CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210854Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210854
Review #1

Drug Name/Dosage Form	Baloxavir Marboxil Tablets Trademark "Xofluza" is proposed
Strength	20 mg and 40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Shionogi

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Apr 24, 2018	All
Amendment	Jun 13, 2018	Quality
Amendment	Jun 20, 2018	Quality
Amendment	Jun 28, 2018	Quality
Amendment	Jul 5, 2018	Labeling
Amendment	Jul 13, 2018	Quality
Amendment	Jul 30, 2018	Quality
Amendment	Aug 10, 2018	Quality
Amendment	Aug 20, 2018	Quality
Amendment	Sep 5, 2018	Quality
Amendment	Sep 5, 2018	Labeling
Amendment	Sep 18, 2018	Container Labels

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance & Drug Master Files	Rajan Pragani	Suong (Su) Tran Charles Jewell
Drug Product, EA & Labeling	Erika Englund	Balajee Shanmugam
Process, Facility & Microbiology	Christine Falabella	Arwa ElHagrasy
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	
OND Project Manager	Victoria Tyson	
OND CDTL	Mary Singer	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III	See DP review				
	Type IV	See DP review				
	Other					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126653	Baloxavir Marboxil Tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	None			
Pharmacology/Toxicology	None			
CDRH	None			
Clinical	None			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 210854 is recommended for **APPROVAL** from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

This NDA describes 20 and 40 mg baloxavir marboxil tablets, with the proposed proprietary name of Xofluza. Baloxavir marboxil is a prodrug that is converted to the active form (baloxavir; S-033447) through hydrolysis. Baloxavir inhibits the endonuclease activity ("cap-snatching") of the polymerase acidic protein, an enzyme in the influenza RNA polymerase complex required for viral gene transcription.

Proposed Indication(s) including Intended Patient Population	Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.
Duration of Treatment	Single dose of 40 or 80 mg
Maximum Daily Dose	80 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance:
The drug substance baloxavir marboxil is a complex organic molecule that is converted in vivo to the active metabolite S-033447 (b) (4) after metabolism. The structure and absolute stereochemistry of baloxavir marboxil was verified by single crystal x-ray determination. As a low solubility compound, particle size is controlled in the drug substance specification at NMT (b) (4) um (which was found to be acceptable from the Biopharmaceutics perspective) and the process is specific for polymorphic (b) (4) (the most stable form). Shionogi has provided data to support (b) (4) remains during stability studies, and it is monitored in the specification by the IR identification test, which can differentiate (b) (4) from other polymorphic forms.

The acceptance criteria of the specified impurities in the drug substance specification are appropriate from the product quality perspective, and are qualified from the safety perspective. The applicant's submitted a thorough risk assessment for mutagenic impurity control, which was deemed appropriate. Mutagenic impurities most likely to advance to the drug substance, (b) (4) appropriately controlled in

(b) (4)

The analytical test methods for related impurities and stereoisomeric impurities were validated and sufficiently specific for individual impurities that are very similar in structure. The 12-month long-term and 6-month accelerated stability data on 3 primary batches supports the proposed retest period of (b) (4) months (b) (4) Shionogi's proposal to test annual stability batches at the initial and yearly time points is aligned with ICH Q7 recommendation of testing one batch per year at least annually to confirm the stability. For additional details, see Rajan Pragani's Drug Substance Review, below.

Drug Product

XOFLUZA 20 mg Tablets are white to light yellow, oblong shaped film-coated tablets debossed with "S772" 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. (b) (4) Product is packaged in blister packs as two or four 20 mg tablets, and one or two 40 mg tablets

The drug product specifications are acceptable to support the identity, strength, purity, and quality of the product. The submitted analytical methods and validation were reviewed and found acceptable. (b) (4) but the applicant described that other polymorphic forms are possible. The drug substance has low solubility, and in the original NDA submission there was no description of the stability of the polymorphic form of the drug substance in the drug product. On request, the applicant submitted the XRPD of the 20 mg and 40 mg tablets after 6 months at accelerated stability conditions, and 18 months at long term stability. This information is acceptable to support that the polymorphic form of the drug substance is stable in the drug product.

The applicant submitted 18 months of long term stability data for the 20 mg tablet, and 6 months of long term stability data for the 40 mg tablet. Six months of accelerated stability data was submitted for both strengths. The submitted stability data is consistent with the agreed stability data request from the PreNDA meeting (Oct 31, 2017; IND 126653). A single expiration date is assigned because the stability profile of both strengths is similar. The only degradation product that increased in the stability studies was S-033447, which is the parent compound produced from prodrug hydrolysis. The requested 24 month expiration date at 25° (b) (4) is acceptable for both strengths.

The NDA describes a single primary container closure system for the drug product: (b) (4) The NDA has 2 proposed secondary container closure systems: the DosePak (b) (4) The same number of tablets could

be packaged in either of these configurations. The product is not light sensitive as supported by photostability studies. The use of either the DosePak (b) (4) acceptable from a chemistry perspective. However, on Aug 18, 2018 the applicant informed the FDA that only the DosePak will be used for US launch supplies, after the DosePak passed (b) (4) testing. For additional details, see Erika Englund's Drug Product Review, below.

Process:

(b) (4)

The applicant has already marketed 10 mg and 20 mg dosages of the same drug product for the Japanese market since February 2018. The 40 mg dosage included in this application is new and the applicant manufactured 3 registration batches of this dosage along with 3 other registration batches of 20 mg dosages in support of this application.

(b) (4)

(b) (4)

Facilities:
The applicant has provided facility information for 9 facilities involved in the manufacture of the drug substance, manufacture of the drug product, release testing, stability testing, drug substance intermediate testing (b) (4) primary packaging/labelling, bulk product storage, final packaged drug product storage, and drug product release. The applicant has included several sites that are in current supply chains for Roche and Genentech, collaborators of Shionogi for this drug product (i.e. F. Hoffman-La Roche, Genentech USA, Genentech Inc.). All facilities listed in this application are acceptable to support this NDA. A Submission Overall Manufacturing Facility Status of Approve was entered in Panorama on Sept 19, 2018.

There were 2 facilities included in the 356h Form, drug product manufacturing site (Shionogi & Co. Ltd., FEI #3004544937) and drug product analytical testing site (Shionogi Analytical Center Co. Ltd., FEI #3014317465), had not been previously inspected by the FDA. Pre-approval inspections (PAI) were scheduled for these facilities between 7/23/18 and 7/27/18. The following aspects were evaluated at the drug product manufacturing site: readiness for manufacturing (location and verification of all equipment listed in registration batch records), conformance to application (verification of methods, analytical methods used, intended master batch records, and biobatch/clinical batch records), and data integrity. The drug product analytical testing site inspection focused on data integrity audits, verifying analytical methods, stability chamber to be used, and adequacy of written procedures/training for analytical staff. The outcomes of these inspections were VAI and NAI for Shionogi & Co. Ltd. and Shionogi Analytical Center Co. Ltd., respectively. There were no objectionable conditions found at either site and both facilities are able to support the acceptability of this application. For the remaining facilities, it was determined that no additional PAIs were required based on reviewing the most recent inspections for each facility, acceptable profiles, and their intended use. Thus, all facilities were determined to be acceptable for NDA 210854. For additional details, see Christine Falabella's Facility Review, below.

Biopharmaceutics:
The provided PK information for the lower 20 mg strength, (b) (4) of the formulations and comparative dissolution profiles between the 20 mg and 40 mg strengths, and PK linearity over a dose range of 6 mg to 80 mg, are appropriate and support the approval of the biowaiver request for the proposed higher 40 mg strength, and therefore the request for a waiver of conducting a BE study, comparing the 40-mg Tablet with the 20-mg Tablet which was used in the Phase 3 pivotal study, is granted.

The proposed dissolution method and the revised acceptance criterion for batch release and stability testing, shown in the table below, are acceptable.

USP Apparatus	Speed (RPM)	Medium	Acceptance Criterion
II (Paddle)	50	0.07% w/v (for the 20 mg) or 0.16% w/v (for the 40 mg) CTAB* in phosphate buffer, pH 6.8, 900 mL/37°C	NLT (b) (4)% (Q) at 30 minutes

* CTAB = cetyltrimethylammonium bromide

The formulation, manufacturing process and site proposed for the commercial drug product are the same as for the drug product used in the phase 3 pivotal studies, except for the minor change in tablet image. The provided comparative dissolution data support the tablet image change. For additional details, see Qi Zhang's Biopharmaceutics Review, below.

Environmental Assessment:

The applicant claimed categorical exclusion from the requirement to submit an Environmental Assessment (EA) according to 21 CFR 25.31(b). This CFR reference is applicable to this NDA. According to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.21). For additional details, see the Regional Information / Environmental section in Erika Englund's Drug Product Review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

The recommendations in Erika Englund's Labeling Review (below) have been conveyed to OND for consideration during labeling finalization.

D. Final Risk Assessment (see Attachment)

Stephen Miller

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Date: 9/20/2018 03:20:33PM
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Comments: ATL for NDA 210854

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	XOFLUZA(baloxavir marboxil) tablets
Dosage form, route of administration	Tablets: 20 mg and 40 mg, Oral
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	No

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	20 mg and 40 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets are white to light yellow, oblong shaped and film coated. The 20 my and 40 mg debossed text is also described

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Tablets
Active moiety expression of strength with equivalence statement (if applicable)	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Oral product. All of the inactive ingredients are listed. A request will be included in the PI to list the inactive ingredients in alphabetical order.
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	cap-dependent endonuclease (CEN) inhibitor
Chemical name, structural formula, molecular weight	MW = 571.55. Molecular Weight and name also listed. The chemical name is different from the USAN chemical name. A request to update the name will be included in the PI.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	A statement will be included in the PI that the tablets have a white to light yellow film coating

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Tablets per card is listed
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to light yellow oblong film coated tablets debossed with "⟟772" on one side and "20" on the other side.. NDC number included. Tablets not scored
Special handling (e.g., protect from light)	No
Storage conditions	Store XOFLUZA in its blister package at 20ºC to 25ºC (68ºF to 77ºF);
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Shionogi and Co.

Reviewer's Assessment of Package Insert: ***{Adequate}***

Originally, both the Dosepak (b) (4) container closure systems were submitted to the NDA. During the review cycle, the applicant clarified that the Dosepak had not been confirmed (b) (4) Refer to the drug product review for a further discussion. On 08/20/2018, the applicant confirmed that the Dosepak container closure system (b) (4) and respective labeling from the NDA. This labeling review only covers the product packaged in the Dosepak container closure system. The NDC numbers on the Dosepak container labeling are consistent with the NDC numbers in the PI.

The product is not a salt, and the salt equivalency statement is not applicable to this product. There were minor edits recommended for the PI including listing the inactive ingredients in alphabetical order, and including a description of the film coating as white to light yellow.

(b) (4)

Baloxavir marboxil is listed in the USAN, with the following entry below.

(b) (4)

A comment will be included in the PI that the chemical name should be updated to be consistent with the entry in the USAN USP Dictionary.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the inner card label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Xofluza™ (baloxavir marboxil) tablet or Xofluza™ (baloxavir marboxil) tablets	Same as inner card
Dosage strength	40 mg single dose (1 tablet) 40 mg single dose (2 tablets) 80 mg single dose (2 tablets) 80 mg single dose (4 tablets)	Same as inner card. There is small text on the label for the multiple tablets indicating the quantity of API/tablet. We will send a comment to DMEPA regarding the small text for the strength per tablet.
Net contents	1, 2 or 4 tablets	
"Rx only" displayed prominently on the main panel	"Rx only" is not on the inner card. The inner card is physically attached to the outer carton. The outer carton has "Rx only" predominately displayed on the main panel.	yes
NDC number (21 CFR 207.35(b)(3)(i))	NDC 50242-860-01 (1x40) NDC 50242-828-02 (2x20) NDC 50242-860-02 (2x40) NDC 50242-828-04 (4x20)	Same as inner card
Lot number and expiration date (21 CFR 201.17)	Provide space in the container labeling for the lot number and expiration date, per 21 CFR 201.17.	No
Storage conditions	Not on inner card	Store in blister package at 20° to 25° (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature
Bar code (21CFR 201.25)	yes	Yes

Name of manufacturer/distributor	Not on inner card	Made in Japan Distributed by: Genentech USA,. Inc. A Member of the Roche Group South San Francisco, CA 94080-4990 Manufactured by: Shionogi & Co., Ltd. 2-5-1 Mishima, Settsu Osaka 566-0022, Japan
And others, if space is available		

Reviewer's Assessment of Labels: ***{Adequate}***

The labeling from the 07/05/2018 amendment is evaluated in this section.

The container closure system includes a cardboard outer carton. There are two tabs (A and B). The patient would press the A tab, and pull the B tab to slide out the inner card. The inner card and carton stay physically connected. The NDC number is repeated on both the inner card and outer carton, and is consistent with the NDC numbers in the PI.

We have two comments to share with DMEPA regarding the addition of space for the lot and expiration date, and the size of the font for the strength.

The following comments will be shared with DMEPA:

1. *The strength of the individual tablets is in smaller text than the strength of the combined total quantity of tablets in each carton. We defer to DMEPA concerning the acceptability of this display of strength.*
2. *The container labeling should include space for the lot and expiration date.*

List of Deficiencies:

Recommended edits were shared with OND and DMEPA.

Overall Assessment and Recommendation:

Adequate with revisions.

Primary Labeling Reviewer Name and Date:

Erika E. Englund, Ph.D.

08/24/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Stephen P. Miller, Ph.D.

09/06/2018

Erika Englund

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Date: 9/06/2018 04:48:20PM
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Stephen Miller

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Comments: For B. Shanmugam

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BIOPHARMACEUTICS

NDA: 210854
Submission Type: 505(b)(1) (NME)
Drug Product Name/Strength: XOFLUZA™ (baloxavir marboxil) Tablets, 20 mg and 40 mg
Route of Administration: Oral
Dosage Form: Immediate release tablets.
Applicant Name: Shionogi Inc.
Intended for Use: A cap-dependent endonuclease inhibitor indicated for the treatment of influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

REVIEW SUMMARY

The Biopharmaceutics review is focused on
(1) the evaluation of the adequacy of the proposed dissolution method and acceptance criterion,
(2) bridging throughout product development, and
(3) the biowaiver request for the higher 40 mg strength of the proposed drug product.

Dissolution Method and Acceptance Criterion: The proposed dissolution method and the revised acceptance criterion for batch release and stability testing, shown in the table below, are acceptable.

USP Apparatus	Speed (RPM)	Medium	Acceptance Criterion
II (Paddle)	50	0.07% w/v (for the 20 mg) or 0.16% w/v (for the 40 mg) CTAB* in phosphate buffer, pH 6.8, 900 mL/37°C	NLT (b) (4)% (Q) at 30 minutes

* CTAB = cetyltrimethylammonium bromide

Bridging of Products: The formulation, manufacturing process and site proposed for the commercial drug product are the same as for the drug product used in the phase 3 pivotal studies, except for the minor change in tablet image. The provided comparative dissolution data support the tablet image change.

Biowaiver Request: The provided PK information for the lower 20 mg strength, (b) (4) of the formulations and comparative dissolution profiles between the 20 mg and 40 mg strengths, and PK linearity over a dose range of 6 mg to 80 mg, are appropriate and support the approval of the biowaiver request for the proposed higher 40 mg strength, and therefore the request for a waiver of conducting a BE study, comparing the 40-mg Tablet with the 20-mg Tablet which was used in the Phase 3 pivotal study, is granted.

BIOPHARMACEUTICS REVIEW RECOMMENDATION: *ADEQUATE*

From the Biopharmaceutics perspective, NDA 210854, for XOFLUZATM™ (baloxavir marboxil) Tablets, 20 mg and 40 mg, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD **9/14/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Elsbeth Chikhale, PhD **9/14/2018**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	4/24/2018	Original submission
0018 (19)	7/13/2018	Quality/Response to information request dated 6/11/2018
0029 (30)	9/5/2018	Quality/Response to information request dated 8/21/2018

➢ BCS DESIGNATION

No BCS designation request was submitted to FDA nor was required.

Aqueous Solubility: Baloxavir marboxil exhibits pH-independent low solubility across the physiological pH range at 37°C (**Table 1**).

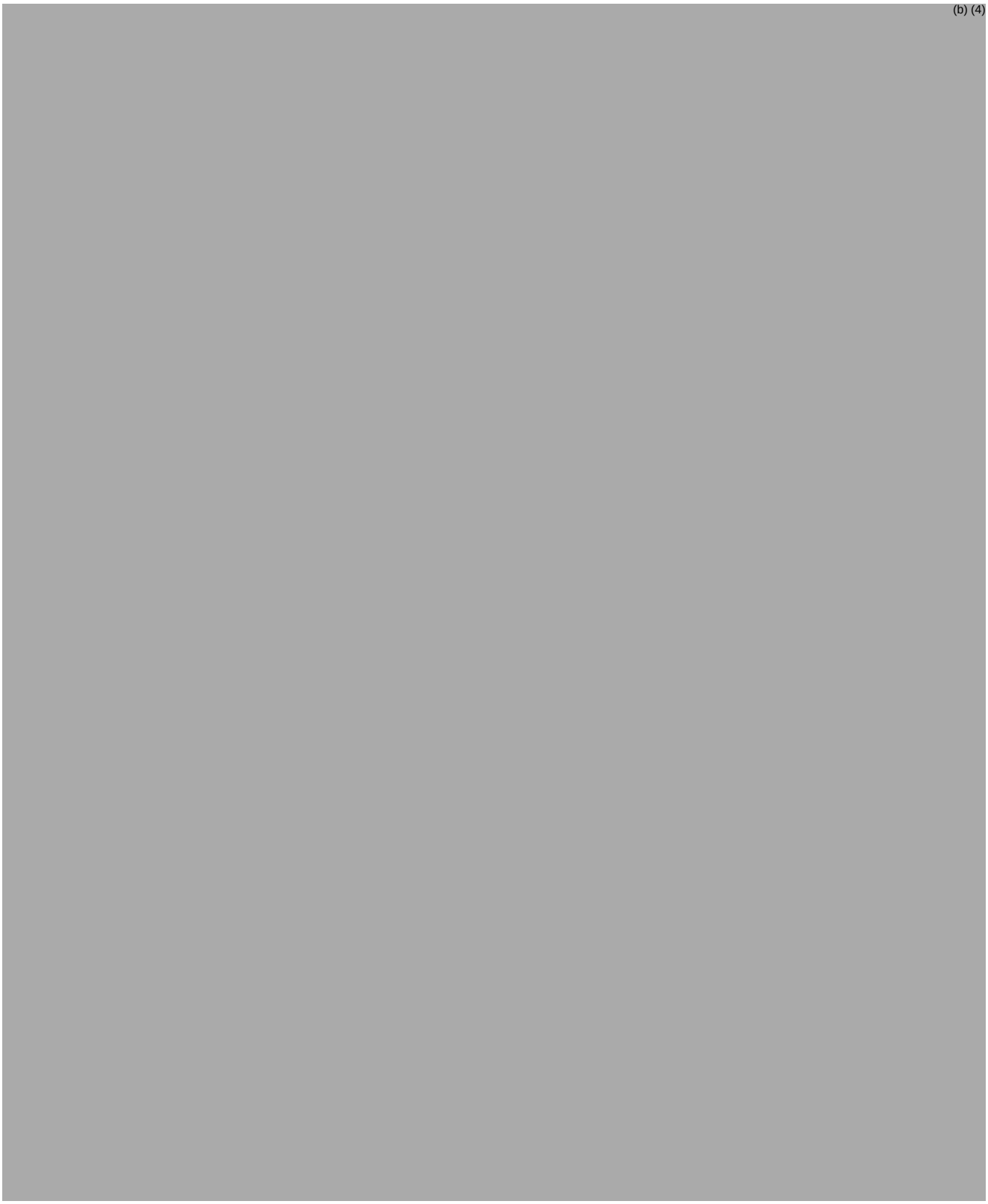
Table 1: Drug Substance Solubility Data at 37°C in pH Range 1 To 6.8

Solvent	Solubility of API (µg/mL) at 37°C
Water	18.4
Hydrochloric acid buffer solution, pH 1.2	20.6
Diluted MacIlvaine buffer solution, pH 3.0	20.2
Diluted MacIlvaine buffer solution, pH 4.0	19.3
Diluted phosphate buffer solution, pH 6.8	18.9

Permeability: Baloxavir marboxil (S-033188) is a prodrug that is almost completely converted to its active form, baloxavir (S-033447) following oral administration. In an in vitro bi-directional permeability study using the Caco-2 cells (Report S-033188-PF-111-N), the apparent permeability coefficient (P_{app}) values of baloxavir marboxil (prodrug) with concentrations of 10 µM were moderate, with the absorptive (apical to basolateral) P_{app} of 6.34×10^{-6} cm/sec and secretory (basolateral to apical) of 27.9×10^{-6} cm/sec. The P_{app} values for the active form, baloxavir were low, with the absorptive P_{app} of 0.495×10^{-6} cm/sec and secretory permeability of 3.12×10^{-6} cm/sec. Both baloxavir marboxil and baloxavir were suggested as substrates of P-gp. The absolute bioavailability of Baloxavir marboxil has not been established.

- **DISSOLUTION INFORMATION**

(b) (4)



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(b) (4)

[redacted]

Validation of Dissolution Method:

An HPLC assay method is used to quantify the drug in the dissolution samples. The Drug Product Reviewer has determined that the HPLC method is acceptable based on the provided information. Refer to the Drug Product Review, for the evaluation of the HPLC method for analyzing the dissolution samples.

The dissolution method robustness is validated with respect to paddle speed (b) (4) 50 rpm) dissolution medium temperature (b) (4) of 37°C), and media pH (b) (4) pH unit).

Reviewer's Assessment: ***Adequate***

Overall, based on sink conditions and complete dissolution, as well as, discriminating ability of the method towards API particle size, formulation and manufacturing process changes, the proposed dissolution method is considered adequate for quality control purposes and is validated.

Dissolution Acceptance Criterion:

The dissolution profiles collected from the Phase 3 clinical and primary stability batches at lot release are summarized in **Tables 3 and 4**, and **Figure 7**.

Table 3: Summary of Mean In Vitro Dissolution Data For 20 mg Tablet (Dissolved Amount (%))

Time (Minutes)		Batch Number					
		S16009-HAL	S16010-HAL	S16016-HAL	0001	0002	0003
10	Min. - Max.	(b) (4)					
	Means	53.1	57.1	58.1	53.3	53.0	52.0
	RSD (%)	24	7.5	4.0	6.4	11	4.3
20	Min. - Max.	(b) (4)					
	Mean	83.9	85.5	85.8	81.9	83.4	81.1
	RSD (%)	5.6	1.5	0.9	2.2	2.1	2.1
30	Min. - Max.	(b) (4)					
	Mean	93.2	93.3	95.4	89.7	92.0	90.0
	RSD (%)	1.8	0.5	0.3	1.4	0.9	1.7
45	Min. - Max.	(b) (4)					
	Mean	97.1	96.2	98.2	94.0	96.0	95.1
	RSD (%)	1.2	0.3	0.4	1.3	0.7	1.5
60	Min. - Max.	(b) (4)					
	Mean	98.0	97.1	98.9	95.5	97.3	96.6
	RSD (%)	1.2	0.4	0.5	1.2	0.7	1.2

RSD: Relative standard deviation

a 6 vessels

S16009: White oblong shaped film-coated tablets; used in clinical study and primary stability.
S16010 and S16016: White oblong shaped film-coated tablets debossed with trade mark and '771' on one side and '20' on the other side; used in primary stability.
0001-0003: White to light yellow, oblong shaped film-coated tablets debossed with trade mark and '772' on one side and '20' on the other side; used in process validation.

Table 4: Summary of Mean In Vitro Dissolution Data For 40 mg Tablet (Dissolved Amount (%))

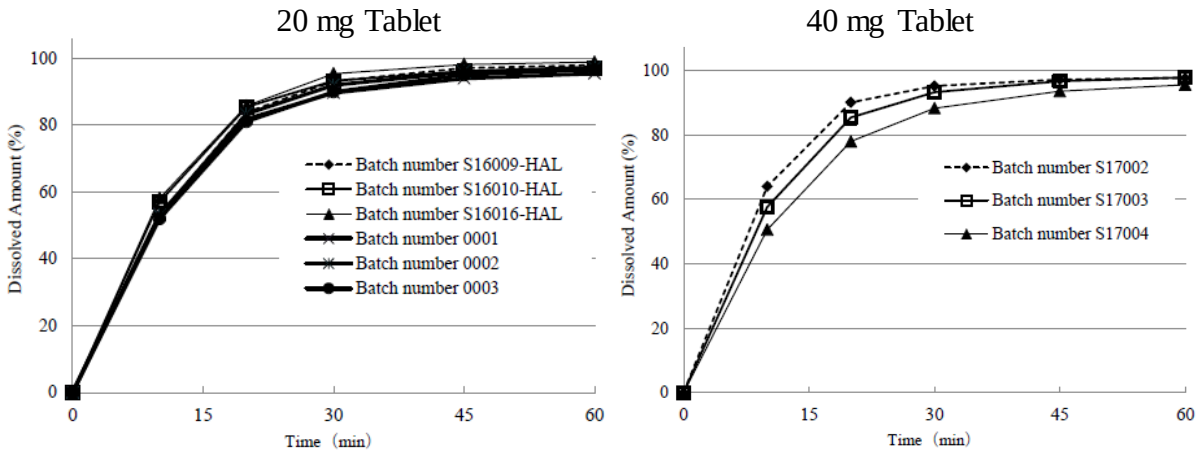
Time (Minutes)		Batch Number		
		S17002	S17003	S17004
10	Min. - Max.	(b) (4)		
	Means	64.0	57.6	50.6
	RSD (%)	9.5	13	12
20	Min. - Max.	(b) (4)		
	Mean	90.1	85.4	78.0
	RSD (%)	1.6	3.7	4.0
30	Min. - Max.	(b) (4)		
	Mean	95.2	93.3	88.3
	RSD (%)	1.2	1.7	1.3
45	Min. - Max.	(b) (4)		
	Mean	97.2	96.7	93.6
	RSD (%)	1.4	1.3	0.8
60	Min. - Max.	(b) (4)		
	Mean	97.7	97.9	95.6
	RSD (%)	1.3	1.3	0.7

RSD: Relative standard deviation

a 6 vessels

S17002: White oblong shaped film-coated tablets; used in primary stability.
S17003 and S17004: White oblong shaped film-coated tablets debossed with 'ABX8' on one side and '40' on the other side; used in primary stability.

Figure 7: Dissolution Profiles for 20 mg and 40 mg Tablets



The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) at 30 minutes is unacceptable. The provided mean dissolution data showed that the clinical and exhibit batches at release reached more than (b) (4)% drug release at 30 minutes. All batches at all stability time points tested passed dissolution at Stage 1 of Q(b) (4)% at 30 minutes. On 9/5/2018, the Applicant has agreed to the FDA's recommended acceptance criterion of NLT (b) (4)% (Q) at 30 minutes. The Applicant provided the revised drug product specifications table with the updated acceptance criterion for the dissolution test.

Note that the tablet image was changed from not debossing (Batches S16009 and S17002) to debossing (Batches S16010, S16016, S17003 and S17004). All the batches reached > (b) (4)%

dissolution at 30 minutes, and the dissolution profiles are similar when compared to the dissolution profile of the pivotal clinical batch S16009 (f_2 = 78.58 and 72.89 for S16009 vs. S16010 and S16009 vs. S16016, respectively; f_2 = 56.67, 76.76, and 66.10 for S16009 vs. S17002, S16009 vs. S17003, and S16009 vs. S17004). Overall the dissolution data support the image change. Also, see the "Bridging of Products" section.

***Reviewer's Assessment:* Adequate**

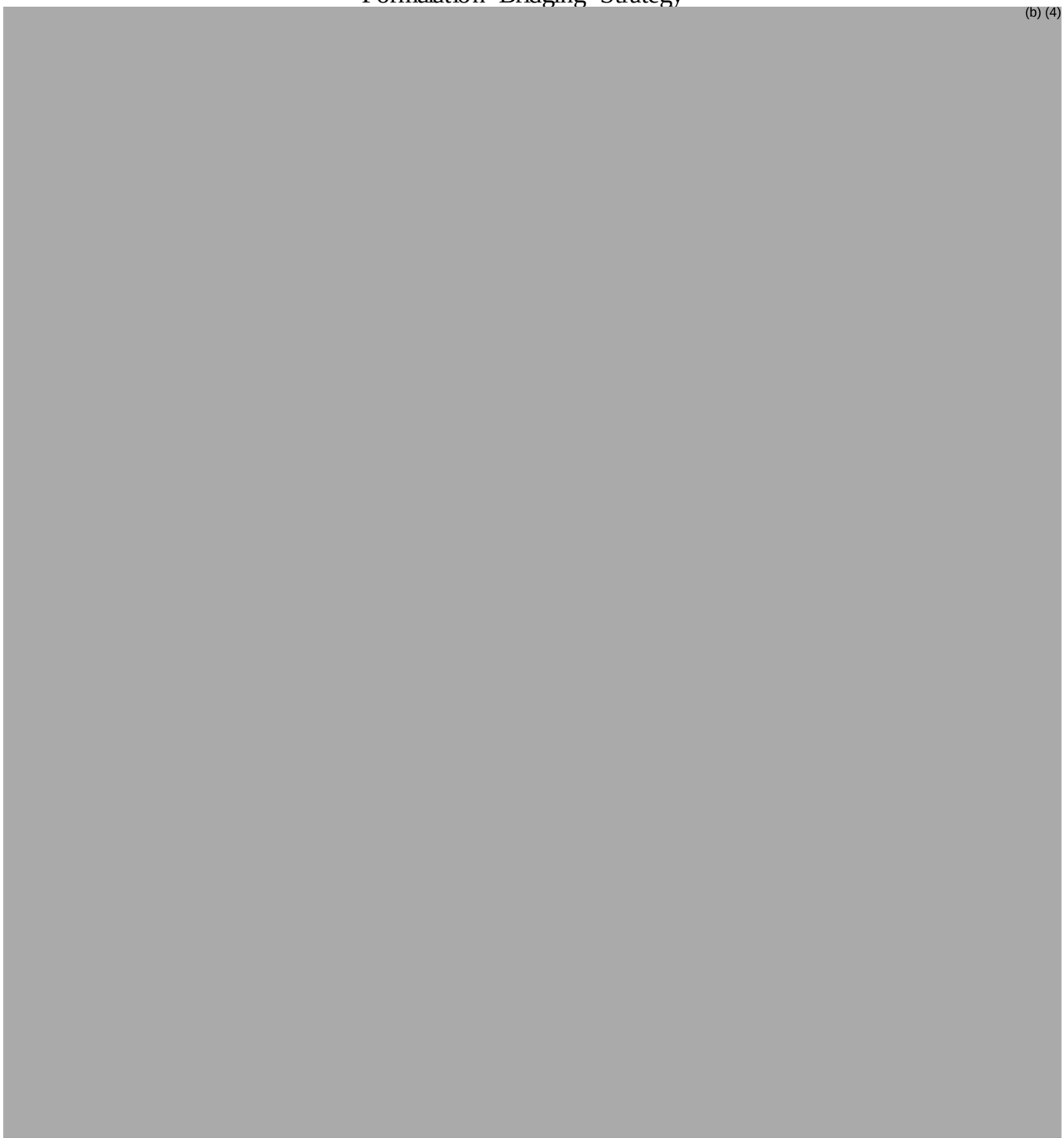
Based on the provided dissolution data, the revised dissolution acceptance criterion of (b) (4)% (Q) at 30 minutes is acceptable.

➢ BRIDGING OF PRODUCTS

A total of five oral formulations of baloxavir marboxil (oral suspension, and Formulation A, B, C, D tablets) were studied at various stages of drug product development (**Figure 8**). The proposed commercial drug product formulation is the same as Formulation D, 20 mg film coated tablets that was used in the pivotal Phase 3 studies T0831 and T0822, except that the commercial tablets were debossed and the tablets in the pivotal Phase 3 studies (Batch #16009) were not debossed. Complete comparative dissolution data demonstrate the dissolution rates were not influenced by the image change between the Phase 3 (Batch S16009, not debossing) and primary stability batches (Batches S16010 and S16016, with debossing) (**Table 3** and **Figure 7**). The manufacturing site of the Phase 3 batches is also the proposed commercial site. The Applicant plans to market both 20 mg and 40 strengths of the proposed baloxavir marboxil tablets. However, the 40-mg Tablet has never been used in any clinical studies. The Applicant submitted a biowaiver request for the 40 mg higher strength to the NDA.

The Phase 1 ADME study T0817 was conducted with baloxavir marboxil oral suspension, and the Phase 1 food effect PK study T0813 was conducted with Formulation C, 20 mg film coated tablets. Relative BA studies were conducted for oral suspension vs. Formulation C at a 20 mg dose. There were minor formulation changes between Formulation C and D, but the changes did not impact the dissolution profiles in multiple pH media (pH 1.2, 3.0, and 6.8), water and the proposed QC dissolution medium (0.07% CTAB in pH 6.8 buffer) (**Figure 9**). Both Formulation B and D were used in the Phase 1 food effect PK study T081F and Phase 3 T0822 pediatric study in Japan. The formulation change between Formulation B, 10 mg Tablet (uncoated) and Formulation D, 20 mg Tablet (b) (4) is considered as SUPAC-IR-Level 3 change (b) (4) The provided PK data demonstrate that Formulation B 10 mg Tablet (uncoated) was not BE to the Formulation D 20 mg Tablet (coated). The 10 mg tablets (coated and uncoated) are not planned for commercial use in the United States. Refer to the Clinical Pharmacology and Clinical Review for the final determination of the adequacy of PK and clinical bridging among the 10 mg and 20 mg Tablets.

Figure 8: Schematic Diagram of Oral Formulations Used in Clinical Development and Formulation Bridging Strategy



***Reviewer's Assessment*: Adequate**

Comparative dissolution profiles support Formulation C and D. The proposed commercial drug product formulation is the same as Formulation D, the formulation used in the Phase 3 studies, except the tablet image. Complete dissolution profile data support bridging (i.e., the change of the image) between the Phase 3 (Batch S16009, not debossing) and the primary stability batches (S16010 and S16016, with debossing). The manufacturing site of the clinical batches is also the proposed commercial site.

➢ BIOWAIVER REQUEST

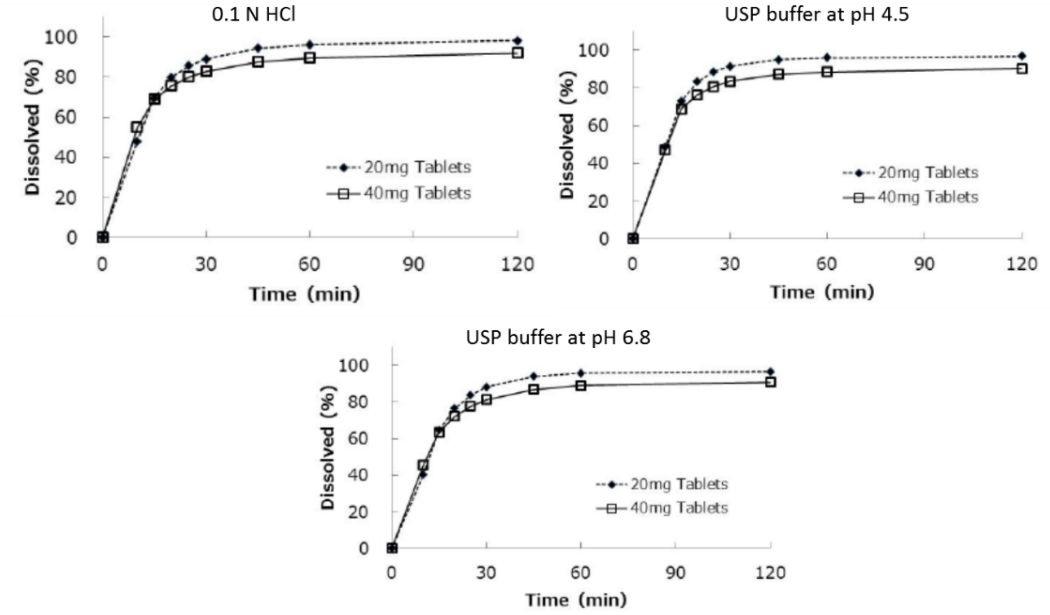
The Applicant's request for a waiver of conducting a PK and/or in vivo BA/BE studies for the proposed higher strength (40 mg) tablets is supported by the following:

(1) the 20 mg and 40 mg tablets have a) the same dosage form, i.e. immediate release oral tablet; b) same manufacturing process; (b) (4) (**Table 5**);
(2) the 20 mg and 40 mg tablets have comparable dissolution profiles in three media (0.1 N HCl, USP buffers at pH 4.5 and 6.8) with or without surfactant (**Figures 10 and 11**);
(3) there are acceptable PK data for the proposed lower 20 mg strength;
(4) evidence of PK linearity over the dose range of 6 to 80 mg (**Figure 12**; Refer to the Clinical Pharmacology Review for the evaluation of the adequacy of PK linearity).

Table 5: Composition of the Proposed 20 mg and 40 mg Drug Product

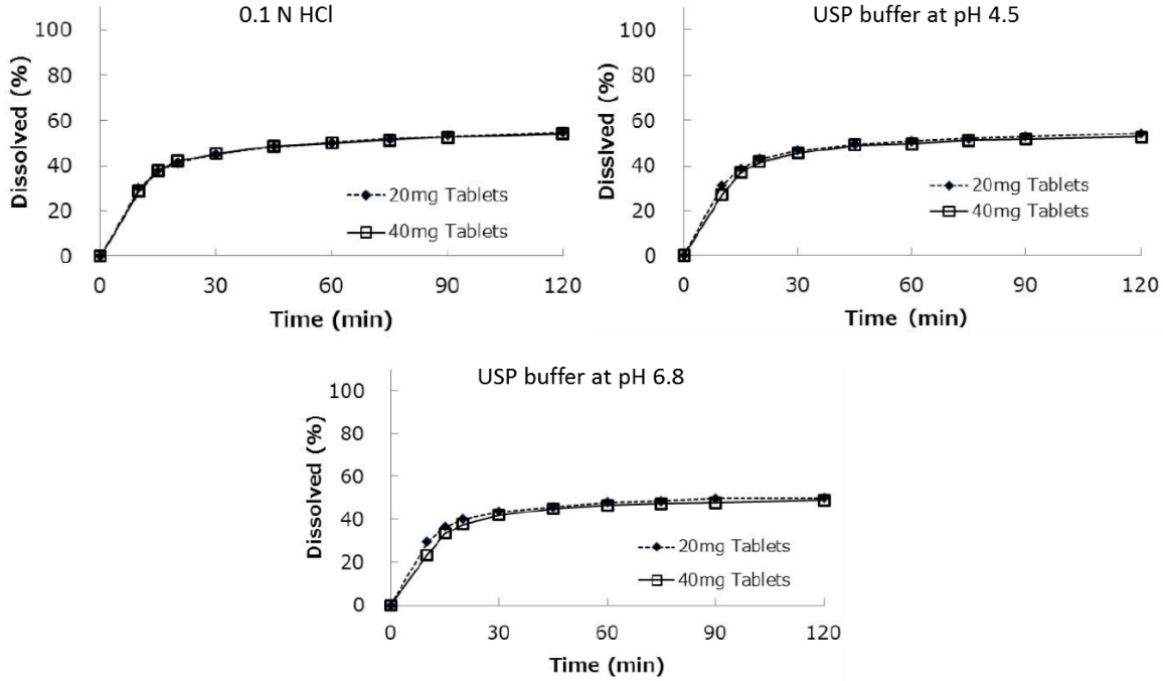
Component	Function	Quality Standard	Amount per Tablet (mg)	
			20 mg Tablet	40 mg Tablet
S-033188 Drug Substance [a]	Active ingredient	In-house standard	20	40
Lactose Monohydrate [a]	(b) (4)	NF/Ph.Eur./JP	(b) (4)	
Croscarmellose Sodium		NF/Ph.Eur./JP		
Povidone (K value: 25)		USP/Ph.Eur./JP		
Microcrystalline Cellulose		NF/Ph.Eur./JP		
Sodium Stearyl Fumarate		NF/Ph.Eur./JPE		
Purified Water [b]		USP/Ph.Eur./JP		
Weight of Core Tablet				
(b) (4)		In-house standard		
		USP/Ph.Eur./JP		
Talc		USP/Ph.Eur./JP		
(b) (4)				
				(b) (4)

Figure 10: Comparative Dissolution Profiles with Surfactant (0.07% CTAB) For One Unit-Tablet of 20 mg Vs. One Unit Tablet of 40 mg



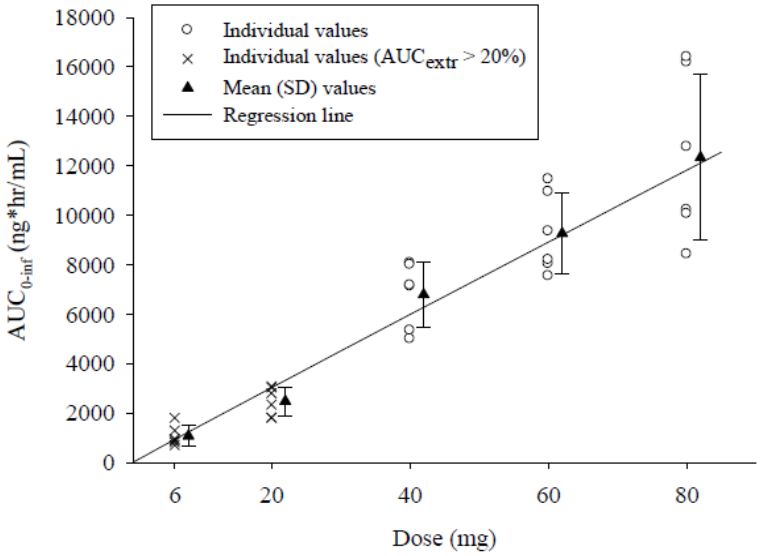
Notes: f_2 = 65, 62, and 62 in 0.1 N HCl, at buffer pH 4.5 and 6.8, respectively.

Figure 11: Comparative Dissolution Profiles Without Surfactant for Two Unit Tablets of 20 mg Vs. One Unit Tablet of 40 mg



Notes: f_2 = 99, 75, and 68 in 0.1 N HCl, at buffer pH 4.5 and 6.8, respectively; Use of 2 units of 20 mg tablet is to correct different sink conditions due to limit solubility of baloxavir marboxil.

Figure 12: Correction Between the Dose of Baloxavir Marboxil and the $AUC_{0\text{-}Inf}$ of Baloxavir



Reviewer's Assessment*: *Adequate

The provided PK information for the lower 20 mg strength, (b) (4) of the formulations and comparative dissolution profiles between the 20 mg and 40 mg strengths, and PK linearity over a dose range of 6 mg to 80 mg, are appropriate and support the approval of the biowaiver request for the proposed higher 40 mg strength, and therefore the waiver for conducting PK and or BA/BE studies, for the 40-mg tablets is granted per 21 CFR § 320.22 (d)(2).

- **OVERALL RECOMMENDATION: Adequate**

From the Biopharmaceutics perspective, NDA 210854, for XOFLUZA™ (baloxavir marboxil) Tablets 20 mg, 40 mg, is recommended for **APPROVAL**.

LIST OF BIOPHARMACEUTICS INFORMATION REQUESTS (IRs)

IR dated 6/28/2018:

To support approval of your biowaiver request for the proposed 40 mg highest strength tablets, provide comparative dissolution profile data (n=12, individual, mean, RSD) generated using one unit tablet for the 20 and 40 mg strengths, in three different dissolution media (i.e., 0.1N HCl, and USP buffer media at pH 4.5 and 6.8) with and without 0.07% CTAB.

IR dated 8/20/2018:

FDA recommends a revised dissolution acceptance criterion of "NLT (b)(4)% (Q) at 30 minutes" for the proposed baloxavir marboxil tablet 20 mg and 40 mg. Please update your drug product release and stability specifications accordingly.

Qi Zhang

Digitally signed by Qi Zhang
Date: 9/14/2018 05:53:19PM
GUID: 547e178000007695c91eb10380b07939

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 9/14/2018 10:01:04PM
GUID: 50743ccc000031928b54eba1769a5df9

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for Baloxavir Marboxil Tablets – NDA 210854

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**	(b) (4)	Acc	
Physical stability (solid state)	Low solubility (b) (4)	**M**		Acc	
Content uniformity	Drug load (b) (4)	**M**		Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV	Low -solubility API Single-tier particle size control	**M**		Acc	

			(b) (4)		
Impurities	Impurities requiring qualification for safety	**M**		Acc	
Patient Use Considerations		**L**		Acc	

Stephen Miller

Digitally signed by Stephen Miller
Date: 9/20/2018 02:39:13PM
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Comments: ATL for NDA 210854