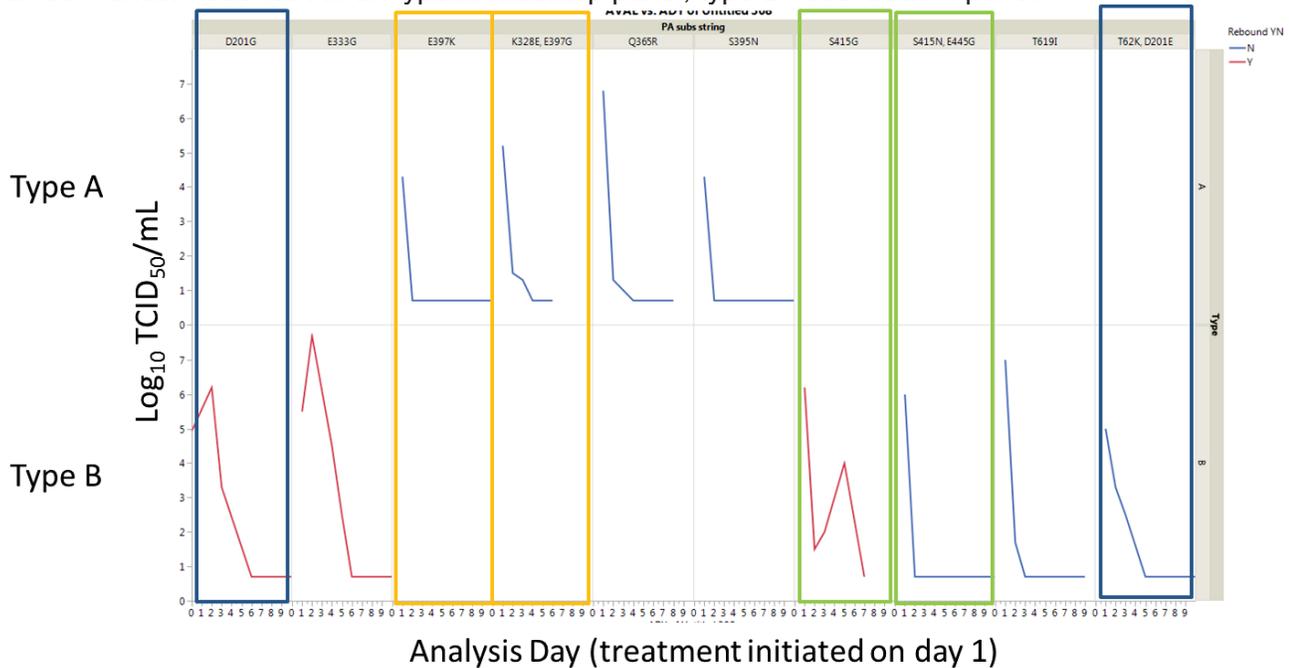
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APPENDIX 7:

FDA analysis: Virus shedding kinetics of subjects with treatment-emergent potential RASs. All treatment-emergent substitutions observed in subjects with an identified potential RAS substitution are listed in the bar above each graph (see Table 4.2.1). Like-colored boxes indicate subjects matched by the identity of their potential RAS observed in T0832. Substitutions identified in other studies are not boxed (see Table 4.2.1). Red curves indicate virus rebound. Type A virus: top panel; type B virus: bottom panel.



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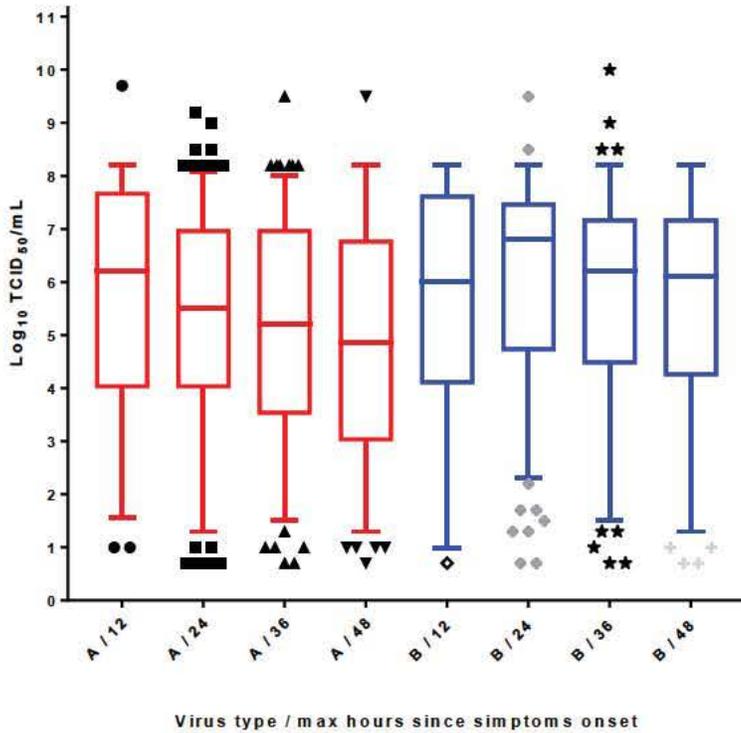
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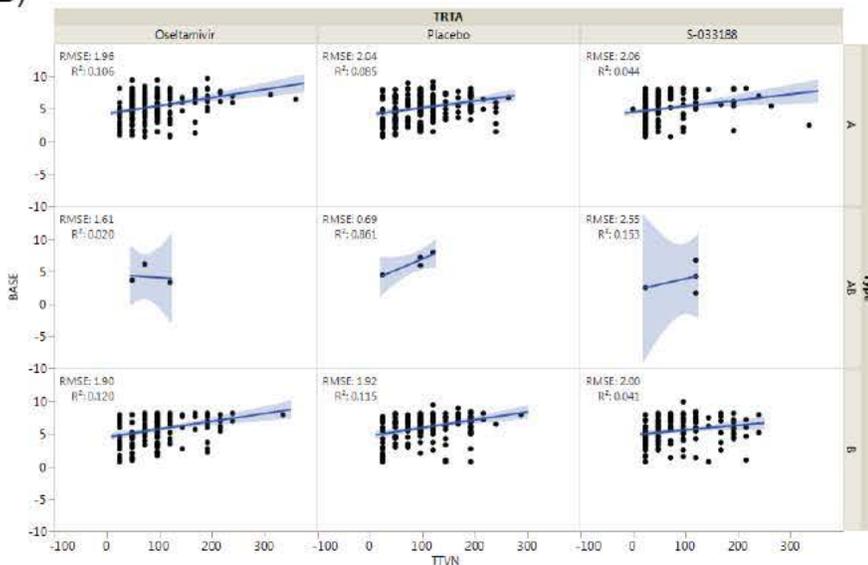
APPENDIX 8:

FDA analysis: Association of baseline virus shedding with time since symptoms onset (A), time to virus negativity (B) time to improvement of symptoms (TTIS, hours) (C), and time to resolution of fever (TTRF, hours). Includes all RT-PCR-positive subjects who were positive for virus at baseline and randomized, regardless of ITTI status. Treatment arm refers to actual treatment received. BASE: baseline virus shedding. A) Samples processed >96 hours post collection were excluded. Interquartile and 95 percentiles are shown (Prism 7.0, Graphpad Software Inc., San Diego). B-D) Root mean square error (RSME) and R<sup>2</sup> values are shown (JMP 12.1, SAS, Cary, NC).

A)



B)



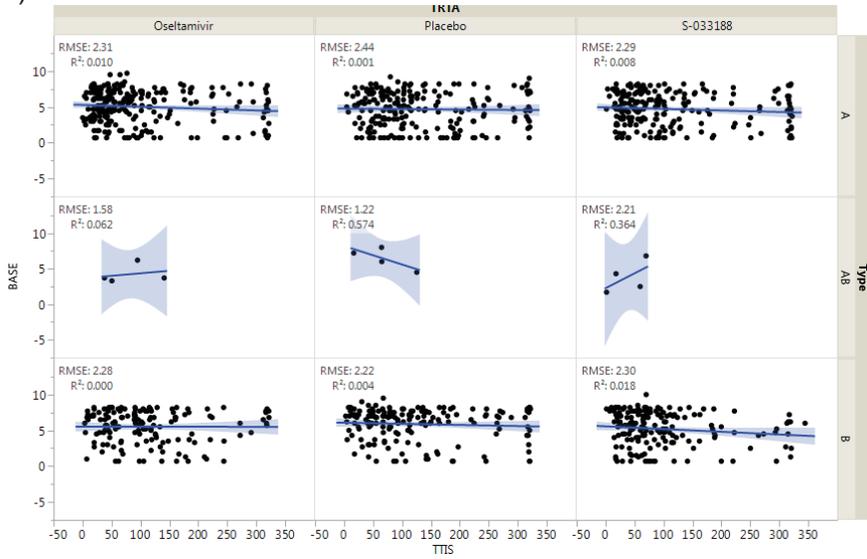
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

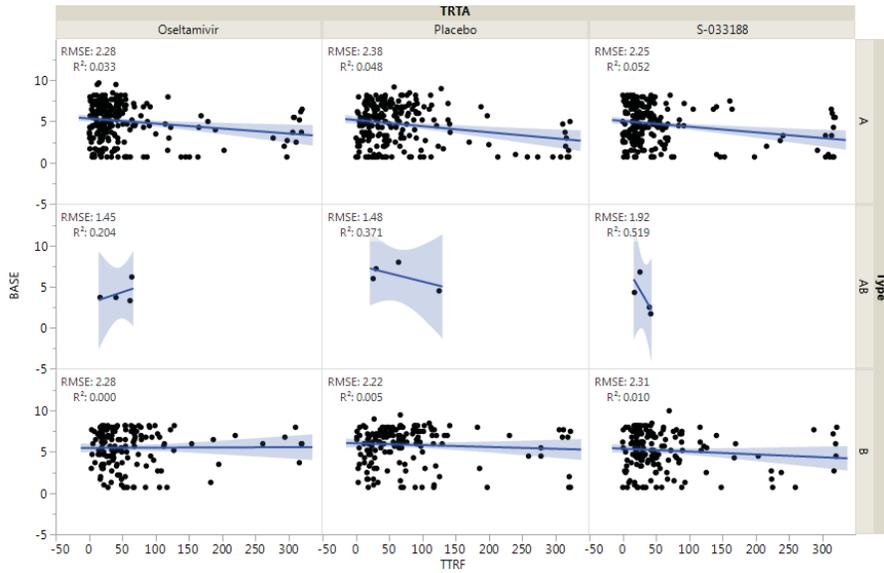
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C)



D)



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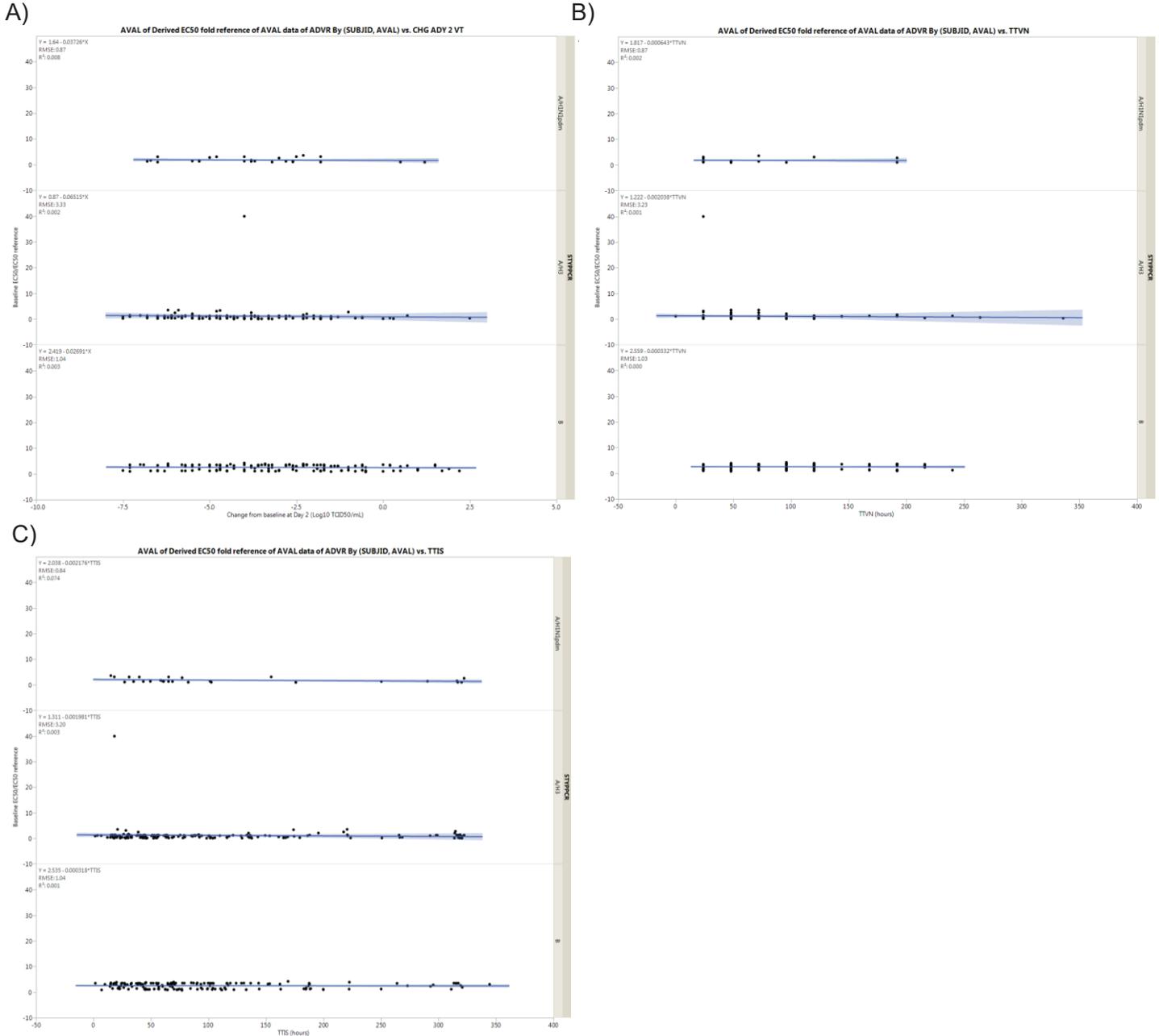
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

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APPENDIX 9:

FDA analysis: Baseline EC<sub>50</sub> value fold change association with change from baseline at Day 2 (A), time to virus negativity (TTVN, hours) (B), and time to improvement of symptoms (TTIS, hours) (C). Includes all baloxavir marboxil-treated subjects with influenza virus type/subtype determined and (for virologic endpoints) who were positive for virus at baseline (no subjects were censored based on ITTI status or sample processing turn-around time). Linear equations, root mean square error (RSME), and R<sup>2</sup> values are shown (JMP 12.1, SAS, Cary, NC).



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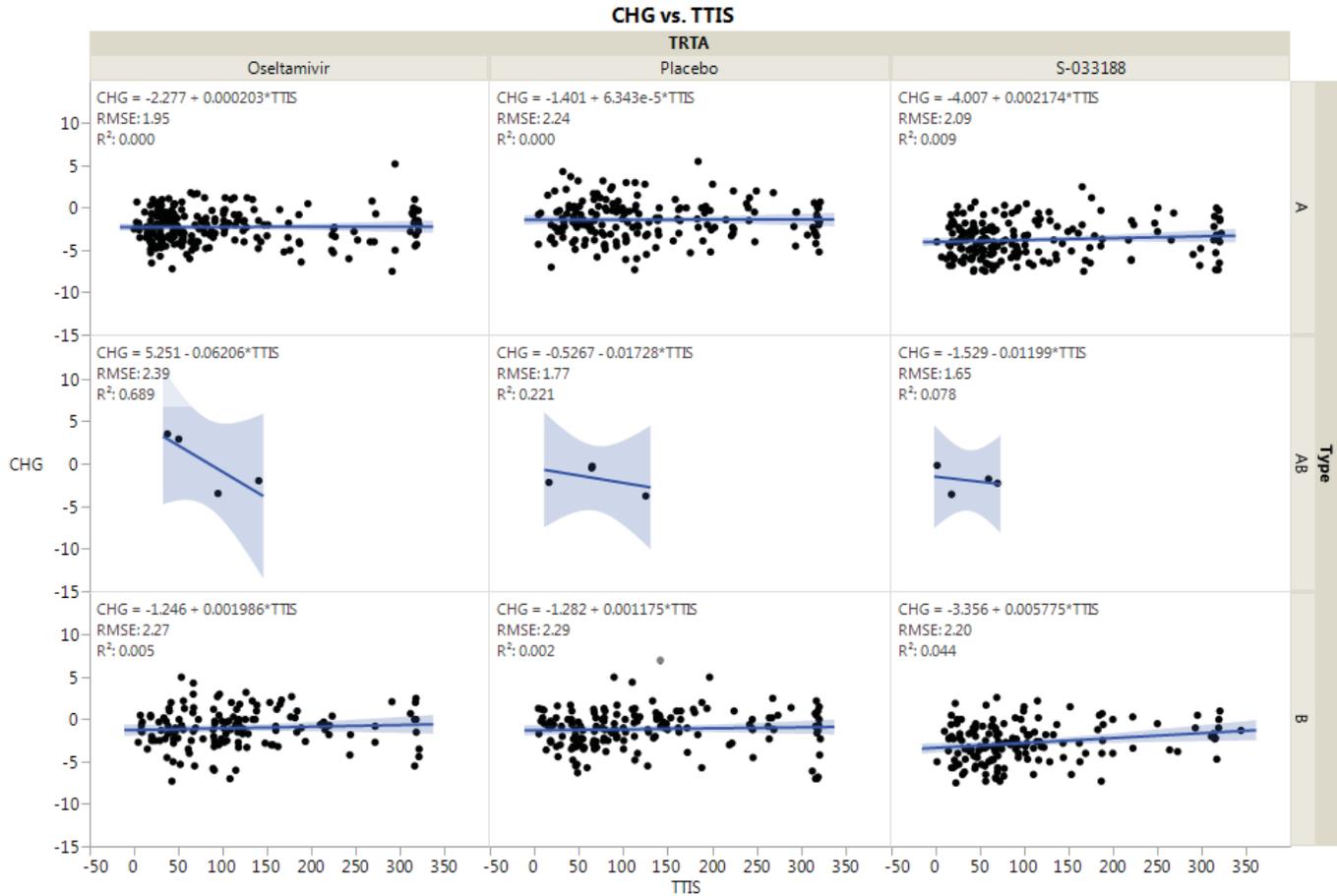
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

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APPENDIX 10:

FDA analysis: Association of the change from baseline at Day 2 (24 hours post treatment) (CHG) and time to improvement of symptoms (TTIS, hours). All subjects positive for virus at baseline, evaluated for virus titer at Day 2 were included in the analysis (no subjects were censored based on ITTI status or sample processing turn-around time). Linear equations, root mean square error (RMSE), and R<sup>2</sup> values are shown (JMP 12.1, SAS, Cary, NC).



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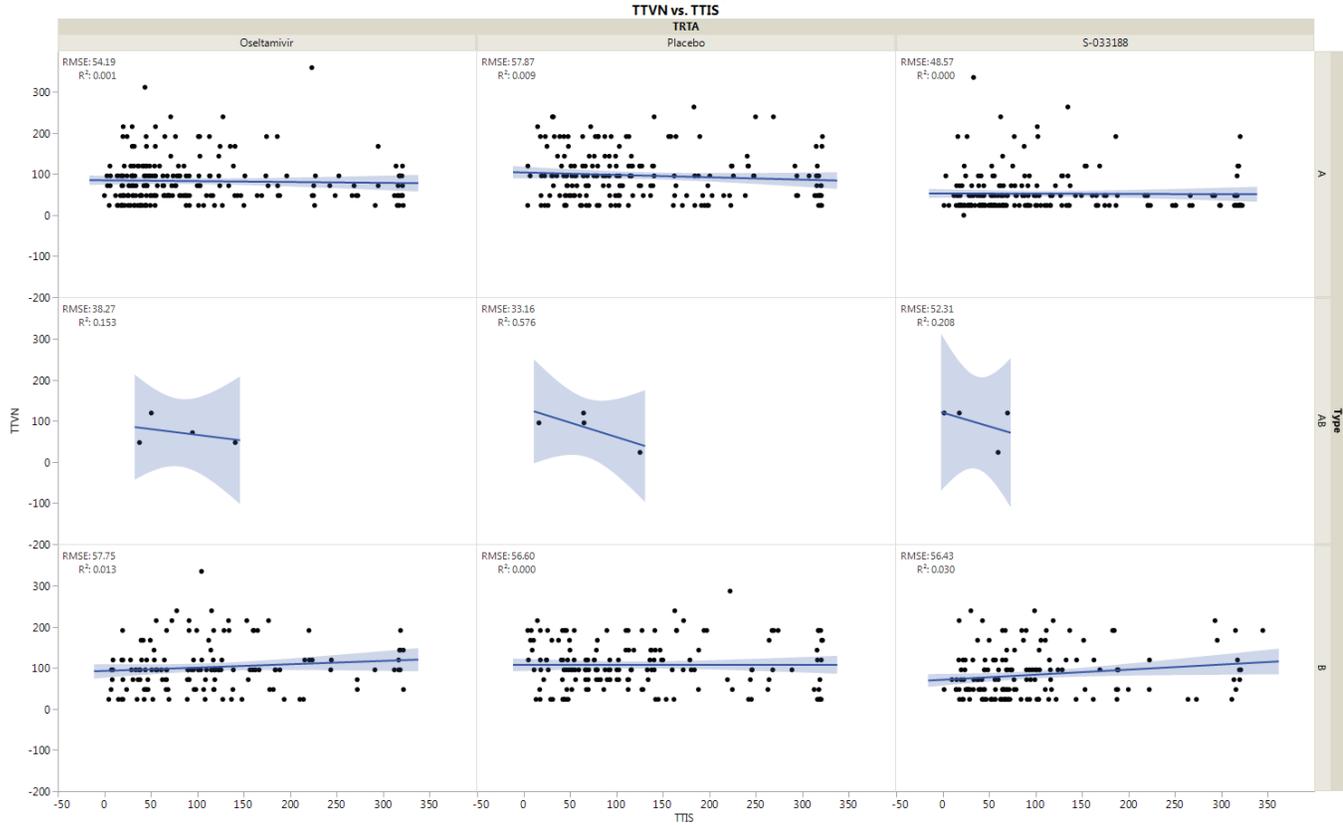
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 11:

FDA analysis: Association of time to first time point of virus negativity (TTVN, hours) and time to improvement of symptoms (TTIS, hours). Subjects with positive for virus at baseline were included in the analysis. No subjects were censored based on ITTI status or sample processing turn-around time. Root mean square error (RMSE) and  $R^2$  values are shown (JMP 12.1, SAS, Cary, NC).



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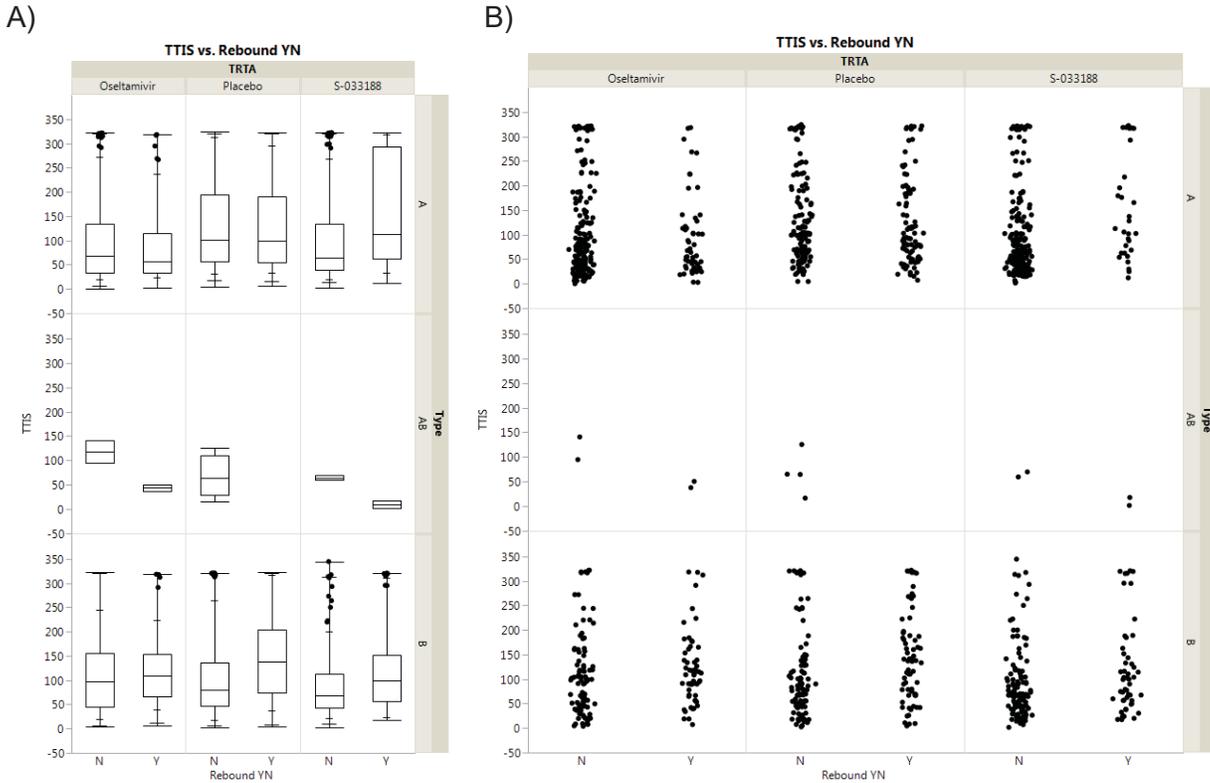
VIROLOGY REVIEW

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**APPENDIX 12:**

FDA analysis: Time to improvement of symptoms (TTIS, hours) in subjects with (Y) and without (N) virus rebound. Subjects with positive for virus at baseline were included in the analysis. No subjects were censored based on ITTI status or sample processing turn-around time. Box and whisker plots (A) and individual data points (B) are displayed separately. Analysis performed in JMP 12.1 (SAS, Cary, NC).



**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

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**Virology Reviewer: William Ince, Ph.D.**

**APPENDIX 13: SDN 120 – Response to information request to sponsor sent 5/23/2019.**

**Virology request for information 1:** Please provide a complete list of all viruses, along with their respective cell culture EC<sub>50</sub> values, used to generate the summary statistics provided in the updated labeling under Section 12.4 *Antiviral Activity*.

**Sponsor’s response:** The sponsor provided the requested data in the table below (Table 1).

**Virology follow-up:** Adequate response. The data included in Table 1 are consistent with the cell culture antiviral activity summary statistics reported in the proposed labeling and determined independently from data submitted previously.

**Table 1:** Cumulative cell culture antiviral activity data reported by the sponsor.

Type/Sub type	Strain	Mean EC50 (nM)	SD	Reference
A/H1N1	A/WSN/33	0.76	0.36	S-033188-EB-112-N
A/H1N1	A/WSN/33-NA/H274Y	0.49	0.2	S-033188-EB-112-N
A/H1N1	A/Kadoma/3/2006	0.94	0.23	S-033188-EB-097-N
A/H1N1	A/Osaka/129/2009	0.26	0.03	S-033188-EB-097-N
A/H1N1	A/Osaka/180/2009 a	0.48	0.07	S-033188-EB-097-N
A/H1N1	A/Nagasaki/10N073/2011	0.2	0.1	S-033188-EB-097-N
A/H1N1	A/Kyoto/10K124/2011a	0.35	0.14	S-033188-EB-097-N
A/H1N1	A/Kyoto/10K118/2011	0.8	0.46	S-033188-EB-097-N
A/H1N1	A/Hokkaido/13H020/2014	0.99	0.17	S-033188-EB-097-N
A/H1N1	A/Nagasaki/13N019/2014	0.52	0.15	S-033188-EB-097-N
A/H1N1	A/Nagasaki/13N059/2014a	0.66	0.12	S-033188-EB-097-N
A/H1N1	A/Hokkaido/07H002/2008	1.55	0.78	S-033188-EB-227-N
A/H1N1	A/Nagasaki/07N020/2008a	0.73	0.38	S-033188-EB-227-N
A/H1N1	A/Brisbane/59/2007	1.85	0.2	S-033188-EB-239-N
A/H1N1	A/California/7/2009	1.18	0.13	S-033188-EB-239-N
A/H1N1	A/Mississippi/03/2001	1	0.27	S-033188-EB-299-N
A/H1N1	A/Mississippi/03/2001- NA/H274Y	0.5	0.18	S-033188-EB-299-N
A/H1N1	A/Perth/265/2009 (H1N1pdm)	0.46	0.17	S-033188-EB-299-N
A/H1N1	A/Perth/261/2009- NA/H274Y (H1N1pdm)	1.17	0.21	S-033188-EB-299-N
A/H1N1	A/California/12/2012 (H1N1pdm)	0.78	0.19	S-033188-EB-312-N
A/H1N1	A/Maryland/08/2013 (H1N1pdm)	0.6	0.18	S-033188-EB-312-N
A/H1N1	A/Texas/23/2012-NA/H274Y (H1N1pdm)	0.61	0.15	S-033188-EB-312-N
A/H1N1	A/Louisiana/08/2013- NA/H274Y (H1N1pdm)	0.83	0.26	S-033188-EB-312-N
A/H1N1	A/North Carolina/4/2014- NA/H274Y (H1N1pdm)	1.19	0.12	S-033188-EB-312-N
A/H1N1	A/New Caledonia/20/1999 (H1N1)	1.09	0.47	S-033188-EB-318-N
A/H1N1	A/California/04/2009 (H1N1pdm)	0.43	0.15	S-033188-EB-318-N
A/H1N1	A/Mexico/4108/2009 (H1N1pdm)	0.46	0.08	S-033188-EB-318-N
A/H1N1	A/Bayern/69/2009 (H1N1pdm)	0.34	0.17	S-033188-EB-318-N
A/H1N1	A/Christchurch/16/2010 (H1N1pdm)	0.54	0.41	S-033188-EB-318-N
A/H1N1	A/St. Petersburg/100/2011 (H1N1pdm)	0.78	0.87	S-033188-EB-318-N
A/H1N1	A/South Africa/3626/2013 (H1N1pdm)	1.34	0.49	S-033188-EB-318-N
A/H3N2	A/Victoria/3/75	0.76	0.19	S-033188-EB-112-N
A/H3N2	A/Hong Kong/8/68	0.35	0.06	S-033188-EB-112-N
A/H3N2	A/Hyogo/10K051/2011	0.66	0.34	S-033188-EB-097-N
A/H3N2	A/Niigata/10F017/2011	0.43	0.05	S-033188-EB-097-N
A/H3N2	A/Niigata/11F027/2012	0.9	0.35	S-033188-EB-097-N
A/H3N2	A/Tokyo/11 M003/2012	0.49	0.06	S-033188-EB-097-N
A/H3N2	A/Hokkaido/12H048/2013	0.56	0.02	S-033188-EB-097-N
A/H3N2	A/Niigata/12F392/2013	0.68	0.36	S-033188-EB-097-N
A/H3N2	A/Kyoto/13SK042/2014	0.49	0.07	S-033188-EB-097-N
A/H3N2	A/Nagasaki/13N033/2014	0.42	0.06	S-033188-EB-097-N
A/H3N2	A/Niigata/05F067/2006	0.38	0.14	S-033188-EB-227-N
A/H3N2	A/Nagasaki/05N007/2006	0.8	0.18	S-033188-EB-227-N
A/H3N2	A/Kyoto/06K110/2007	0.55	0.22	S-033188-EB-227-N
A/H3N2	A/Victoria/361/2011	1.87	0.06	S-033188-EB-239-N
A/H3N2	A/New York/39/2012	0.74	0.28	S-033188-EB-239-N
A/H3N2	A/Texas/50/2012	1	0.14	S-033188-EB-239-N
A/H3N2	A/Switzerland/9715293/2013	1.04	0.57	S-033188-EB-239-N
A/H3N2	A/Fukui/20/2004	1.02	0.28	S-033188-EB-299-N
A/H3N2	A/Fukui/45/2004-NA/E119V	0.83	0.19	S-033188-EB-299-N
A/H3N2	A/Washington/01/2007	2.39	0.85	S-033188-EB-312-N
A/H3N2	A/Texas/12/2007-NA/E119V	2.63	0.5	S-033188-EB-312-N
A/H3N2	A/Bethesda/956/2006- NA/R292K	1.35	0.39	S-033188-EB-312-N
A/H3N2	A/New York/55/2004	0.58	0.12	S-033188-EB-318-N
A/H3N2	A/Wisconsin/67/2005	1.76	0.69	S-033188-EB-318-N
A/H3N2	A/Indiana/08/2011	0.73	0.16	S-033188-EB-318-N
A/H3N2	A/Indiana/10/2011	2.12	0.24	S-033188-EB-318-N
A/H3N2	A/Perth/16/2009	1.56	0.43	S-033188-EB-318-N
A/H3N2	A/Hong Kong/4801/2014	0.96	0.21	S-033188-EB-318-N
A/H3N2	A/Panama/2007/1999	1.04	0.55	S-033188-EB-318-N
A/H3N2	A/Wyoming/03/2003	1.35	0.25	S-033188-EB-318-N
A/H3N2	A/Wellington/01/2004	1.04	0.56	S-033188-EB-318-N
A/H3N2	A/Netherlands/525/2014	0.63	0.08	S-033188-EB-318-N
A/H3N2	A/Louisiana/50/2017	0.89	0.27	S-033188-EB-318-N
A/H3N2	A/Louisiana/49/2017- PA/138M	11.2	5.19	S-033188-EB-318-N
B	B/Maryland/1/59	4.85	2.42	S-033188-EB-112-N

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019**

**Virology Reviewer: William Ince, Ph.D.**

B	B/Hong Kong/5/72	4.33	2.69	S-033188-EB-112-N
B	B/Kyoto/10K131/2011	4.01	1.64	S-033188-EB-097-N
B	B/Hokkaido/11H011/2012	5.28	0.26	S-033188-EB-097-N
B	B/Gunma/12G045/2013	5.04	1.83	S-033188-EB-097-N
B	B/Gunma/13G004/2014	11.26	1.2	S-033188-EB-097-N
B	B/Niigata/06F075/2007	4.72	1.75	S-033188-EB-227-N
B	B/Gunma/06G040/2007	5.97	0.58	S-033188-EB-227-N
B	B/Kyoto/08K015/2009	5.04	1.52	S-033188-EB-227-N
B	B/Kyoto/11K272/2012	4.39	1.26	S-033188-EB-227-N
B	B/Nagasaki/13N013/2013	4.03	0.84	S-033188-EB-227-N
B	B/Niigata/13F044/2014	3.33	0.59	S-033188-EB-227-N
B	B/Kyoto/13K042/2014	5.96	2.96	S-033188-EB-227-N
B	B/Phuket/3073/2013	9.24	2.93	S-033188-EB-239-N
B	B/Malaysia/2506/2004	12.26	2.47	S-033188-EB-239-N
B	B/Brisbane/60/2008	10.61	3.2	S-033188-EB-239-N
B	B/Wisconsin/1/2010	13	1.68	S-033188-EB-239-N
B	B/Massachusetts/2/2012	9.53	2.49	S-033188-EB-239-N
B	B/Texas/2/2013	11.91	1.31	S-033188-EB-239-N
B	B/Perth/21/2001	6.8	1.9	S-033188-EB-299-N
B	B/Perth/21/2001- NA/D198E	4.88	3.61	S-033188-EB-299-N
B	B/Memphis/20/1996	5.07	2.5	S-033188-EB-312-N
B	B/Memphis/20/1996-NA/R152K	2.67	0.54	S-033188-EB-312-N
B	B/Florida/4/2006	13.67	6.68	S-033188-EB-318-N
B	B/Brisbane/33/2008	7.84	1.52	S-033188-EB-318-N
B	B/Hubei- Wujiagang/158/2009	5.54	2.15	S-033188-EB-318-N
B	B/Jiangsu/10/2003	14.23	1.7	S-033188-EB-318-N
B	B/England/393/2008	7.74	4.77	S-033188-EB-318-N
B	B/Paris/1762/2009	9.91	3.33	S-033188-EB-318-N
B	B/Johannesburg/3964/2012	10.9	2.23	S-033188-EB-318-N

**Virology request for information 2:** Please provide an update of available data on cell culture susceptibility of treatment-emergent variants observed in clinical studies of baloxavir marboxil.

**Virology follow-up:** Adequate response. The sponsor provided updated cumulative cell culture susceptibility data for cloned variants with specific substitutions or combinations of substitutions identified in clinical studies (determined in plaque reductions assays, as previously described for phenotypic resistance analyses of cloned virus [[N210854.000](#)]). Cell culture susceptibility from 3 additional study reports are included in the cumulative list of susceptibility data (Table 2).

**Table 2:** Cumulative cell culture antiviral activity data of viruses carrying substitutions identified in clinical studies to date.

Type/subtype	Strains	Mean EC50 (nM)	SD	Fold-change	Reference
A/H1N1	rgA/WSN/33 (H1N1)	0.42	0.12	N/A	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-NA/H274Y (H1N1)	0.32	0.06	0.77	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/A36V (H1N1)	1.5	0.37	3.59	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/V545T (H1N1)	0.31	0.11	0.73	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/I38T (H1N1)	11.37	1.85	27.24	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/I38F (H1N1)	4.43	1.95	10.61	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/A20S (H1N1)	0.5	0.27	1.19	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33- PA/A20S+I38T (H1N1)	11.43	2.6	27.38	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33- PA/A20S+I38F (H1N1)	3.38	1.16	8.1	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/E23K (H1N1)	1.98	0.48	4.74	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PB2/A221T (H1N1)	0.38	0.06	0.9	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PB2/I310M (H1N1)	0.29	0.08	0.71	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PB2/T333I (H1N1)	0.24	0.02	0.58	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PB1/M92T (H1N1)	0.33	0.05	0.79	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PB1/V418I (H1N1)	0.3	0.1	0.71	S-033188-EB- 235-N
A/H1N1	rgA/WSN/33-PA/E119D (H1N1)	2.7	1.5	6.46	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75 (H3N2)	1.13	0.51	N/A	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75-PA/A36V (H3N2)	6.87	2.76	6.09	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75-PA/I38T (H3N2)	63.8	3.4	56.59	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75-PA/I38F (H3N2)	22.69	10.82	20.13	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75-PA/E23K (H3N2)	6.2	2.86	5.5	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75- PA/E119D (H3N2)	5.09	2.48	4.51	S-033188-EB- 235-N
B	rgB/Maryland/1/59	10.73	5.52	N/A	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/F36A	8.46	0.88	0.79	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/F36V	8.6	3.17	0.8	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/I38T	61.79	9.17	5.76	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/I38F	25.59	0.54	2.39	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/E23K	8.73	0.56	0.81	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/G548R	12.17	1.88	1.13	S-033188-EB- 235-N
B	rgB/Maryland/1/59-PA/E120D	21.1	11.06	1.97	S-033188-EB- 235-N
A/H3N2	rgA/Victoria/3/75 (H3N2)	0.83	0.28	N/A	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/L28P (H3N2)	2.15	0.13	2.58	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/L28P+V63I (H3N2)	2.4	0.32	2.88	S-033188-EB- 276-N

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 210854 S-001 SDN: 077 (SN 0066)      DATE REVIEWED: 8/13/2019**

**Virology Reviewer: William Ince, Ph.D.**

A/H3N2	rgA/Victoria/3/75-PA/V63I (H3N2)	1.44	0.33	1.73	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75- PA/R356K (H3N2)	0.8	0.49	0.96	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/A37T (H3N2)	6.78	4.04	8.13	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/I38T*	40.76	11.94	48.9	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+E623K (H3N2)	35.34	16.12	42.41	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/I38M (H3N2)	11.48	1.43	13.77	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/N412D (H3N2)	0.45	0.02	0.54	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/V517A (H3N2)	0.43	0.22	0.52	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/E623K (H3N2)	1	0.29	1.2	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/S632P(H3N2)	0.61	0.28	0.74	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/E199G (H3N2)	3.72	1.37	4.46	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75-PA/K362R (H3N2)	1.05	0.66	1.25	S-033188-EB- 276-N
A/H1N1	rgA/WSN/33 (H1N1)	0.31	0.11	N/A	S-033188-EB- 276-N
A/H1N1	rgA/WSN/33-PA/I465M (H1N1)	0.29	0.05	0.93	S-033188-EB- 276-N
A/H1N1	rgA/WSN/33-PA/I38M (H1N1)	4.07	1.84	13.15	S-033188-EB- 276-N
B	rgB/Maryland/1/59	5.19	1.29	N/A	S-033188-EB- 276-N
B	rgB/Maryland/1/59- PA/I38M	41.71	14.71	8.04	S-033188-EB- 276-N
A/H3N2	rgA/Victoria/3/75 (H3N2)	1.15	0.59	N/A	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T (H3N2)	57.33	6.81	49.76	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/S60P (H3N2)	0.46	0.22	0.4	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+S60P (H3N2)	55.55	4.64	48.21	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/T162A (H3N2)	1.96	0.3	1.7	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB1/I205M (H3N2)	0.73	0.17	0.63	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB1/M290T (H3N2)	0.39	0.24	0.34	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB2/D60G (H3N2)	1.06	0.15	0.92	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/D60G (H3N2)	49.37	19.05	42.85	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB2/V105M (H3N2)	0.67	0.18	0.58	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB2/K197R (H3N2)	1.56	0.69	1.36	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+PB2/K197R (H3N2)	23.12	20.73	20.07	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB2/K353R (H3N2)	0.84	0.22	0.73	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PB2/I385V (H3N2)	0.74	0.13	0.64	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38V (H3N2)	2.11	0.81	1.83	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/E23G (H3N2)	2.75	1.48	2.39	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/G99E (H3N2)	0.71	0.28	0.61	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/A183V (H3N2)	0.59	0.4	0.51	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/G186D (H3N2)	0.21	0.13	0.18	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I201T (H3N2)	1.26	0.61	1.1	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I38T+I201T (H3N2)	39.09	5.29	33.92	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/R212C (H3N2)	0.79	0.33	0.68	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/S224F (H3N2)	0.9	0.84	0.78	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/A231V (H3N2)	0.67	0.3	0.58	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/C241F (H3N2)	0.65	0.17	0.56	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/E23G+C241F (H3N2)	2.04	1.35	1.77	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/P271S (H3N2)	0.6	0.22	0.52	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/G299R (H3N2)	1.54	0.77	1.34	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/G316R (H3N2)	0.3	0.07	0.26	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/T357A (H3N2)	1.07	0.86	0.93	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/R385K (H3N2)	1.22	0.46	1.06	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/S395N (H3N2)	0.7	0.44	0.6	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/S405C (H3N2)	0.8	0.62	0.69	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I421T (H3N2)	1.26	1.14	1.1	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/L482I (H3N2)	0.6	0.06	0.52	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/E493G (H3N2)	0.51	0.39	0.44	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/I545M (H3N2)	0.49	0.17	0.43	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/M561I (H3N2)	1.05	0.23	0.91	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/V602I (H3N2)	1.31	0.76	1.14	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/E623G (H3N2)	1.2	0.72	1.04	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/E630K (H3N2)	0.46	0.19	0.4	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/G316R+E630K (H3N2)	0.41	0.18	0.36	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/L649M (H3N2)	0.47	0.1	0.41	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75-PA/V668I (H3N2)	0.93	0.48	0.81	S-033188-EB- 290-N
A/H1N1	rgA/WSN/33 (H1N1)	0.45	0.22	N/A	S-033188-EB- 290-N
A/H1N1	rgA/WSN/33-PA/I38V (H1N1)	0.97	0.8	2.18	S-033188-EB- 290-N
B	rgB/Maryland/1/59	10.07	5.45	N/A	S-033188-EB- 290-N
B	rgB/Maryland/1/59- PA/T60V	8.63	3.28	0.86	S-033188-EB- 290-N
B	rgB/Maryland/1/59- PA/D112N	6.17	3.22	0.61	S-033188-EB- 290-N
B	rgB/Maryland/1/59- PA/E333K	7.08	1.88	0.7	S-033188-EB- 290-N
B	rgB/Maryland/1/59- PA/Y361H	10.42	3.7	1.03	S-033188-EB- 290-N
A/H3N2	rgA/Victoria/3/75 (H3N2)	1.05	0.35	N/A	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75-PA/I38T (H3N2)	26.18	7.76	24.85	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB1/I517M (H3N2)	1.02	0.18	0.97	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB2/R101G (H3N2)	0.85	0.14	0.8	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB2/M202L (H3N2)	1.8	0.36	1.7	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB2/R209K (H3N2)	0.55	0.15	0.53	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB2/M475I (H3N2)	1.38	0.37	1.31	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PB2/S12L (H3N2)	0.91	0.3	0.86	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PA/E199G (H3N2)	2.95	0.3	2.8	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75- PA/E199G+PB2/S12L (H3N2)	2.87	0.41	2.73	S-033188-EB- 319-N
A/H1N1	rgA/WSN/33 (H1N1)	0.47	0.05	N/A	S-033188-EB- 319-N
A/H1N1	rgA/WSN/33-PA/I38T (H1N1)	20.53	5.13	43.92	S-033188-EB- 319-N
A/H1N1	rgA/WSN/33-PB1/K757N (H1N1)	0.47	0.1	1	S-033188-EB- 319-N
A/H3N2	rgA/Victoria/3/75-PA/I38T (H3N2)	45.74	8.66	25.489	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I38M (H3N2)	6.561	1.71	3.6561	S-033188-EB-329-N
A/H3N2	rgA/Victoria/3/75-PA/I201T (H3N2)	1.438	0.48	0.8013	S-033188-EB-329-N

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 210854 S-001 SDN: 077 (SN 0066)      DATE REVIEWED: 8/13/2019**

**Virology Reviewer: William Ince, Ph.D.**

A/H3N2	rgA/Victoria/3/75-PA/I38M+I201T (H3N2)	16.40	7.92	9.1406	S-033188-EB-329-N
B	rgB/Maryland/1/59	11.29	3.82	N/A	S-033188-EB-329-N
B	rgB/Maryland/1/59-PA/E680K	8.786	1.05	0.7789	S-033188-EB-329-N
A/H1N1	rgA/WSN/33(H1N1)	0.36	0.03	N/A	S-033188-EB-335-N
A/H1N1	rgA/WSN/33(H1N1)	6.9	2.94	19.16	S-033188-EB-335-N
A/H1N1	rgA/WSN/33(H1N1)	8.52	2.87	23.66	S-033188-EB-335-N
A/H1N1	rgA/WSN/33(H1N1)	0.38	0.07	1.07	S-033188-EB-335-N
A/H1N1	rgA/WSN/33(H1N1)	0.33	0.08	0.92	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75	0.73	0.41	N/A	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/I38T	14.8	5.86	20.33	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/L28V	1.47	0.78	2.02	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/K34E	1.43	1.6	1.96	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/P68L	0.89	0.4	1.23	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/L71M	0.46	0.08	0.64	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/V90A	0.83	0.45	1.14	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75-PA/T98N	0.38	0.08	0.52	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/D160G	0.59	0.16	0.81	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/R192H	0.62	0.1	0.85	S-033188-EB-335-N
A/H3N2	rgA/Victoria/3/75- PA/E397K	0.56	0.39	0.77	S-033188-EB-335-N
B	rgB/Maryland/1/59	7.6	5.22	N/A	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/R7K	9.45	3.43	1.24	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/S25G	7.2	1.8	0.95	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/T62K	3.67	1.25	0.48	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/D201E	7.58	1.89	1	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/D201G	10.32	1.08	1.36	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/E333G	9.58	2.7	1.26	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/N354K	10.58	2.31	1.39	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/S415G	9.3	2.45	1.22	S-033188-EB-335-N
B	rgB/Maryland/1/59- PA/S415N	11.91	0.72	1.57	S-033188-EB-335-N

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

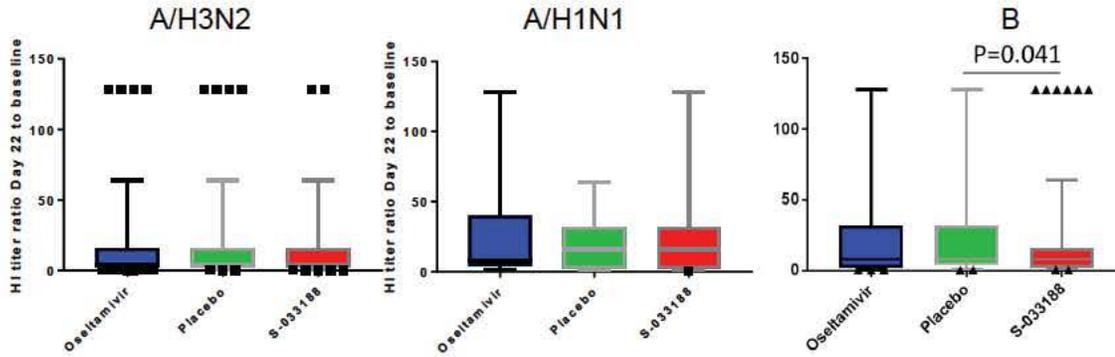
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 14:

FDA analysis: Ratio of Day 22 (day 16-30) to Day 1 (baseline) anti-influenza antibody hemagglutination inhibition (HI) titers by treatment arm. A) A/H3N2, B) A/H1N1 (to H1N1pdm strain), and C) type B (to Yamagata strain)(see ADIS dataset). Prism 7.0, Graphpad Software Inc., San Diego, CA.



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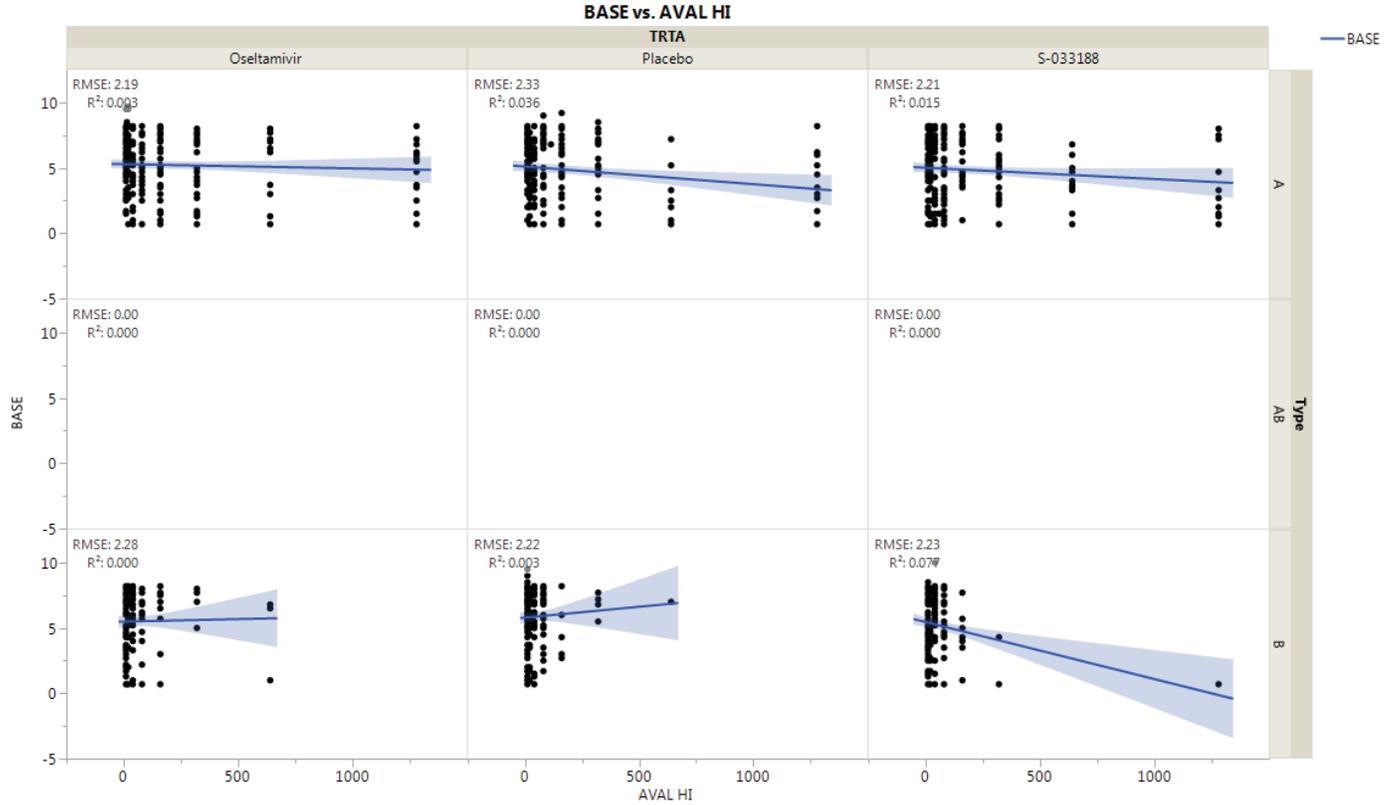
VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

APPENDIX 15:

FDA analysis: Baseline HI titer (AVAL HI) by baseline virus titer (BASE). Excludes subjects who were co-infected. HI titer is to the virus strain matching the infecting virus. For H1N1 infections, H1N1pdm HI titer was used; for type B infections, Yamagata titer was used (see ADIS dataset). JMP 12.1, SAS, Cary, NC.



DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

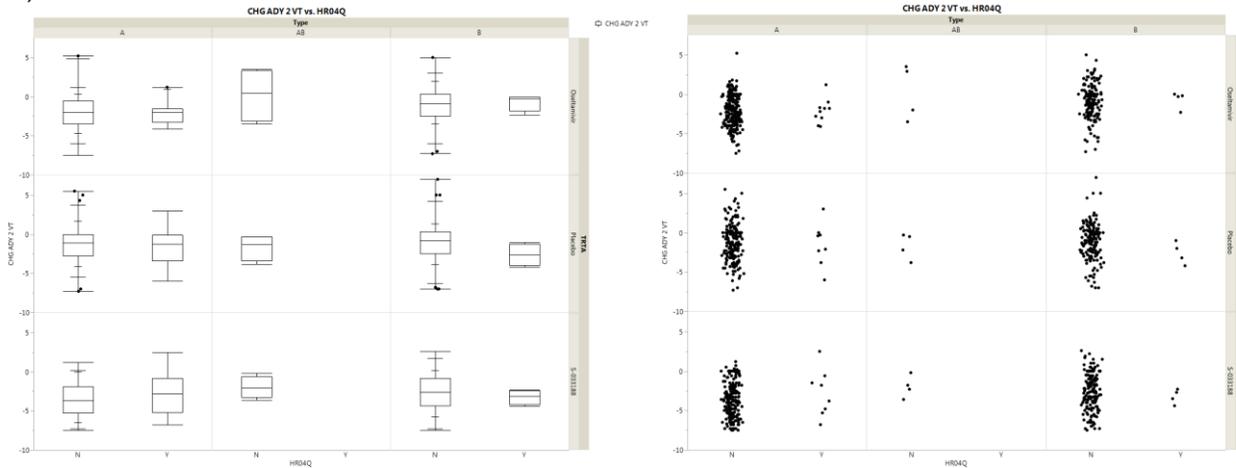
NDA: 210854 S-001 SDN: 077 (SN 0066) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.

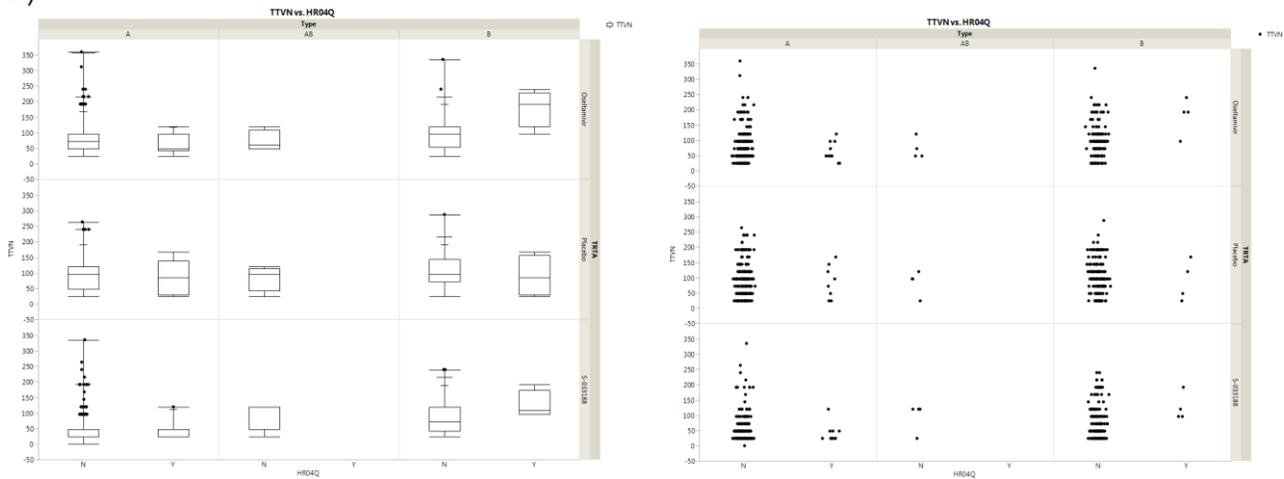
APPENDIX 16:

FDA analysis: Change from baseline at Day 2 (CHG ADY 2 VT) in virus titer (A) and time to first negative time point (TTVN) (B) by immunosuppression status (HR04Q Y/N). Box and whiskers represent quantiles. JMP 12.1, SAS, Cary, NC.

A)



B)



DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

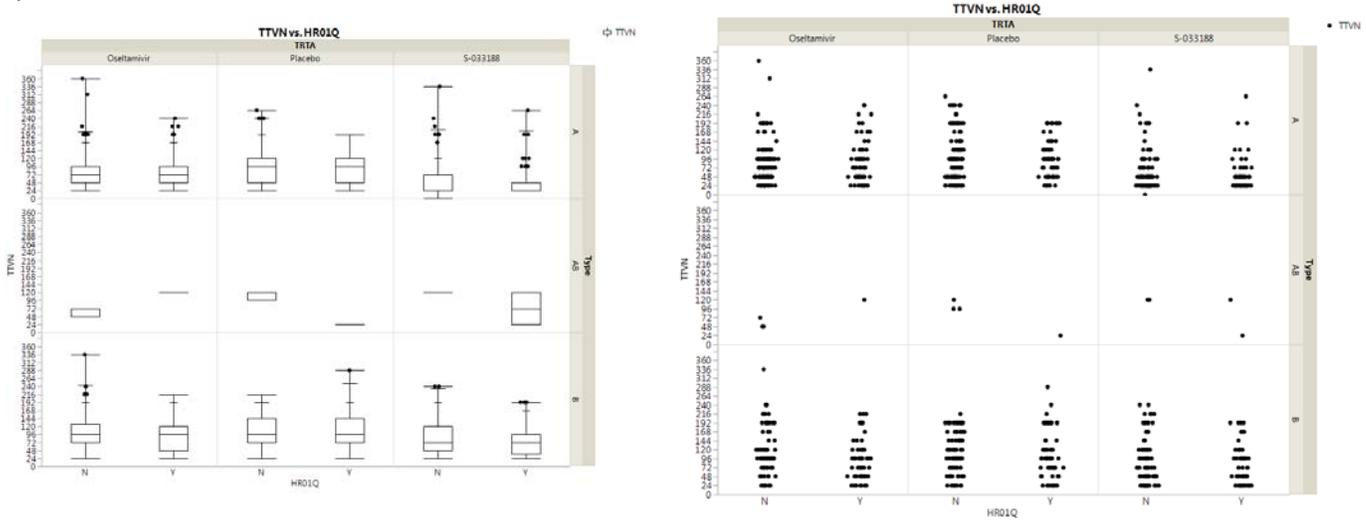
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Virology Reviewer: William Ince, Ph.D.

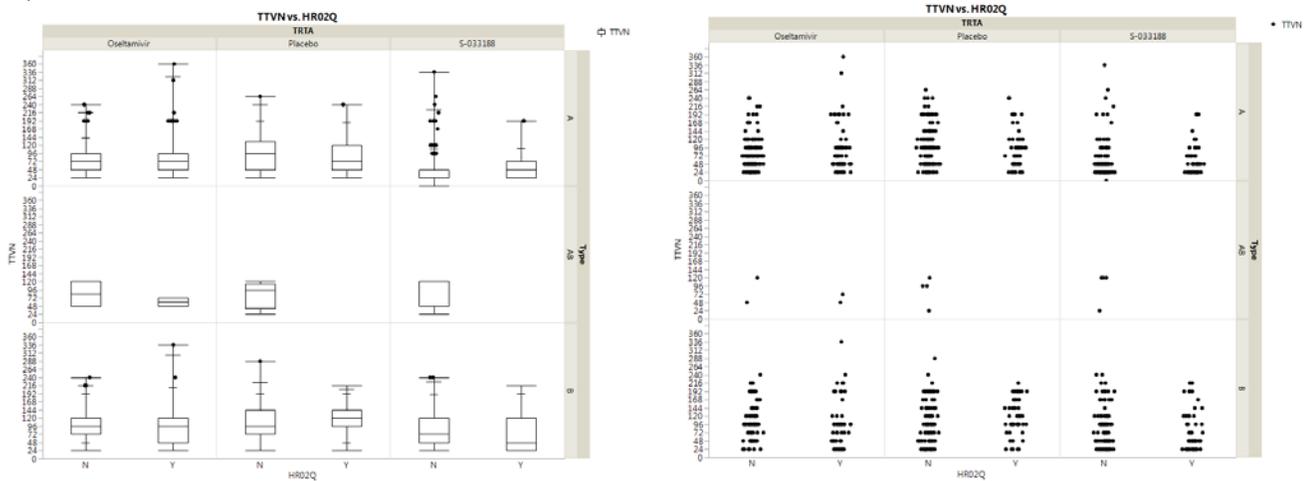
APPENDIX 17:

FDA analysis: Time to first negative time point (TTVN) by risk factor. A) Asthma or chronic lung disease; B) Endocrine disorders; C) Neurological and neurodevelopmental disorders; D) Heart disease; E) More than or equal to 65 years of age; F) Blood disorders; G) Metabolic disorders; H) Morbid obesity; I) Sex. Box and whiskers represent quantiles. JMP 12.1, SAS, Cary, NC

A)



B)



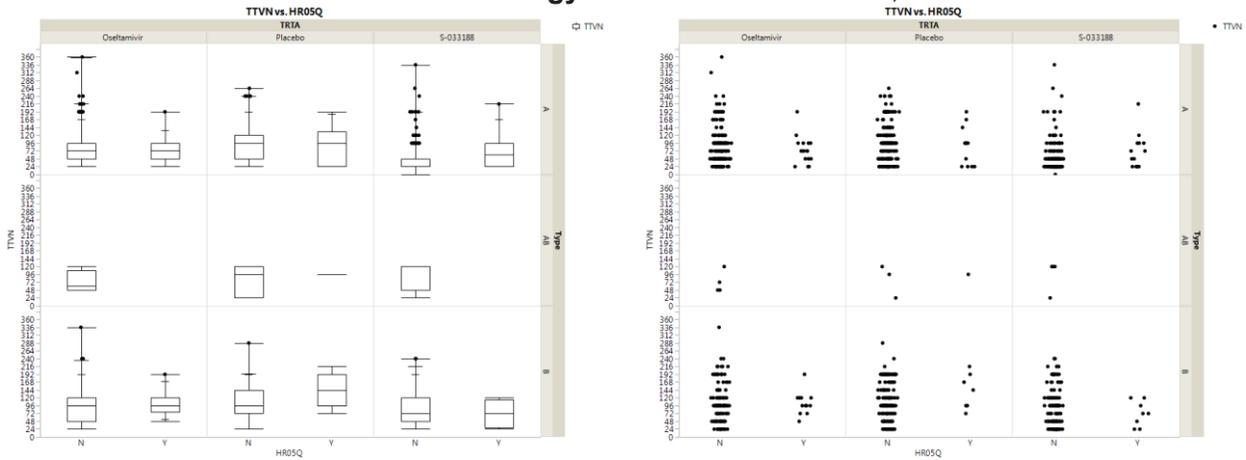
C)

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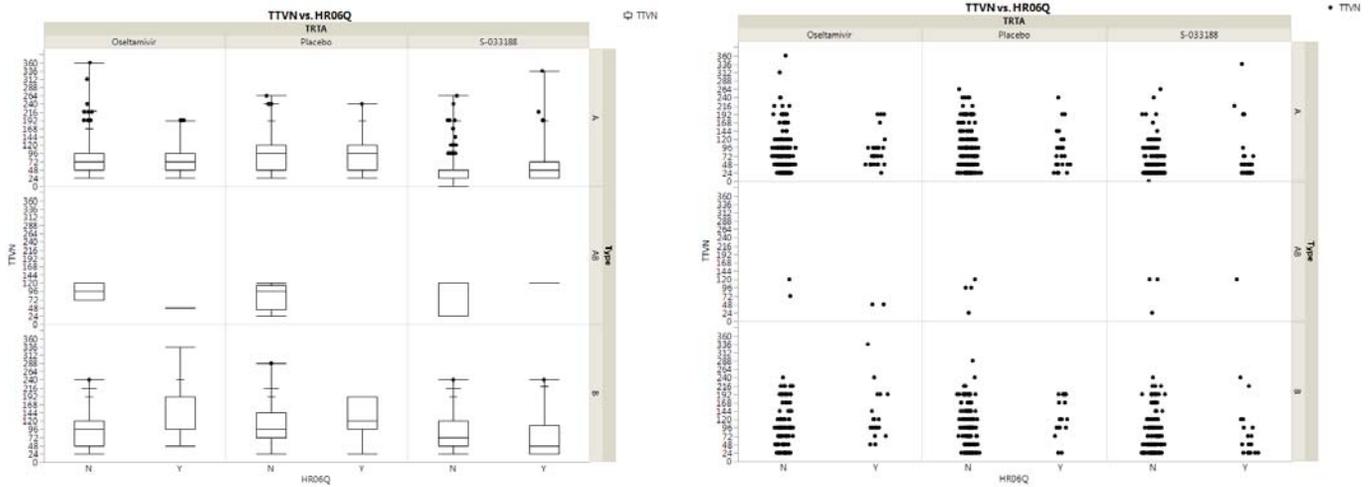
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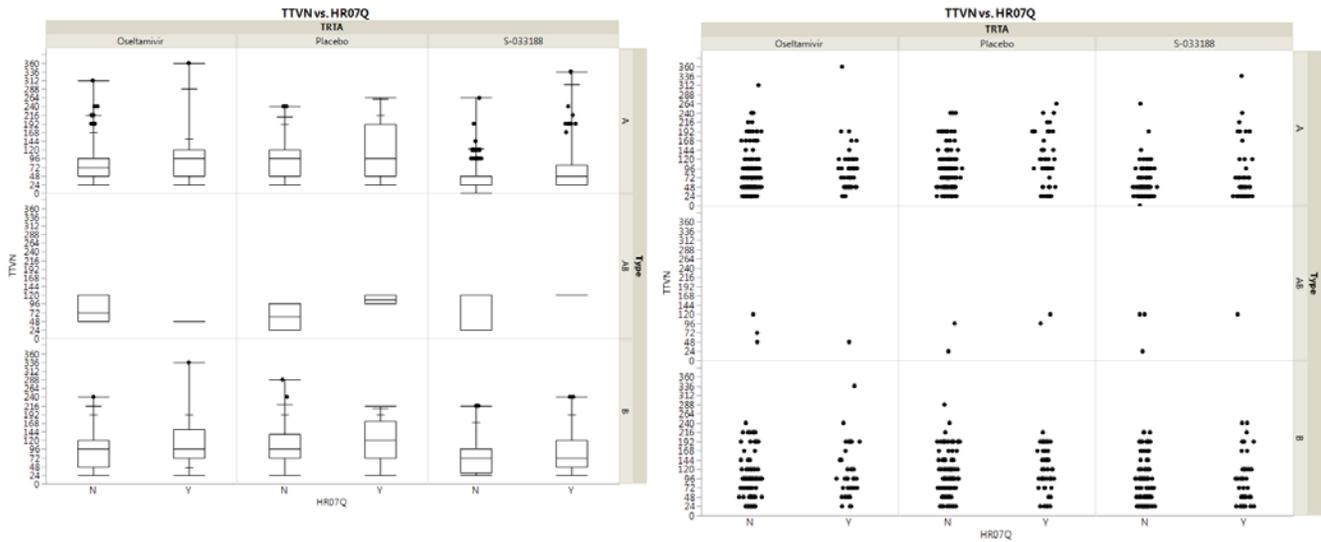
Virology Reviewer: William Ince, Ph.D.



D)



E)



F)

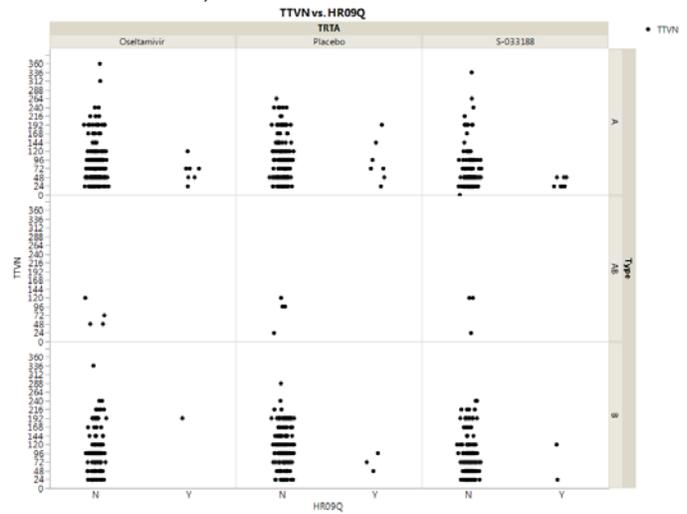
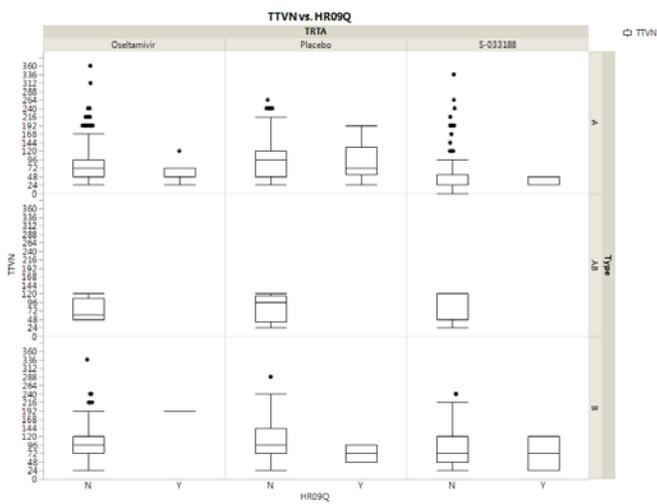
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

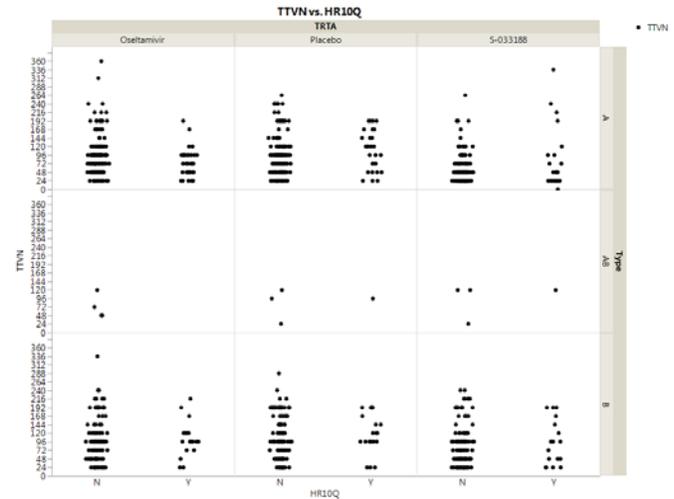
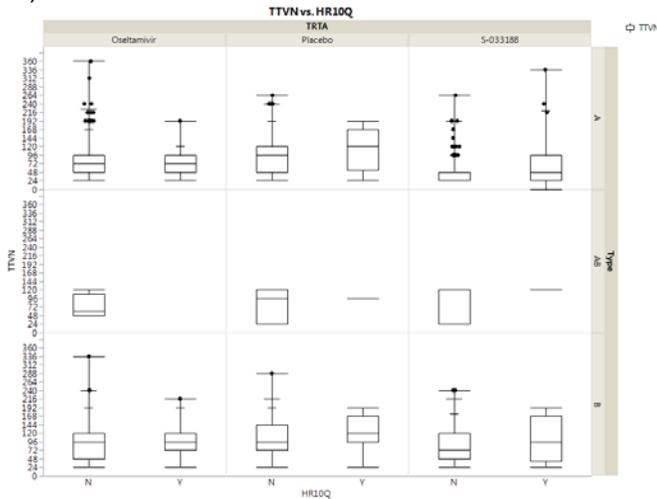
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DATE REVIEWED: 8/13/2019

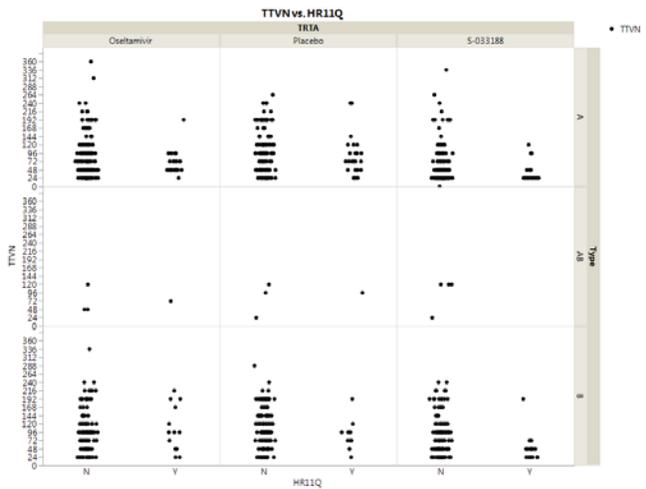
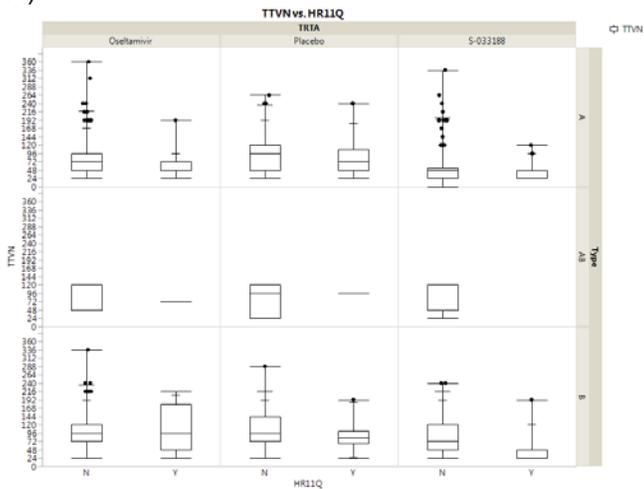
Virology Reviewer: William Ince, Ph.D.



G)



H)



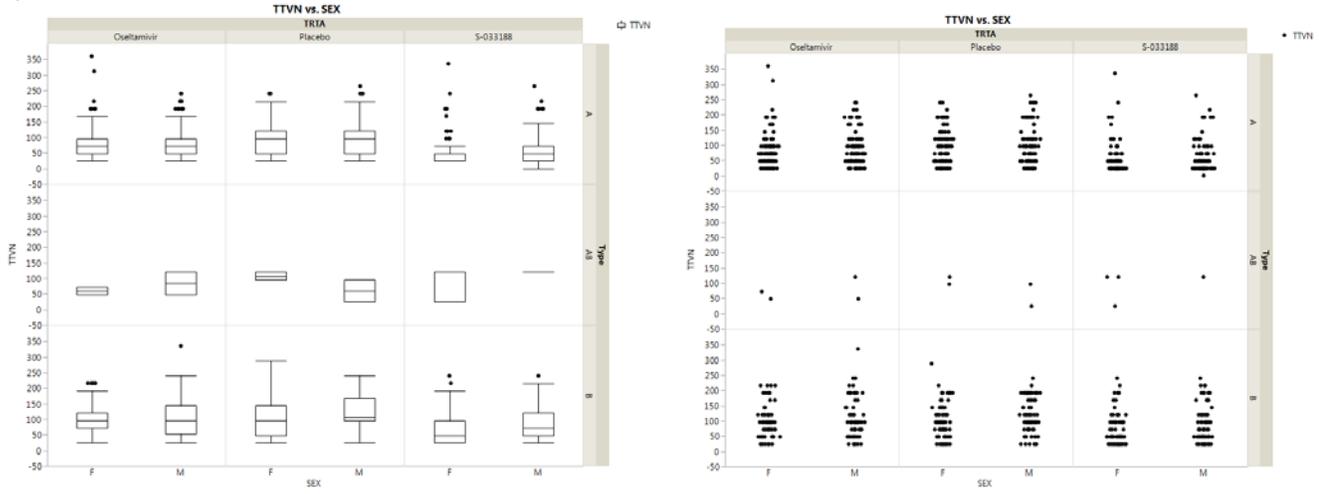
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Virology Reviewer: William Ince, Ph.D.

l)



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VIROLOGY REVIEW

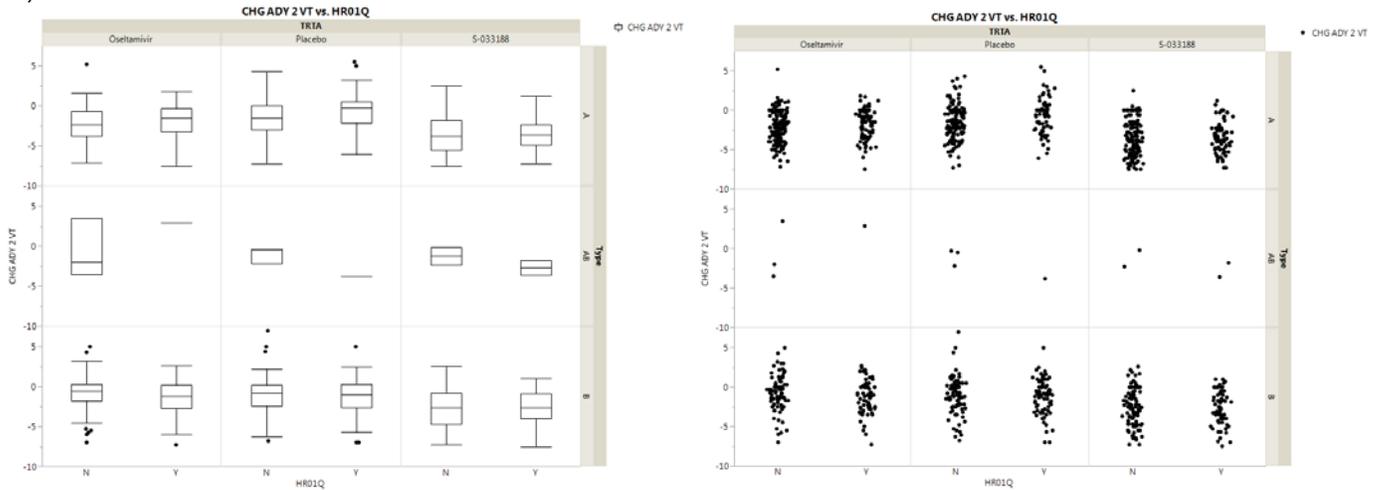
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Virology Reviewer: William Ince, Ph.D.

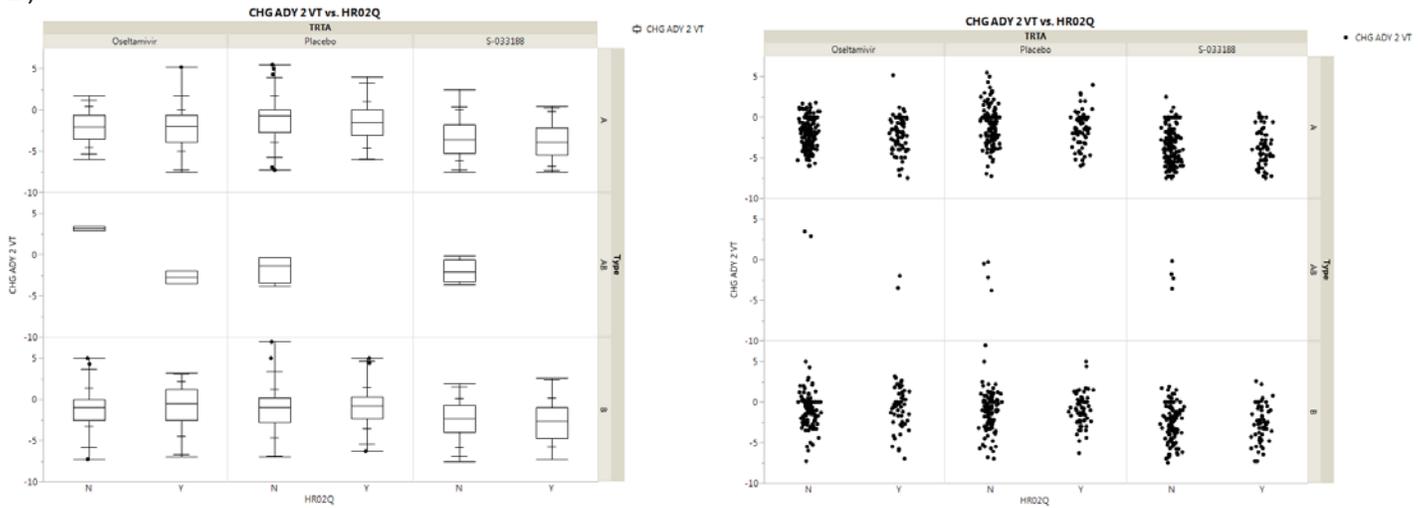
APPENDIX 18:

FDA analysis: Change from baseline in virus titer at Day 2 (CHG ADY 2 VT) by risk factor. A) Asthma or chronic lung disease; B) Endocrine disorders; C) Neurological and neurodevelopmental disorders; D) Heart disease; E) More than or equal to 65 years of age; F) Blood disorders; G) Metabolic disorders; H) Morbid obesity; I) Sex. Box and whiskers represent quantiles. JMP 12.1, SAS, Cary, NC

A)



B)



C)

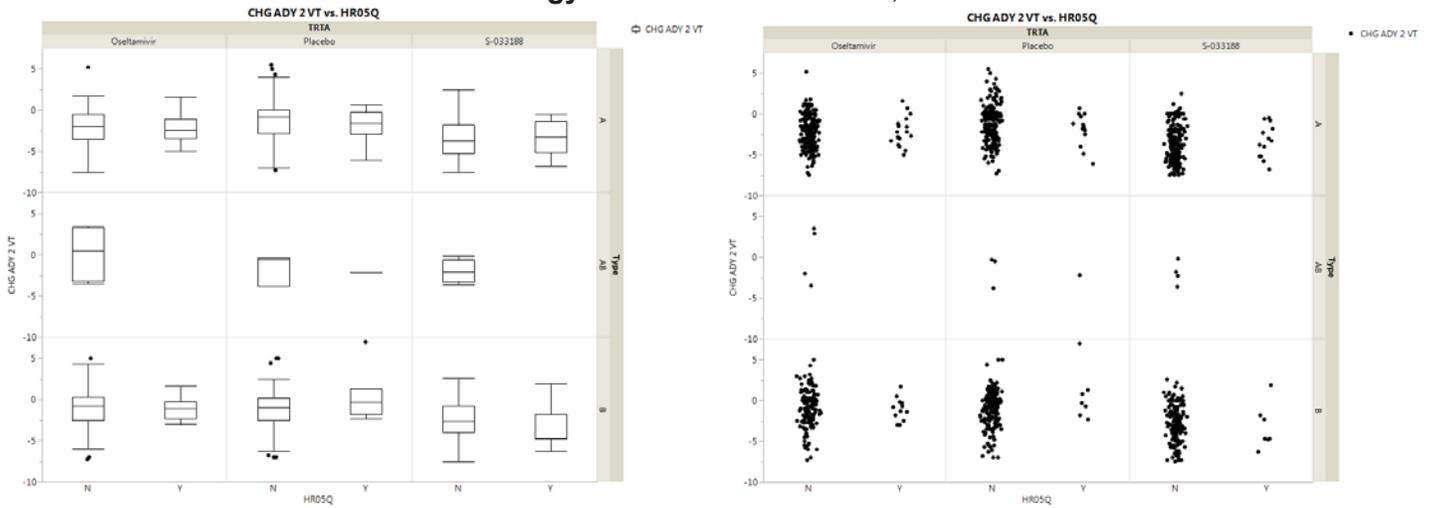
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

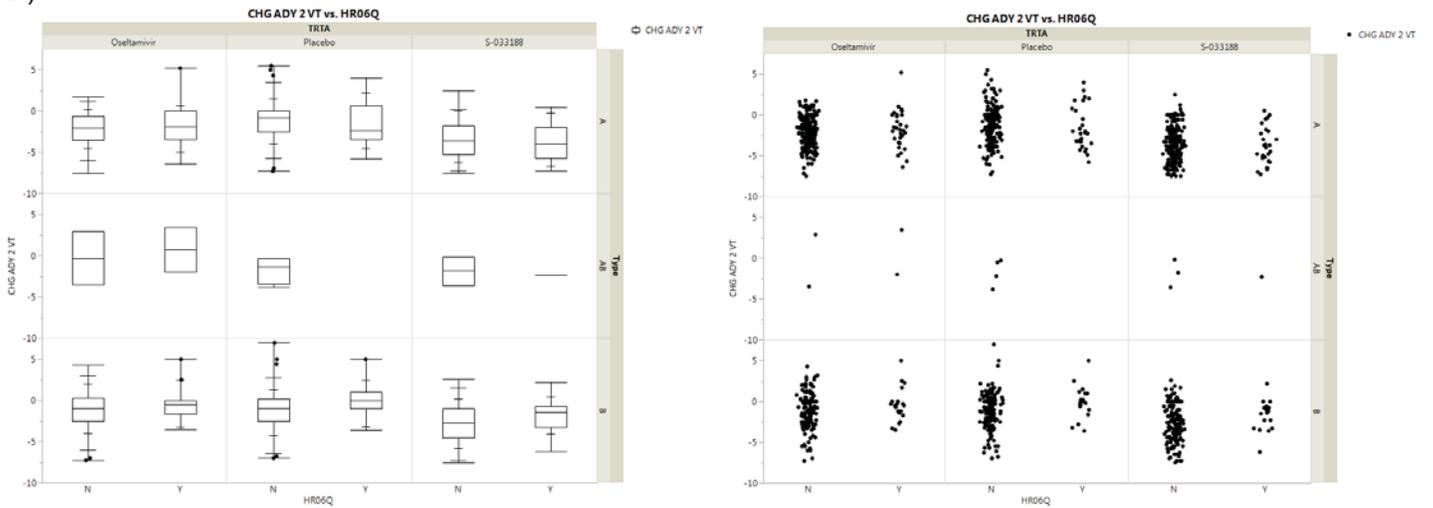
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DATE REVIEWED: 8/13/2019

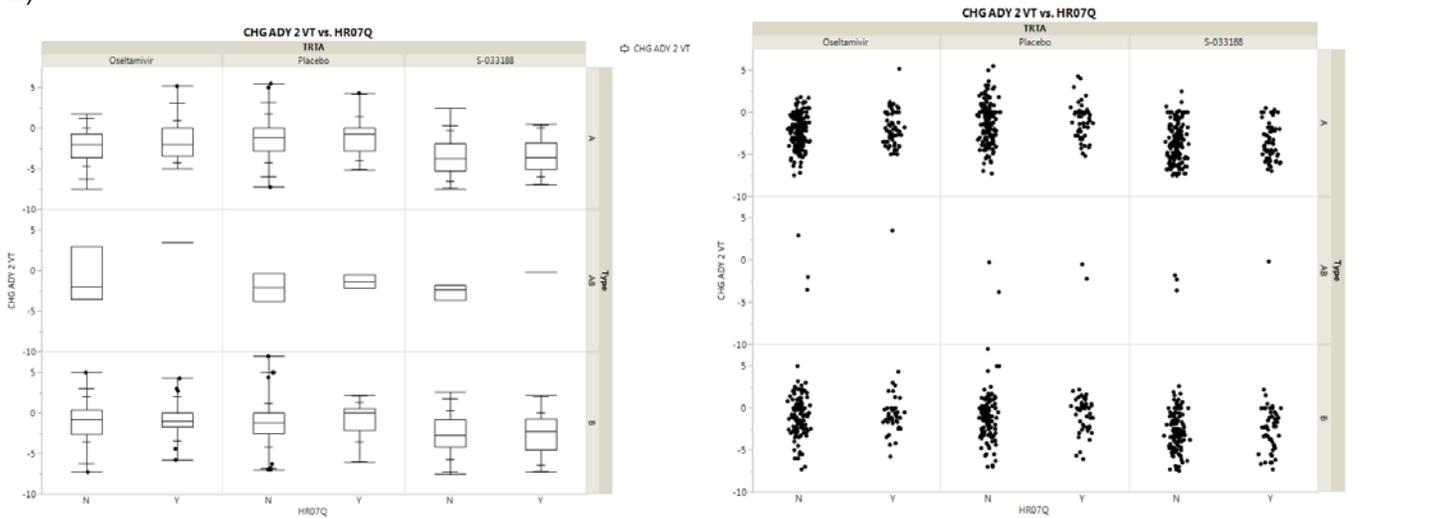
Virology Reviewer: William Ince, Ph.D.



D)



E)



F)

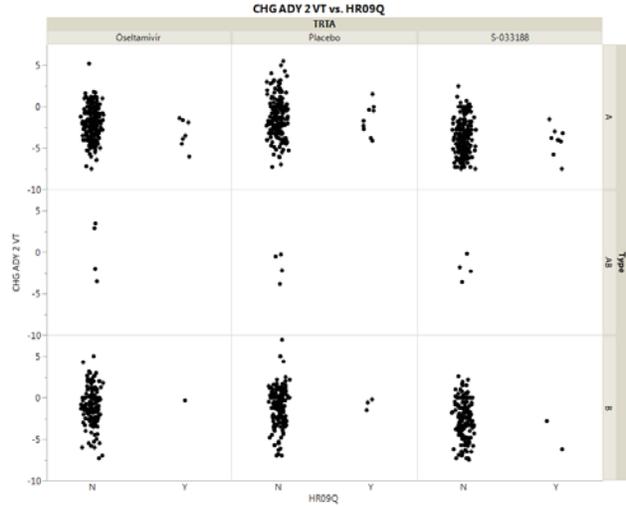
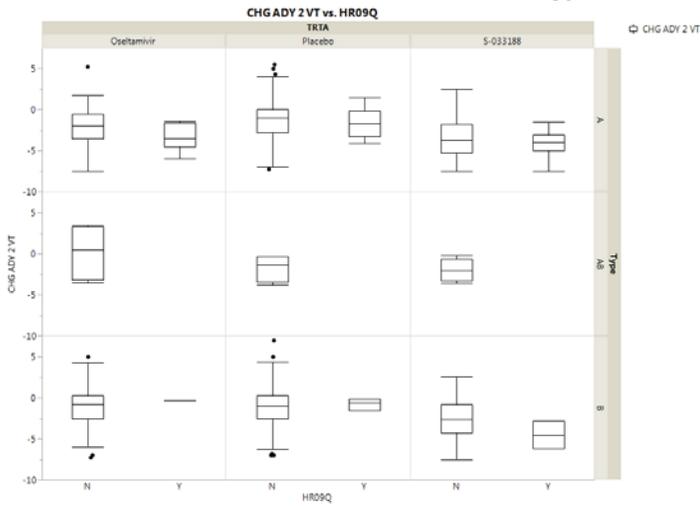
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

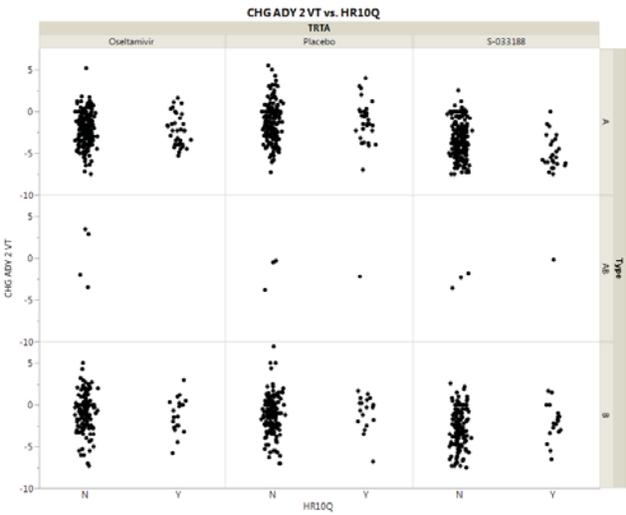
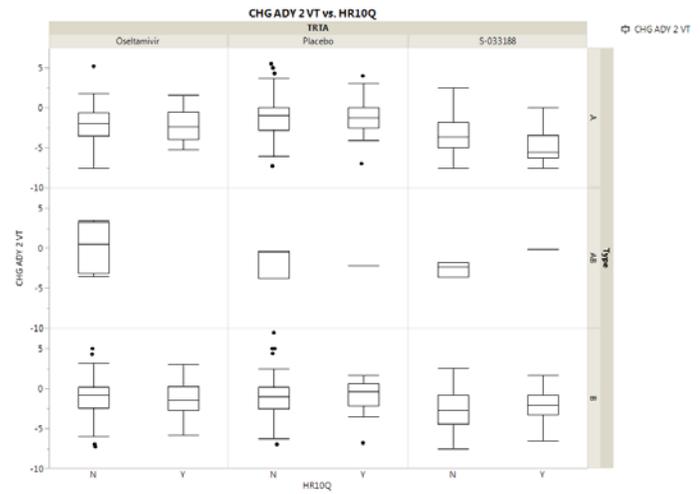
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DATE REVIEWED: 8/13/2019

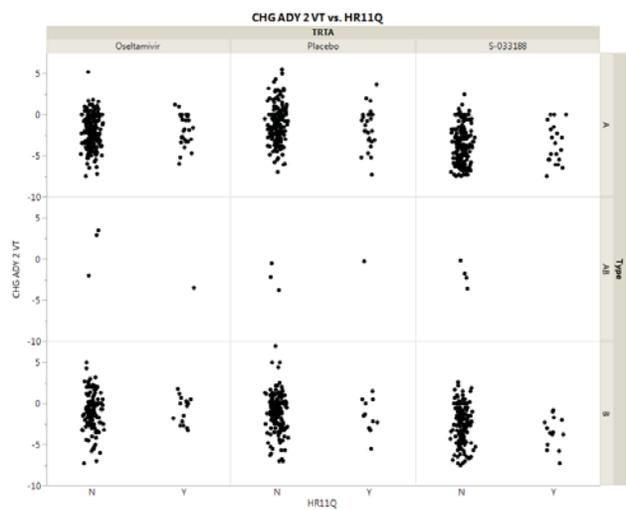
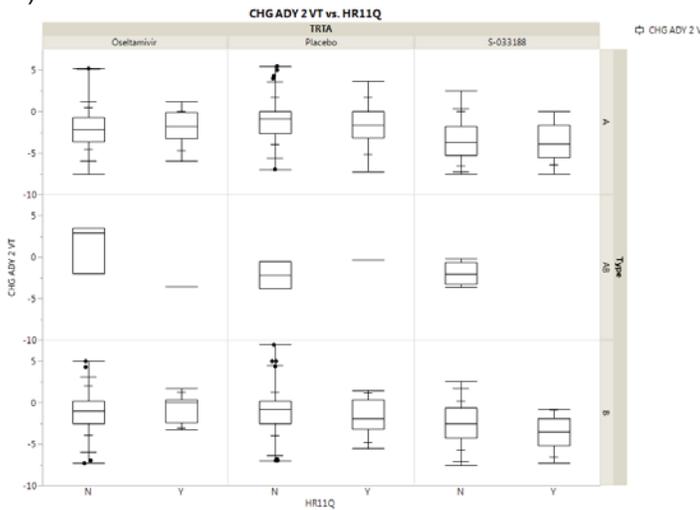
Virology Reviewer: William Ince, Ph.D.



G)



H)



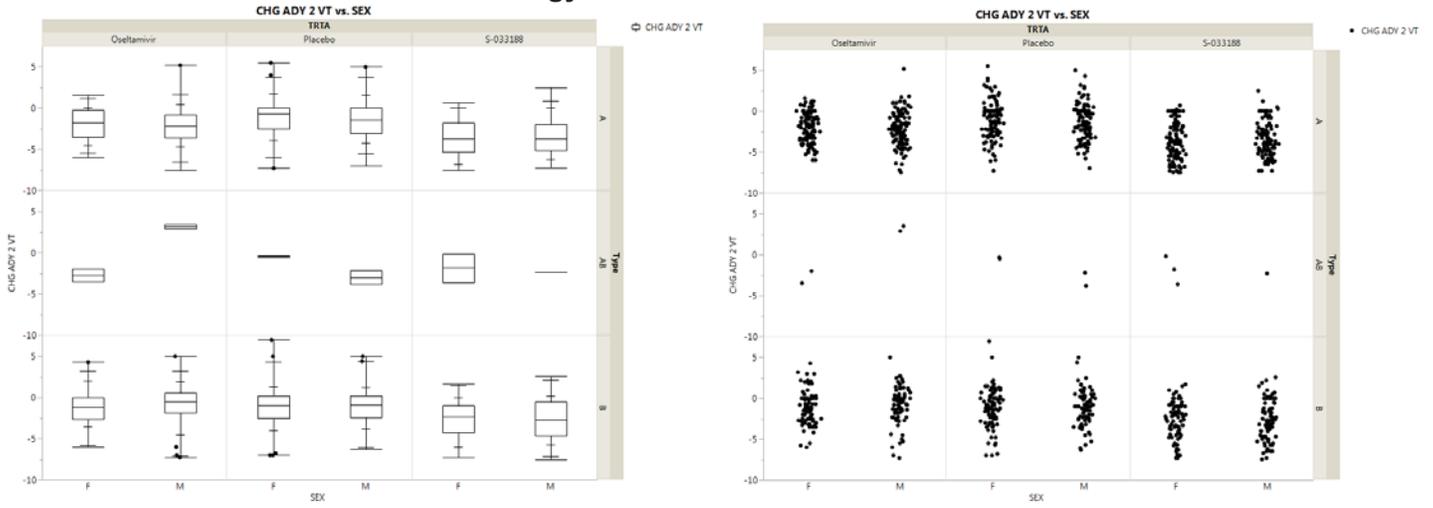
I)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 210854 S-001 SDN: 077 (SN [0066](#)) DATE REVIEWED: 8/13/2019

Virology Reviewer: William Ince, Ph.D.



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/s/  
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WILLIAM L INCE  
08/15/2019 12:18:35 PM

JULIAN J O REAR  
08/15/2019 01:11:56 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**CLINICAL PHARMACOLOGY**  
**REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

<b>NDA Number (SDN)</b>	210854 (77)	
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\NDA210854\210854.enx">\\CDSESUB1\evsprod\NDA210854\210854.enx</a>	
<b>Submission Date</b>	01/04/2019	
<b>Submission Types</b>	Efficacy Supplement (S-01)	
<b>Brand Name</b>	XOFLUZA®	
<b>Generic Name</b>	Baloxavir Marboxil	
<b>Dosage Regimen</b>	<b>Patient Body Weight (kg)</b>	<b>Recommended Oral Dose</b>
	40 kg to less than 80 kg	Single dose of 40 mg
	At least 80 kg	Single dose of 80 mg
<b>Route of Administration</b>	Oral	
<b>Proposed Indication</b>	Treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications.	
<b>Applicant</b>	Hoffmann-La Roche/Genentech, Inc	
<b>OCP Review Team</b>	Hazem E. Hassan, PhD, MS, RPh, RCDS Simbarashe Zavada, PhD Jihye Ahn, PharmD Chao Liu, PhD Vikram Arya, PhD, FCP	

† Baloxavir marboxil (S-033188) and XOFLUZA® are used interchangeably in this review.

‡ Baloxavir (S-033447) is the active metabolite of baloxavir marboxil (S-033188). Baloxavir and S-033447 are used interchangeably in this review.

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6. Pharmacometrics Review..... 8

## 1. Executive summary

XOFLUZA® (Baloxavir marboxil, S-033188), is a prodrug that is rapidly metabolized to its active form, baloxavir (S-033447). Baloxavir is a first-in-class inhibitor of endonuclease activity of the polymerase acidic protein, which is necessary for replication of influenza viruses. XOFLUZA® is indicated for treatment of acute uncomplicated influenza in patients 12 years of age and older who are otherwise healthy and who have been symptomatic for no more than 48 hours. The recommended oral dosage of XOFLUZA® is a single dose (40 or 80 mg based on body weight) within 48 hours of symptom onset with or without food. XOFLUZA® is to be avoided with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc).

The Applicant submitted an efficacy supplement a) to fulfill PMC 3503-7 which states that “Submit the clinical trial 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” and b) to seek an indication for the use of XOFLUZA® to treat patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications.

To support the proposed indication, the Applicant conducted pivotal Trial 1602T0832 entitled “A Phase 3, Multicenter (global), Randomized, Double-blind Trial of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications”. The primary objective of the trial was to evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo by measuring the time to improvement of influenza symptoms (TTIS) in patients with influenza. In this trial, patients  $\geq 12$  yr with influenza A and/or B infection and at high risk of developing influenza complications, received the approved XOFLUZA® dosing regimen (a single dose of 40 or 80 mg based on body weight) within 48 hours of symptom onset. PK, antiviral activity, and safety data were collected.

The basis of approval of XOFLUZA® in patients at high risk of developing influenza complications is the safety and efficacy data in this trial, 1602T0832 (please refer to the clinical review for assessment of safety and efficacy). The applicant compared exposures of baloxavir in this trial with the exposures in previously conducted Phase 3 trial in otherwise healthy subjects. The results ([Table 2](#)) indicated that the mean systemic exposures of baloxavir are comparable in adults and adolescents influenza patients who are at high risk of developing influenza-related complications and those who are otherwise healthy.

## 2. OCP Recommendations

The Office of Clinical Pharmacology has reviewed the application and determined that the information provided supports the approval of this application. The labeling recommendations, key review issue, and comments are summarized below.

## 3. Summary of Labeling Recommendations (Clinical Pharmacology Relevant Sections Only)

The following clinical pharmacology related information will be added in XOFLUZA® USPI:

### Section 12 Clinical Pharmacology

#### Sub-Section 12.2 Pharmacodynamics (Exposure-Response Relationships subtitle)

- The existing language in the exposure-response sub-section was modified to provide additional clarity and include a new sub-population. The final language is as follows: “When XOFLUZA is dosed by weight, as recommended (40 mg in patients weighing 40-80 kg; and 80 mg in patients weighing at least 80 kg), no difference in baloxavir exposure-response (time to alleviation of influenza symptoms in the Otherwise Healthy population or time to improvement of influenza symptoms in the High Risk population) relationship has been observed”.

#### Sub-Section 12.3 Pharmacokinetics

- Add the following statement: “The pharmacokinetic profile of XOFLUZA® was similar for adults and adolescents who were otherwise healthy and those at high risk of developing influenza-related complications.”

## 4. Key Clinical Pharmacology Review Issue

- In trial 1602T0832, for both types A and B influenza, the baloxavir treated group with the lowest Bayesian estimated baloxavir  $C_{24}$  ( $C_{24} < 20$  ng/mL) showed a longer TTIS than the placebo group (Table 1). The review focused on determining whether the longer TTIS in the baloxavir group relative to the placebo group can solely be attributed to lower baloxavir exposures.

**Table 1: Median TTIS by Baloxavir C<sub>24</sub> Category and Difference from Placebo and Oseltamivir Groups in the Phase 3 High Risk (HR) Trial 1602T0832**

Bayesian-estimated C <sub>24</sub> Category (ng/mL)	Virus Type A				Virus Type B			
	N	Median Time to Improvement of Influenza Symptoms (hours)	Median Difference from the Placebo Group (hours)	Median Difference from the Oseltamivir Group (hours)	N	Median Time to Improvement of Influenza Symptoms (hours)	Median Difference from the Placebo Group (hours)	Median Difference from the Oseltamivir Group (hours)
<20	13	165.2	63.9	98.70	6	102.5	9.3	4.50
20 to <40	70	76.2	- 24.9	9.70	46	87.8	- 5.4	- 10.20
40 to <60	63	77.8	- 23.3	11.30	57	68.9	- 24.3	- 29.10
≥ 60	62	56.4	- 44.7	- 10.10	55	69.7	- 23.5	- 28.30
Placebo	214	101.1	-	-	167	93.2	-	-
Oseltamivir	236	66.5	-	-	148	98.0	-	-

Notes:

Negative median difference values indicate a treatment effect in favor of baloxavir.

The median difference from the Placebo Group column has been added for completeness.

Source: HR Additional Outputs PK Report, Table 3(1).

The review team explored subjects' demographics and baseline characteristics to identify potential influential covariates for TTIS. The identified influential covariates for TTIS included baseline symptom composite score, age and sex. Many subjects in the exposure range (C<sub>24</sub> < 20 ng/mL) had higher baseline composite symptom score (≥15) and as a result, the observed longer TTIS in this subcategory relative to placebo may be due to subjects' baseline disease severity (refer to section 6. Pharmacometrics review for more details).

## 5. Individual Trial Review

### **Trial 1602T0832** ([EDR Link](#))\*

*\*This review focuses only on the clinical pharmacology aspects of this trial (Please refer to clinical review regarding efficacy and safety).*

#### **Title:**

A Phase 3, Multicenter, Randomized, Double blind Trial of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications.

**Trial Period:** 11 Jan 2017 - 20 April 2018

#### **Objectives:**

Primary objectives:

- To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo by measuring the TTIS in patients with influenza.

#### **Main Inclusion Criteria:**

Patients ≥ 12 years of age with influenza, who:

- Have fever with an axillary temperature of ≥ 38°C and at least 1 of the general symptoms (headache, feverishness or chills, muscle or joint pain, and fatigue) with moderate-to-severe intensity and at least 1 of the respiratory symptoms (cough, sore throat, and nasal congestion) with moderate-to-severe intensity due to influenza, within 48 hours of onset of influenza symptoms at the pre-dose examinations.

- The onset of influenza symptoms was defined as either the time of the first increase of 1°C or more than the patient's normal body temperature or the occurrence of at least one new general or respiratory symptom.
- Are considered at high risk for influenza complications (as defined by the Centers for Disease Control [CDC]).
- Are women of childbearing potential and agree to use a highly effective method of contraception for 3 months after the first dosing of trial drug.

**Test Product, Dose and Mode of Administration:**

Test drug: Baloxavir marboxil 20-mg tablets

Dose and Mode of Administration:

- Baloxavir marboxil group: single oral dose (40 or 80 mg for patients with body weight < 80 kg or ≥80 kg, respectively) of baloxavir marboxil on Day 1 + oral oseltamivir placebo BID on Days 1 to 5
- Placebo group: single oral dose of baloxavir marboxil placebo on Day 1 + oral oseltamivir placebo BID on Day 1 to 5
- Oseltamivir group: single oral dose of baloxavir marboxil placebo on Day 1 + oral oseltamivir 75 mg BID on Days 1 to 5

**Trial Design:**

Randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled trial designed to evaluate the efficacy and safety of a single oral dose of baloxavir marboxil (40 or 80 mg depending on body weight) in patients ≥ 12 years old with influenza A and/or B infection, within 48 hours of symptom onset, and at high risk of developing influenza complications. Patients were randomized in a 1:1:1 ratio to receive a single, oral dose of baloxavir marboxil, repeated doses of oseltamivir, or placebo. Blood samples were collected at Visit 2 (Day 2) and Visit 4 (Day 5). Samples were also collected from some patients 0.5 to 4 hours postdose at Visit 1 (Day 1), at Visit 3 (Day 3), and at Visit 6 (Day 15).

**Bioanalytical method:**

The precision and accuracy were acceptable for calibration curve and QC runs. All samples were analyzed within the long-term storage stability duration.

**Results:**

***Main Subject Demographics and Baseline Disease Characteristics***

The proportion of adolescent patients (12 to 19 years of age) was 4.9%, 5.7%, and 4.4% in the baloxavir marboxil, oseltamivir, and placebo groups, respectively. Baseline characteristics such as composite symptom scores and body temperature at baseline were also similar among the treatment groups. In each of the treatment groups, the time period between the onset of influenza and the trial treatment was most commonly > 12 to ≤ 24 hours or

> 24 to ≤ 36 hours. In the intention to treat infection (ITTI) population, the proportion of patients who weighed ≥ 80 kg in each treatment group was 38.4% to 40.1% across the treatment groups. Most patients were white (ranging from 45.9% to 50.3% across the treatment groups) or Asian (ranging from 40.7% to 43.0% across the treatment groups) in the ITTI population. The predominant influenza virus strains tested in this trial were the A/H3 subtype (46.9% to 48.8%) and the B subtype (38.3% to 43.5%) in each treatment group.

### Pharmacokinetics

**Table 2. Comparison of Baloxavir PK parameters in High Risk (HR) and otherwise healthy (OwH) Patients by Body Weight and Race**

Race	Dose (body weight)	Population	No. of Subjects (N for Obs. C <sub>24</sub> )	C <sub>max</sub> (ng/mL)	AUC <sub>0-inf</sub> (ng • hr/mL)	Modelled C <sub>24</sub> (ng/mL)	Observed C <sub>24</sub> (ng/mL)
All Patients	40 mg (< 80 kg)	HR T0832	234 (137)	83.5 (13.3–355)	5320 (730.3–16180)	47.2 (8.42–134)	52.1 (5.77–231)
		OwH T0831	368 (233)	96.4 (14.0–244)	6160 (1100–14690)	54.5 (10.8–122)	56.0 (5.81–158)
	80 mg (≥ 80 kg)	HR T0832	144 (95)	86.7 (7.87–236)	6415 (928.1–15720)	56.9 (6.58–164)	62.9 (5.86–198)
		OwH T0831	78 (56)	107 (28.7–243)	8009 (2229–18330)	68.7 (21.7–156)	74.9 (17.5–209)
Non-Asian	40 mg (< 80 kg)	HR T0832	96 (58)	60.8 (13.3–156)	3706 (730.3–8637)	35.6 (8.42–84.3)	35.9 (5.77–90.2)
		OwH T0831	59 (39)	67.2 (14.0–142)	3866 (1100–9040)	38.9 (10.8–103)	37.2 (7.35–81.4)
	80 mg (≥ 80 kg)	HR T0832	118 (81)	79.7 (7.87–236)	5722 (928.1–15720)	53.0 (6.58–164)	58.7 (5.86–198)
		OwH T0831	44 (30)	92.1 (28.7–206)	6510 (2229–15600)	60.1 (21.7–156)	62.9 (17.5–209)
Asian	40 mg (< 80 kg)	HR T0832	138 (79)	99.3 (24.8–355)	6442 (2379–16180)	55.3 (20.5–134)	64.0 (25.4–231)
		OwH T0831	309 (194)	102 (23.9–244)	6598 (2186–14690)	57.5 (18.5–122)	59.8 (5.81–158)
	80 mg (≥ 80 kg)	HR T0832	26 (14)	119 (40.5–204)	9563 (4804–15710)	74.4 (32.1–110)	87.6 (33.8–126)
		OwH T0831	34 (26)	126 (33.3–243)	9949 (4122–18330)	79.8 (27.0–132)	88.7 (39.3–142)

HR T0832; Trial 1602T0832, OwH T0831; Trial 1602T0831, C<sub>max</sub>, AUC<sub>0-inf</sub>; Bayesian estimation based on the OwH population pharmacokinetic model. Observed C<sub>24</sub>; the observed plasma concentrations at 20 to 28 hours post-dose, Arithmetic mean (minimum-maximum) are shown for all PK parameters.

Source: Summary of Clinical Pharmacology, P. 34

**Table 3. Bayesian-Estimated Baloxavir C<sub>max</sub> and AUC<sub>0-inf</sub> for Patients with Adverse Events (>2%) and Serious Adverse Events and Patients without Adverse Events or Serious Adverse Events in the Phase 3 HR 1602T0832 Trial**

	Adverse Events with ≥ 2% Frequency					Serious <sup>e</sup> Adverse Events	Without Adverse Events ≥ 2% Frequency or Serious <sup>e</sup> Adverse Event	
	Overall	Bronchitis	Diarrhoea	Nausea	Sinusitis			
N	65 <sup>a</sup>	21	19 <sup>b</sup>	16 <sup>c</sup>	14	3 <sup>d</sup>	595	
C <sub>max</sub> (ng/mL)	Mean	88.0	84.0	84.6	96.6	81.8	81.3	75.5
	SD	52.8	48.5	50.8	67.0	39.1	34.0	42.1
	Min	13.3	15.3	25.7	13.3	30.6	44.2	7.84
	Median	75.8	67.2	73.9	96.3	77.2	88.8	66.3
	Max	241	221	236	241	172	111	355
AUC <sub>0-inf</sub> (ng • hr/mL)	Mean	5852	5759	5635	6083	5354	5794	5181
	SD	3044	3095	3143	3391	2418	1310	2614
	Min	1197	1935	1924	1197	2207	4611	692.6
	Median	5108	5108	4866	6182	5260	5569	4711
	Max	15200	13150	15200	13040	10080	7202	16180

<sup>a</sup> Five patients with no evaluable plasma concentration data were not included.

<sup>b</sup> One patient with no evaluable plasma concentration data was not included.

<sup>c</sup> Four patients with no evaluable plasma concentration data were not included.

<sup>d</sup> Two patients with no evaluable plasma concentration data were not included.

<sup>e</sup> In the HR PK Report, 'Severe' Adverse Events were specified; however, 'Serious' Adverse Events were actually used.

Source: HR PK Report, Table 18.

- Baloxavir exposure in adults and adolescents in the HR trial 1602T0832 were comparable to those in the OWH healthy trial 1602T0831 (Table 2).
- Baloxavir C<sub>max</sub> and AUC<sub>inf</sub> in patients with adverse events (>2% frequency) or serious adverse events was similar to those without such events, indicating lack of correlation between adverse events and baloxavir exposure (Table 3).

## 6. Pharmacometrics Review

Baloxavir plasma samples from patients in Trial 1602T0832 were collected at 24 hours post-dose (C<sub>24</sub>; allowable time window of 20 to 28 hours) and 96 hours post-dose (C<sub>96</sub>; allowable time window of Day 5 to 6). The applicant also estimated Bayesian PK parameters (C<sub>max</sub>, AUC<sub>0-∞</sub>, C<sub>24</sub>, C<sub>72</sub>, and C<sub>96</sub>) following a single dose of baloxavir marboxil based on the previously developed population PK model in OWH patients. The population PK model had been previously reviewed as part of the original NDA submission and was deemed to be acceptable.

As there is reasonable agreement between observed  $C_{24}$  and estimated  $C_{24}$ , Bayesian estimations of PK parameters were acceptable for exposure-response (E-R) analyses.

The applicant performed E-R analyses using the data obtained from Trial 1602T0832. Primary efficacy endpoints used in E-R analyses was time to improvement of influenza symptoms (TTIS), and secondary efficacy endpoint was time to alleviation of symptoms (TTAS). The applicant also evaluated E-R relationship with change from baseline in influenza virus titer.  $C_{24}$  of baloxavir was used as the exposure metric. Applicant utilized linear regression for TTIS, and TTAS and  $E_{max}$  model to explore the relationship between  $C_{24}$  and change from baseline in influenza virus titer. E-R relationship was also evaluated with baloxavir  $C_{24}$  as a categorical variable defined by <20, 20 to <40, 40 to <60, and  $\geq$ 60 ng/mL.

The applicant made the following conclusions based on their E-R analysis:

- TTIS was numerically shorter than placebo for all  $C_{24}$  categories, with exception of the lowest exposure category ( $C_{24} < 20$ ng/mL) ([Table 1](#)). Similar trend was also observed for the secondary endpoint, TTAS.
- The primary efficacy endpoint, TTIS, tends to decrease with increasing observed  $C_{24}$ , which suggests a positive E-R relationship. This linear relationship was statistically significant based on p-value of the linear model ( $p < 0.05$ ) for combined Type A and B. However, when virus type A or B were separately considered, a statistical significance was not confirmed. Similar results were seen for the secondary endpoint, TTAS.
- Table 4 presents the relationship between  $C_{24}$  with the change from baseline in virus titer on Day 2. For virus type A, the median change from baseline in virus titer was numerically greater for baloxavir compared with placebo for all  $C_{24}$  categories. For virus type B, mean change from baseline in virus titer were less compared to placebo in the lowest  $C_{24}$  category ( $C_{24} < 20$  ng/mL). For both type A and B, there appears to be a trend with increasing  $C_{24}$  associated with greater virus titer reduction.

**Table 4: Median Change from Baseline in Virus Titer on Day 2 by Baloxavir C<sub>24</sub> category and difference from Oseltamivir and Placebo Group in the Phase 3 HR Trial 1602T0832**

Bayesian-estimated C <sub>24</sub> Category (ng/mL)	Virus Type A (log <sub>10</sub> [TCID <sub>50</sub> /mL])			Virus Type B (log <sub>10</sub> [TCID <sub>50</sub> /mL])				
	N	Median Change from Baseline in Virus Titer	Median Difference from Placebo Group	Median Difference from Oseltamivir Group	N	Median Change from Baseline in Virus Titer	Median Difference from Placebo Group	Median Difference from Oseltamivir Group
< 20	12	-2.40	-1.00	-0.10	6	-0.50	0.30	0.50
20 to < 40	55	-3.60	-2.20	-1.30	40	-1.90	-1.10	-0.90
40 to < 60	56	-4.00	-2.60	-1.70	54	-2.60	-1.80	-1.60
≥ 60	53	-4.50	-3.10	-2.20	49	-4.00	-3.20	-3.00
Placebo	185	-1.40	-	-	154	-0.80	-	-
Oseltamivir	207	-2.30	-	-	133	-1.00	-	-

Notes: Negative median difference values indicate a treatment effect in favor of baloxavir. The median difference from the Placebo Group column has been added for completeness.

The review team noted that in the descriptive summary of TTIS by C<sub>24</sub> category ([Table 1](#)), median TTIS values were 165.2 and 102.5 hours for the lowest C<sub>24</sub> category (< 20 ng/mL) for type A and B, respectively. These values were numerically longer than those for corresponding placebo group, which were 101.1 and 93.2, for type A and B, respectively. Similar pattern was observed in virologic response for Virus Type B in patients in the lowest C<sub>24</sub> category (< 20 ng/mL). Overall, there appears to be a trend of positive E-R relationship (shorter TTIS and TTAS associated with increasing C<sub>24</sub>). This trend should be interpreted with caution as applicant's analyses did not address the potential confounding effects from patient's baseline characteristics. In addition, the sample size of the lowest category (<20 mg/mL) is small (n=19; total for type A and type B) relative to the other C<sub>24</sub> categories.

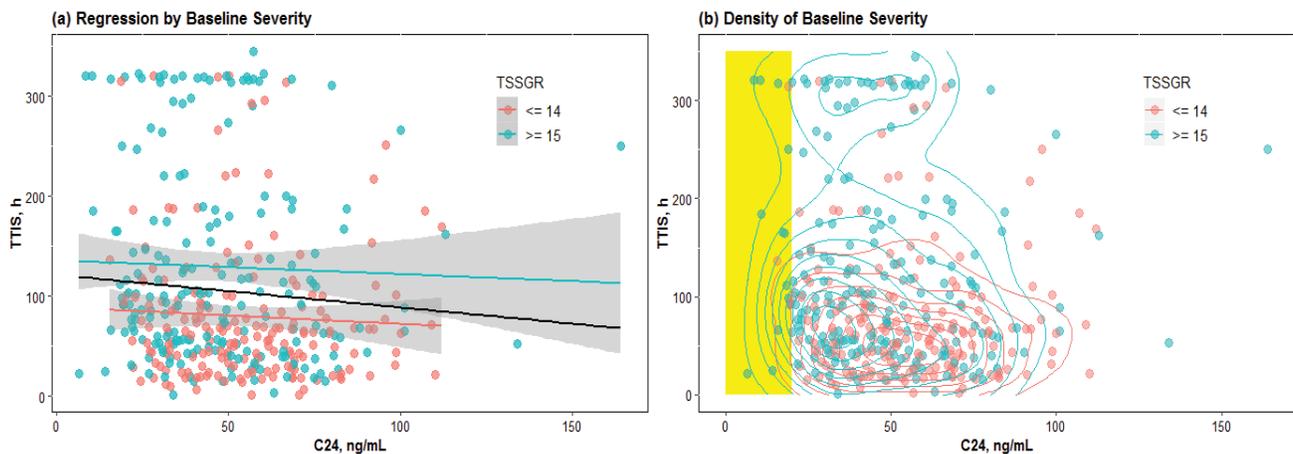
The review team conducted additional analyses to further explore the E-R analysis conducted by the applicant. First, the relationship between C<sub>24</sub> and TTIS was re-evaluated with alternative C<sub>24</sub> categories (by quartiles) to facilitate comparison of groups with similar sample size Table 5 shows summary statistics of median TTIS by C<sub>24</sub> quartiles. In all C<sub>24</sub> quartile groups, median TTIS values were numerically shorter compared to those in placebo group, although patients with lower exposure (Q1) tended to have longer TTIS.

**Table 5: Median TTIS by Baloxavir C<sub>24</sub> Category and Difference from Placebo**

C <sub>24</sub> (ng/mL)	Virus Type A			Virus Type B		
	N	Median TTIS (h)	Difference (vs. Placebo)	N	Median TTIS (h)	Difference (vs. Placebo)
Placebo	217	101		169	93	
Q1 [6.58, 33.3)	55	92	-9	36	88	- 5
Q2 [33.8, 49.2)	56	76	-25	44	67	- 26
Q3 [49.2, 66.3)	53	69	-32	45	71	- 22
Q4 [66.3, 164]	53	55	-46	44	69	-24

Source: Review team’s analysis.

Data exploration in demographics and baseline patient characteristics were performed to identify potentially influential covariates for TTIS. Univariate regressions identified age, sex, and baseline symptom composite score as potentially influential covariates for TTIS. Higher baseline symptom composite score, female, and younger age were associated with longer TTIS. And higher baseline symptom composite score and the older age were also associated with lower C<sub>24</sub> values. Because higher baseline symptom composite score, in particular, was associated with lower C<sub>24</sub> values and longer TTIS, E-R relationship was first explored by linear regression stratified by two groups in terms of baseline symptom composite score ( $\geq 15$  and  $\leq 14$ ). Censored observations were treated as TTIS value for a given subject.



**Figure 5: Scatter plots of TTIS and C<sub>24</sub> by baseline symptom composite score subgroup**

Source: Review team’s analysis. TSSGR: Composite symptom score at baseline group ( $\leq 14$  or  $\geq 15$ ). Yellow band presents C<sub>24</sub> < 20 ng/mL.

Linear regressions by strata (blue and red lines) and overall (black line) is shown in Figure 5 (a). When the difference in baseline symptom composite scores is not taken into account, E-R relationship appears to exist (black curve). E-R curves for the two strata were parallel to each other but flatter compared to the unadjusted E-R curve. Figure 5 (b) shows same scatter plot with density estimation for each stratum. The higher baseline symptom scores were more densely distributed in lower  $C_{24}$  region and longer TTIS. Such confounding effect may explain the steeper E-R curve in the unadjusted analysis. Also, the review team noted that majority of subjects in the exposure range ( $C_{24} < 20$  ng/mL) (refer to yellow band in Figure 5 (b)) had composite symptom score  $\geq 15$ . This may support that the longer TTIS observed in the lowest  $C_{24}$  group defined by the applicant may not be solely due to the lower baloxavir exposure but may be confounded by the subjects' baseline disease severity.

Reevaluation of median TTIS with comparable sample sizes by quartile grouping revealed that all baloxavir  $C_{24}$  groups showed shorter TTIS than placebo. The review team's analysis suggests a trend of higher  $C_{24}$  and shorter TTIS, however, when adjusted for potential confounding factors such as baseline symptom composite scores, the trend appears to be less notable.

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**Date:** August 19, 2019

**From:** Michael Norcross, M.D. and Montserrat Puig, Ph.D., Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

**Through:** James Weaver Ph.D., Consult Lead and David Strauss M.D., Ph.D., Director; DARS/OCP

**To:** London Harrison, Division of Antiviral Drug Products, OAP, OND

**Subject:** Xofluza and Serious Drug Adverse Events. NDA 210854

## Executive Summary

Beloxavir marboxil (Xofluza) is a new single-dose anti-influenza drug that inhibits the viral polymerase acidic protein. Although no serious allergic reactions were seen during clinical trials, a number of anaphylactic and hypersensitivity reactions were reported post approval in Japanese patients. The mechanism of these reactions has not been identified. Molecular similarity analysis using QSAR and Clarity programs did not identify structural motifs or similarities with drugs known to cause hypersensitivity reactions. Allergic events could be through IgE or non-IgE (pseudo-allergic, MRGPRX2 receptor) pathways leading to mast cell activation. Allergic mechanisms could be studied in vitro. Studies on Japanese patients who experience reactions would be advised to address the role of classic IgE pathways and possible MRGPRX2 receptor polymorphisms in this population. Genome wide association studies (GWAS) could help to identify other genes linked to reactions, in addition to MRGPRX2. HLA typing could provide insights into delayed cutaneous reactions. Additional clinical trials to study the mechanism of the reaction would not be informative because of the very low incidence of the adverse events. Adding a warning of the risk of allergic and hypersensitivity reactions to the drug label is advised.

## Background

Xofluza (baloxavir marboxil) is indicated for the treatment of acute, uncomplicated influenza in patients 12 years of age and older who have been symptomatic for 48 hours or less. Baloxavir marboxil is a new molecular entity (approved 10/18) with a new mechanism of action for the treatment of influenza. Baloxavir is hydrolyzed to its active metabolite, baloxavir marboxil. Baloxavir inhibits the endonuclease activity of the polymerase acidic protein, resulting in inhibition of influenza RNA syntheses. Baloxavir marboxil is administered as a single oral dose based on body weight. In the original NDA, the safety database was comprised of 1,318 subjects who received baloxavir marboxil followed by another 730 patients with underlying medical conditions. There were no severe adverse events of anaphylaxis, hypersensitivity reactions, or related allergic adverse events observed. However, after approval, a number of post marketing adverse event reports were observed. The sponsor submitted a Safety Update Report that covered over (b) (4) Japanese patients and (b) (4) US patients. Using Samson's criteria for anaphylaxis 5 anaphylactic reaction/shock cases were identified, 4 hypersensitivity reactions, and 7 angioedema events. Most reactions occurred within several hours, but a few within 15-40 minutes and some from 4 to 24 hours. Anaphylactic reactions were accompanied by urticaria, angioedema, mouth and pharyngeal swelling, rash and hypotension in some. A number of patients were hospitalized and treated with steroids and antihistamines. All case reports were from Japan. In addition, 3 cases of erythema multiforme and 6 of Stevens-Johnson Syndrome were reported but the diagnosis was not verified.



## Evaluation

1. *Please comment on the possible association between the chemical structure of baloxavir marboxil or of its' active metabolite, baloxavir and risk of anaphylaxis or hypersensitivity.*

QSAR analysis of baloxavir marboxil and its metabolite did not find a similar chemical structure in the data base with a clear link to anaphylaxis or hypersensitivity. In addition, Clarity molecular predictions performed by R. Racz examining similarity with drugs that bind to a non-IgE receptor in mast cells (MRGPRX2) did not find structural overlaps with high confidence scores. Moreover, the tetrahydroisoquinoline (THIQ) motif described in a number of agonist drugs that bind MRGPRX2 was not found in Baloxavir marboxil using similarity scoring. However, this does not rule out the possibility that Xofluza can trigger mast cells through this receptor.

2. *Please comment on the potential mechanism(s) of baloxavir hypersensitivity*

Mechanisms of anaphylaxis include: 1) IgE mediated, 2) IgG mediated, 3) Complement mediated, and 4) direct mast cell activation through MRGPRX2 (1). IgE and IgG mediated reactions usually require sensitization through multiple exposures to antigens or drugs. In contrast, Xofluza anaphylactoid-like reactions occur after only a single dose of drug, suggesting that direct mast cell activation could be involved possibly through binding to the MRGPRX2 receptor. This receptor has been reported to be crucial for pseudo-allergic drug reactions (2,3). Drugs that bind to MRGPRX2 include NSAIDs, vancomycin, opiates, local anesthetics, fluoroquinolone antibiotics, neuromuscular blockers and others. As noted above, the THIQ motif is found in many of these drugs, but not all. Again, the THIQ motif is not present in Xofluza. Single nucleotide polymorphism (SNPs) studies have identified 30 variants within the coding regions of this receptor. Because rapid drug reactions to Xofluza are rare and currently found only in Japanese, they may occur through a rare variant of the MRGPRX2 receptor. Molecular studies on patients with reactions would be needed to characterize the allergic mechanisms further including analyzing receptor variants. Other contributing factors could include other drugs that sensitize mast cells to MRGPRX2 signaling, but this was not obvious from the diverse list of concomitant meds, many of which are commonly used to treat symptoms of influenza. Patients with delayed adverse event presentation after dosing such as those with erythema multiforme skin reactions and possibly SJS, may have different mechanisms of action. These reactions could involve T cell responses to the drug possibly associated with specific HLA alleles. Critical to understanding the mechanism would be studies on cells from the patients. HLA typing of patients would be valuable in assessing an HLA linkage. Genome-wide association studies could identify a common genetic region in this set of patients linked to the reaction. Again, MRGPRX2 polymorphism could be characterized by gene sequencing of the receptor from patients. Another contributing factor for why reactions are only seen in Japanese could be ethnic differences in drug exposure. The package insert states that US populations have 35% less drug exposure than Asian populations based on PK studies. However, 60 times more Japanese patients have received Xofluza than US patients and therefore additional adverse reactions in the US may develop when comparable numbers of patients are treated.

3. *Please comment on whether preclinical studies would help identify the mechanism(s) of baloxavir marboxil hypersensitivity. What types of preclinical studies would be useful in this regard?*



Laboratory studies can be performed to test Xofluza for activation of mast cells and basophils (3). Xofluza can be tested on transfected cell lines that carry specific MRGPRX2 receptors or variants. Animal studies would not be helpful. As noted above, genetic and functional studies on patient cells could help to define mast cell activation pathways and other immune host cell factors. Again, HLA typing would help to identify whether a common HLA allele or haplotype was carried by the patients. Serum IgE and IgG binding to drug could be tested along with skin testing of patients that experience adverse reactions to verify immediate allergic pathways.

4. *Would a clinical trial be helpful in further evaluation of the mechanism(s) of or risk factors for baloxavir hypersensitivity? If a clinical trial is recommended, please provide comments on the design of such a trial.*

Because the incidence of an allergic reaction is very low, a clinical trial to study the mechanism or risk factors would be impossible. Pretesting patients by skin testing with drug would not be feasible. Studies on the patients that had reactions would be advisable as noted above to identify allergic mechanisms as well as genetic or environmental risk factors.

## Summary and Conclusions

Baloxavir marboxil (Xofluza) is a single dose drug to treat acute influenza infections. Although no serious allergic adverse events were noted during clinical trials, a number of serious anaphylactic and hypersensitivity reactions were reported post approval. QSAR analysis did not identify structural similarities with other drugs associated with hypersensitivity. Allergic mechanisms could be through IgE and non-IgE pathways (MRGPRX2 receptor) leading to mast cell activation. Effects of Xofluza on mast cells and on MRGPRX2-engineered indicator cells could be addressed in vitro. Studies on Japanese patients who experience reactions would be advised to address the role of classic IgE pathways and possible MRGPRX2 polymorphisms in this population. GWAS studies could help to identify genes linked to reactions. HLA typing could provide insight into delayed cutaneous reactions. Additional clinical trials would not be helpful to study the mechanism because of the rarity of the adverse reaction.

## References and Supporting Documents

1. Finkelman, F.D., Knodoun, M.V., and Strait, R. (2016) Human IgE-independent systemic anaphylaxis. *J Allergy Clin Immunol* ; 137:1674-80.
2. Poregski, G., Kwiecien, K., Pawica M., and Kwitniewski. M. (2016) Mas-Related G Protein-coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions. *Frontiers in Immunology*; 9:3027: 1-9.
3. McNeil, B.D. et al. (2015) Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*, 519: 237-240.

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MYUNG JOO P HONG  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210854Orig1s001**

**OTHER REVIEW(S)**

## Division of Antiviral Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 210854/S-001

**Name of Drug:** XOFLUZA<sup>®</sup> (baloxavir marboxil), 20 and 40 mg tablets

**Applicant:** Genentech, Inc.

#### Labeling Reviewed

- The final proposed US Package Insert (USPI) and Patient Package Insert (PPI) dated September 25, 2019 were compared with the last approved label (NDA 210854/Original Submission), approval dated October 24, 2018.
- The final carton and container labels dated October 4, 2019 were compared with the last approved label (NDA 210854/Original Submission), approval dated October 24, 2018

#### Background and Summary Description

XOFLUZA<sup>®</sup> (baloxavir marboxil) is a polymerase acidic (PA) endonuclease inhibitor indicated for treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. The original NDA was approved on October 24, 2018. This supplemental application provides for the following:

1. Revise the **DOSAGE AND ADMINISTRATION, HOW SUPPLIED/STORAGE AND HANDLING** and **PATIENT COUNSELING INFORMATION** sections of the labeling, and the carton and container labeling with revised dosage instructions to prevent the medication errors;
2. Add **Postmarketing Experience** subsection to the **ADVERSE REACTIONS** section and update **PATIENT COUNSELING INFORMATION** to reflect serious postmarketing adverse events;
3. Revise **INDICATIONS AND USAGE, ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS,** and **CLINICAL STUDIES** sections with data to support the use of XOFLUZA for the treatment of acute uncomplicated influenza in patients 12 years of age or older, who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications;
4. Add **Hypersensitivity** subsection to the **WARNINGS and PRECAUTIONS** section;
5. Make corresponding changes to the Patient Information.
6. To fulfill the PMC 3503-7 entitled “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.” The Pivotal Study 1602T0832 titled as “Multicenter (global), Randomized, Placebo/Active control, Double-blind Study in Adults and Adolescents (≥ 12 years and ≥ 40 kg) with Acute Uncomplicated Influenza Who are at High Risk of Developing Influenza-related Complications” was conducted under IND 126,653.

Genentech requested a deferral for pediatric patients from birth to less than 12 years of age.

This supplemental application was submitted on January 4, 2019 and was reviewed under a standard clock with a PDUFA goal date of November 4, 2019.

DAVP reviewed the USPI and PPI (dated September 25, 2019) and carton/container labels (dated October 4, 2019) submitted by Genentech, and no further revisions were made.

### Review

Highlight of Prescribing Information (HL)	
<ul style="list-style-type: none"> <li>● Under <b>RECENT MAJOR CHANGES</b>: This section was updated to reflect the following modifications in the full prescribing information.               <ul style="list-style-type: none"> <li>● Indications and Usage (1) <span style="float: right;">10/2019</span></li> <li>● Dosage and Administration (2) <span style="float: right;">10/2019</span></li> <li>● Contraindications (4) <span style="float: right;">10/2019</span></li> <li>● Warnings and Precautions (5.1) <span style="float: right;">10/2019</span></li> </ul> </li> <li>● <b>“INDICATIONS AND USAGE”</b> was updated to include patients at high risk of developing influenza-related complications.</li> <li>● <b>“DOSAGE AND ADMINISTRATION”</b> was updated to reduce the medication error.</li> <li>● <b>“WARNING AND PRECAUTIONS”</b> was updated to include hypersensitivity reactions identified during post-approval use of XOFLUZA.</li> <li>● <b>“ADEVERSE REACTIONS”</b> was updated to include additional side effects caused by XOFLUZA.</li> <li>● Revision date was updated to “10/2019” in HL.</li> </ul>	
Table of Content	
<p>The following section and sub-sections were added:</p> <ul style="list-style-type: none"> <li>● Section 5.1 (Hypersensitivity)</li> <li>● Section 6.2 (Postmarketing Experience)</li> <li>● Section 14 (Clinical Studies), subsections were created: Section 14.1 (Healthy Patients) and Section 14.2 (High Risk Patients)</li> <li>● Section 15 (References)</li> </ul>	

## Full Prescribing Information (FPI)

- **INDICATION AND USAGE** (Section 1) was updated to include patients at high risk of developing influenza-related complications.
- **DOSAGE AND ADMINISTRATION** (Section 2), Table 1 was revised to reduce medication errors:
  - Single dose of 40 mg and single dose of 80 mg were replaced with “Two 20 mg tablets (blister card contains two 20 mg tablets)” and “Two 40 mg tablets (blister card contains two 40 mg tablets).”
- **CONTRAINDICATIONS** was updated with serious allergic reactions information.
- **WARNINGS AND PRECAUTIONS, Hypersensitivity** subsection (Section 5.1) was added to include serious allergic reactions, e.g., anaphylaxis, angioedema, urticaria and erythema multiforme, reported in post-marketing experience with XOFLUXA.
- **ADVERSE REACTIONS, Clinical Trials Experience** (Section 6.1) was revised to include the updated safety profile of XOFLUZA from placebo-controlled Trials 1, 2, and 3 in healthy adults and adolescents and patients at high risk of developing complications associated with influenza.
- **ADVERSE REACTIONS, Postmarketing Experience** (Section 6.2) was added to include adverse reactions identified during post approval use. The following categories of adverse reaction are added:
  - *Body as a Whole*
  - *Skin and Subcutaneous Tissue Disorders*
  - *Gastrointestinal Disorders*
  - *Psychiatric*
- **Pediatric Use** (Section 8.4) and **Geriatric Use** (Section 8.5) were updated to include safety and effectiveness of XOFLUZA in patients at high risk of influenza complications for: 1) pediatric patients (12 years of age and older weighting at least 40 kg); and 2) subjects 65 years of age and older.
- **CLINICAL PHARMACOLOGY** (Section 12) was modified to provide additional clarity of pharmacodynamic and pharmacokinetic profile from healthy adults and adolescents and patients at high risk of developing influenza-related complications.
- **MICROBIOLOGY** (Section 12.4) was updated with additional antiviral activity data and treatment-emergent resistance-associated substitutions.
- **CLINICAL STUDIES** (Section 14): Sub-sections were created and revised as follows.
  - Section 14.1 was updated for patient population who is “Otherwise Healthy.” Two trials (Trial 1 and Trial 2 [NCT02954354]) were conducted in two different influenza seasons to evaluate the efficacy and safety of XOFLUZA in otherwise healthy subjects with acute uncomplicated influenza.
  - Section 14.2 was added to include patient population who is at “High Risk.” Trial 3 (NCT02949011) was conducted to evaluate the safety and efficacy of a single oral dose of XOFLUXA compared with placebo or oseltamir, in adult and adolescent subjects 12 years of age or older with influenza who were at high risk of developing influenza-related complications. Table 7 was added.

- **REFERNCES** (Section 15) was added to provide CDC guidance for patients at high risk for flu complications.
- **HOW SUPPLIED/STORAGE AND HANDLING** (Section 16) was updated to reduce the medication error and potential safety issues by removing two dose configurations: 1) 1x40 mg tablet per blister card; and 2) 4x20 mg tablets per blister card, which are not currently available in the U.S.
- **PATIENT COUNSELING INFORMATION** (Section 17) was revised to provide clarity for dosing recommendation and information regarding risk of severe allergic reactions was added for consistency with **Hypersensitivity** (Section 5.1).
- Manufacturer name was revised to: Shionogi Pharma Co., Ltd.
- XOFLUZA™ was changed to XOFLUZA® throughout the label.

#### Patient Information

- “**How Should I take XOFLUZA?**” section was updated with concise dosing instructions
- “**What are the possible side effects of XOFLUZA?**” section was updated to include allergic reactions and additional side effect for consistency with Section 5.1 and Section 17 of the PI.
- Manufacturer name was revised to: Shionogi Pharma Co., Ltd.
- Revision date was updated to “10/2019” in Patient Information.

#### Carton and Container Label

- Two dose configurations: 1) 1x40 mg tablet per blister card; and 2) 4x20 mg tablets per blister card, which are not currently available in the U.S Carton and container labels, were removed to reduce the medication error and potential safety issues.
- The presentation of the strength per tablet, net quantity, and total dose statements on the principal display panel (PDP) were revised to provide further clarity on the total dose contained within each blister pack. The revisions were made to mitigate selection errors at the dispensing and administration level by providing clarity on the contents of each packaging configuration. The following changes were made:
  - A. Outer carton principal display panel:
    - Strength statement in the color band was moved to above the color band;
    - The color band was moved down and the total dose and quantity statements were moved to inside the color band; and
    - “Single dose Contains 40 mg total dose” statement was replaced with Usual dosage” statement on the PDP with large font size to increase prominence and to mitigate end users overlooking this important dosing information.

B. Inner carton principal display panel

- Inner card container labels were revised to align with the revisions made to the outer carton principal display panel.

- Please refer to the attached comparison label for major/minor changes.
- Please refer to the DMEPA review for carton and container label revisions.
- Please also refer to the clinical, clinical virology, statistical, and clinical pharmacology reviews.

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This efficacy supplement for XOFLUZA® should be approved.

Myung-Joo Patricia Hong, M.S. *Please refer to electronic signature date*  
Senior Regulatory Project Manager Date

Karen Winestock *Please refer to electronic signature date*  
Chief, Project Management Staff Date

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** October 09, 2019  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 210854  
**Product Name and Strength:** Xofluza (baloxavir marboxil) tablets, 20 mg and 40 mg  
**Applicant/Sponsor Name:** Genentech, Inc (Genentech)  
**OSE RCM #:** 2019-1154-1  
**Tracked Safety Issue #:** 2082  
**DMEPA Safety Evaluator:** Valerie S. Vaughan, PharmD  
**DMEPA Team Leader:** Sevan Kolejian, PharmD, MBA

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#### 1 PURPOSE OF MEMORANDUM

This memorandum evaluates Genentech's responses (Appendix A) to address Xofluza (baloxavir marboxil) tablet overdose medication errors.

The Applicant submitted their mitigation strategies received on September 18, 2019, revised prescribing information, container labels, and carton labeling received on September 25, 2019 and October 4, 2019 for Xofluza (Appendix B). The revisions are in response to recommendations that we made during a previous postmarket medication error review<sup>a</sup> and information requests<sup>b,c</sup>.

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<sup>a</sup> Vaughan, V. Postmarket Medication Error Review for Xofluza (NDA 210854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 13. RCM No.: 2019-1154.

<sup>b</sup> Hong, M. Information Request for Xofluza (NDA 210854/S-001). Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2019 SEP 13. Available at:

[https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80515a49&\\_afRedirect=222220094666936](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80515a49&_afRedirect=222220094666936)

<sup>c</sup> Hong, M. Information Request for Xofluza (NDA 210854/S-001). Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2019 OCT 03. Available at:

[https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8051c60a&\\_afRedirect=222262961303966](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8051c60a&_afRedirect=222262961303966)

## 2 REGULATORY HISTORY

- On June 11, 2019, TSI 2082 was opened for Xofluza (baloxavir marboxil) after the Agency received 8 FAERS reports describing overdose errors with the use of Xofluza.
- On August 13, 2019, in OSE RCM 2019-1154<sup>d</sup>, we concluded that revisions to the Xofluza US prescribing information (USPI) and carton labeling were warranted to address overdose errors with the use of Xofluza. We communicated the following recommendations to Genentech on August 20, 2019.
  - In the USPI, revise Table 1 to provide clarity for prescribing by including the strength and number of tablets that should be prescribed and administered to achieve the prescribed dose.
  - In the USPI, remove reference to the 4 x 20 mg tablets and 1 x 40 mg tablet blister packs in Section 16, given these packaging configurations are not available in the US market.
  - For Xofluza carton labeling, revise the presentation of the strength per tablet, net quantity, and total dose statements on the principal display panel to provide further clarity on the total dose contained within each blister pack.
- On August 26, 2019, in response to recommendations we communicated to Genentech on August 20, 2019, Genentech indicated:
  - that they would revise Table 1 of Section 2 within the USPI to provide clarity on Xofluza dosing (b) (4) and (b) (4)
  - (b) (4)
- On September 4, 2019, in response to the Agency's August 30, 2019 information request<sup>e</sup>, Genentech indicated:
  - they hold (b) (4) units of commercial Xofluza in their warehouse and that there were about (b) (4) units of Xofluza in the US wholesale and retail channels;
  - they plan to ship (b) (4) units into the US market in October 2019 for pre-season stocking in anticipation of the 2019-2020 flu season; and
  - confirmation that they do not plan to market the 4 x 20 mg tablets and 1 x 40 mg tablets blister pack configurations in the U.S. market for the upcoming 2019-2020 flu season.
- On September 18, 2019, in response to the Agency's September 13, 2019 information request<sup>f</sup>, Genentech indicated:

<sup>d</sup> Vaughan, V. Postmarket Medication Error Review for Xofluza (NDA 210854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 13. RCM No.: 2019-1154.

<sup>e</sup> Hong, M. Information Request for Xofluza (NDA 210854/S-001). Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2019 AUG 30. Available at:

[https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80512173&\\_afRedirect=222080723645784](https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80512173&_afRedirect=222080723645784)

<sup>f</sup> Hong, M. Information Request for Xofluza (NDA 210854/S-001). Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2019 SEP 16. Available at:

[https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80515a49&\\_afRedirect=22220094666936](https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80515a49&_afRedirect=22220094666936)

- they would remove reference to the 4 x 20 mg tablets and 1 x 40 mg tablet blister pack configurations from Section 16 of the USPI for Xofluza;
  - they would make changes to the carton labeling for Xofluza a priority moving forward but requests to utilize the current stock of commercial Xofluza for the 2019/2020 flu season to minimize the risk of stockout and shortage;
  - they plan to include dosing information in their educational pieces (i.e., core visual aid, pharmacist visual aid, and dosing card) for healthcare providers with an estimated reach of (b) (4) prescribers and (b) (4) pharmacies via sales calls; and (b) (4) prescribers and a total of (b) (4) pharmacist through non-personal educational channels (i.e., direct mail, email, etc.); and
  - they are drafting a “Dear Healthcare Provider” letter that will include a high-level overview of dosing errors that have occurred with Xofluza, provide clarity on appropriate weight-based dosing of Xofluza, and provide packaging specifics that differentiate between Xofluza doses of 40 mg and 80 mg.
- On September 25, 2019, Genentech submitted revised labels and labeling for Xofluza. They agreed to our container label and carton labeling recommendations and (b) (4) (b) (4)
  - On October 4, 2019, in response to the Agency’s October 3, 2019 information request<sup>§</sup>, Genentech accepted our carton labeling recommendation to increase the font size of the usual dosage statement located on the principal display panel.

### 3 CONCLUSION

We recognize that there is a public health imperative for Xofluza for the 2019-2020 Influenza Season. Therefore, based on the totality of mitigation strategies that Genentech proposes in order to address Xofluza overdose errors, we, in concurrence with the Division, agree with Genentech’s proposal to utilize the current Xofluza carton labeling for the 2019/2020 flu season.

Furthermore, we note that Genentech (b) (4) (b) (4) and we, in concurrence with the Division, find this proposal acceptable.

Our review of the revised USPI, container labels, and carton labeling determined they are acceptable from a medication error perspective and we have no additional recommendations.

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<sup>§</sup> Hong, M. Information Request for Xofluza (NDA 210854/S-001). Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2019 OCT 03. Available at: [https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8051c60a&\\_afRedirect=223803859364769](https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8051c60a&_afRedirect=223803859364769)

## APPENDIX A. RESPONSE TO THE AGENCY'S INFORMATION REQUESTS

- Response to the Agency's Information Request dated August 20, 2019, received on August 26, 2019. Available at:  
<\\cdsesub1\evsprod\nda210854\0138\m1\us\response.pdf>
- Response to the Agency's Information Request dated August 30, 2019, received on September 4, 2019. Available at:  
<\\cdsesub1\evsprod\nda210854\0139\m1\us\response.pdf>
- Response to the Agency's Information Request dated September 13, 2019, received on September 18, 2019. Available at:  
<\\cdsesub1\evsprod\nda210854\0144\m1\us\response.pdf>
- Response to the Agency's Information Request dated September 24, 2019, received on September 25, 2019 (cover letter). Available at:  
<\\cdsesub1\evsprod\nda210854\0152\m1\us\cover.pdf>
- Response to the Agency's Information Request dated October 3, 2019, received on October 4, 2019 (cover letter). Available at:  
<\\cdsesub1\evsprod\nda210854\0156\m1\us\cover.pdf>

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**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** 9/10/19

**To:** Myung-Joo Patricia Hong, M.S.  
Senior Regulatory Health Project Manager  
Division of Antiviral Products (DAVP)

**From:** Nima Ossareh, PharmD, RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Sam Skariah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for XOFLUZA™ (baloxavir marboxil) tablets,  
for oral use

**NDA:** 210854 Supplement 1

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In response to DAVP's consult request dated June 17, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for XOFLUZA™ (baloxavir marboxil) tablets, for oral use. This supplement proposes to update the clinical studies and indication of the PI to include the treatment of acute uncomplicated influenza in patients 12 years of age or older, who have been symptomatic for no more than 48 hours and are at high risk of developing influenza-related complications.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on August 26, 2019, and are provided below.

**PPI:** A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or [nima.ossareh@fda.hhs.gov](mailto:nima.ossareh@fda.hhs.gov).

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 30, 2019

To: Debra Birnkrant, MD  
Director  
**Division of Antiviral Products (DAVP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Ruth Mayrosh, PharmD  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Koung Lee, RPh, MSHS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): XOFLUZA (baloxavir marboxil)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 210854

Supplement Number: S-001

Applicant: Genentech Inc.

## 1 INTRODUCTION

On January 4, 2019, Genentech Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 210854/S-001 for XOFLUZA (baloxavir marboxil) tablets. The purpose of this efficacy supplement is to fulfill postmarketing commitment (PMC 3503-7) and to seek an indication for the use of XOFLUZA (baloxavir marboxil) to treat patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on June 17, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for XOFLUZA (baloxavir marboxil) tablets.

## 2 MATERIAL REVIEWED

- Draft XOFLUZA (baloxavir marboxil) tablets PPI received on January 4, 2019, and received by DMPP and OPDP on August 27, 2019.
- Draft XOFLUZA (baloxavir marboxil) tablets Prescribing Information (PI) received on January 4, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 27, 2019.
- Approved XOFLUZA (baloxavir marboxil) tablets labeling dated October 24, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER  
09/03/2019 08:13:03 AM

## Clinical Inspection Summary

<b>Date</b>	July 25, 2019
<b>From</b>	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
<b>To</b>	Myung-Joo Patricia Hong, Regulatory Project Manager Melisse Baylor, Clinical Reviewer Division of Anti-Viral Drug Products
<b>NDA #</b>	210854/S001
<b>Applicant</b>	Genentech, Inc.
<b>Drug</b>	Xofluza™ (Baloxavir marboxil)
<b>NME</b>	No
<b>Therapeutic Classification</b>	Standard
<b>Proposed Indication</b>	Treatment of influenza in patients 12 years of age and older, who have been symptomatic for no more than 48 hours and are at high risk of developing influenza related complications
<b>Consultation Request Date</b>	February 27, 2019
<b>CIS Goal Date</b>	August 16, 2019
<b>Action Goal Date</b>	September 30, 2019
<b>PDUFA Date</b>	November 4, 2019

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The data from Study S033188-T0832 were submitted to the Agency in support of NDA 210854 S-001. Two clinical sites, Dr. Sady Alpizar, M.D. (Site 205), and Dr. Barry McLean, M.D. (Site 128), were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Sady Alpizar and Dr. Barry McLean. The data from Study S033188-T0832 submitted to the Agency in support of NDA 210854 S-001, appear reliable based on available information.

### II. BACKGROUND

Genentech, Inc., seeks approval to market baloxavir marboxil for the treatment of influenza (b) (4) in patients 12 years of age and older, who have been symptomatic for no more than 48 hours, and are at high risk of developing influenza related complications. This request is based on the results of one Phase 3 Study: Study 1602T0832-T0832.

The following overview of Study S033188-T0832 is intended as background context for interpreting the inspectional findings.

A total of approximately 2157 subjects were to be enrolled: 719 in each treatment group. A total of 2592 subjects signed informed consent and 2184 subjects were randomized: 730 subjects in the baloxavir marboxil group, 725 subjects in the oseltamivir group, and 729 patients in the placebo group. This study was conducted under IND 126653.

Study S033188-T0832 is entitled, “A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications.”

Study Period: Date first subject signed ICD: January 11, 2017  
Date last subject completed the study: April 20, 2018

Primary Objective: To evaluate the efficacy of a single, oral dose of baloxavir marboxil compared with placebo by measuring the time-to-improvement of influenza symptoms in patients with influenza.

Primary efficacy endpoint: For efficacy assessment, subjects self-measured/assessed the following outcome measures from pre-dose on Day 1 through Day 14.

- Body temperature: Axillary temperature was measured by the subject at pre-dose on Day 1 and then 4 times daily (morning, noon, evening, and bedtime) until Day 3 and twice a day (morning and evening) from Days 4 to 14.
- Severity of 7 influenza symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). Severity of the symptoms was assessed by the subject on a 4-point rating scale (0, None; 1, Mild; 2, Moderate; 3, Severe) at pre-dose on Day 1, and then twice a day (morning and evening) until Day 9 and once daily (evening) from Days 10 to 14.
- Assessment of health: Health status was self-assessed by the subject on a scale of 0 (worst possible health) to 10 (normal health [for his/her age and condition]) at pre-dose on Day 1 and then once daily (evening) until Day 14.

Objectives of Inspections:

- verify efficacy endpoints using source documents at the clinical site for each subject
- Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- General compliance with the investigational plan.

### III. RESULTS (by site):

#### 1. Dr. Sady Alpizar, M.D., Tampa, Florida (Site 205)

The site screened 39 subjects and enrolled/randomized 38 subjects. At the time of this inspection two subjects had discontinued treatment due to adverse events: Subject (b) (6) due to renal insufficiency and Subject (b) (6) due to increased liver enzymes.

All 39 subject records were reviewed. The inspection covered a review of the source data and compared it to the data listings submitted to the application. Special attention was given to screening, entry criteria compliance, randomization, documentation of study-specific assessments, efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. Review of regulatory documentation, included but not limited to monitoring records, study medication accountability, delegation of authority and IRB and sponsor communications. There were several noteworthy protocol deviations. Pregnancy testing was not conducted for 2 subjects, (b) (6) and (b) (6) at Day 1/Visit 1 with a lack of documentation (lab results, surgical intervention) to eliminate the pregnancy testing at the pre-dose examination. In addition, immunochemistry testing (HBsAg, HCV Ab, HIV Ab) was not performed prior to enrolling Subject (b) (6). The site performed the pregnancy testing for the two subjects and the immunochemistry testing on the single subject at unscheduled times after enrollment and dosing. All tests had negative results.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. The primary endpoint was verifiable, and all source data matched with the data listings submitted to the application. The data from Site 205, associated with Study 1602T0832 appear reliable. This information is based on preliminary communication with the field; the EIR has not been received from the field at this time.

#### 2. Dr. Barry McLean, M.D., Birmingham, AL (Site 128)

The site screened 53 subjects and 36 subjects were enrolled and received test article; all 36 subjects completed the study. Informed consents were reviewed for all study subjects. A record review was done for all 53 subjects. The inspection focused on review of the source records, both paper and electronic, and comparison of the source data to the data listings submitted to the application. The paper source records included but were not limited to subject study visits regarding collection of laboratory samples, central laboratory results, dosing information, drug compliance, and downloaded subject diary entries regarding self-administration of drug product. The electronic source records for this study were the subject electronic diary entries for recording symptom severity.

Special attention was given to screening, entry criteria compliance, randomization, documentation of study-specific assessments, primary and secondary efficacy endpoints, adverse events reporting, and adherence to protocol. Review of regulatory documentation, financial disclosure forms, drug accountability records, study monitoring visits and reports to the sponsor was performed.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. The efficacy endpoint data were verifiable, and consistent with the data listings submitted to the application. The data from Site 128, associated with Study 1602T0832 appear reliable.

Note: The inspection of Site 225 was canceled since a recent OSI inspection had documented regulatory violations sufficient to justify the sponsor's decision to close the site and censor the data for Study S033188-T0832. Therefore, OSI recommended that inspection of this site (Dr. Mercedes Samson, Site 225 which was included in the original assignment to ORA) was not necessary

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**cc:**

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/s/  
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07/31/2019 02:59:42 PM

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