CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211349
Review #1

Drug Name/Dosage Form	XOSPATA (gilteritinib) Tablets
Strength	40 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Astellas Pharma US, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	29-Mar-18	All
Amendment (SD)	11-Jun-18	DP
Amendment (SD)	12-Jul-18	DP, DS, Process
Amendment (SD)	12-Apr-18	DS
Amendment (SD)	10-May-18	Process
Amendment (SD)	28-Jun-18	Process
Amendment (SD)	25-Jul-18	Process
Amendment (SD)	3-Aug-18	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharron Kelly	Charles Jewel
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Ephrem Hunde	Bogdan Kurtyka
Microbiology	n/a	n/a
Facility	Ephrem Hunde	Ruth
Biopharmaceutics	Akm Khairuzzaman	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

APPEARS THIS WAY ON ORIGINAL

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type II			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117548	Giltertinib tablet development

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 211349 for XOSPATA (gilteritinib) Tablets 40 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance (b) (4) Additionally, OPQ grants a 36-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]". There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 211349 was submitted for XOSPATA (gilteritinib) Tablets 40 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Gilteritinib is a once daily, orally bioavailable, potent, selective, small molecule inhibitor of tyrosine kinases, mainly FMS-like tyrosine kinase 3 (FLT3). XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test. Gilteritinib is an NME that was originally investigated under IND 117548. Gilteritinib was granted orphan (July 2017) and fast-track designation (October 2017) for the treatment of AML. The applicant requested and received a priority review of this application.

Gilteritinib is a small achiral BCS class 4 molecule that is manufactured by Astellas Pharma of Japan (b) (4) The drug product, XOSPATA (gilteritinib) tablets, 40-mg, immediate-release solid oral dosage form containing 40 mg of the active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate), mannitol, hydroxypropyl cellulose, low-substituted hydroxyl-propyl cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol, titanium dioxide and ferric oxide. The drug product is presented as a light yellow, round, film-coated tablet debossed with the Astellas logo and '235' on the same side.

The recommended dosing regimen for XOSPATA (gilteritinib) tablets, 120 mg orally once daily until disease progression or unacceptable toxicity.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 211349 and grants a (b) (4) month re-test period for the drug substance and a **36**-month expiration period for the drug product when stored at USP controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	200 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Gilteritinib is a small achiral molecule that is classified as a BCS class 4 compound. It is a yellow, non-hygroscopic, crystalline solid that is sparingly soluble in water and very slightly soluble in ethanol. Gilteritinib is manufactured by Astellas Pharma of Japan at a commercial batch size (b) (4) kg. Although several manufacturing sites and scales have been employed during development, the synthetic scheme for the manufacture of the drug substance remained unchanged (b) (4) The drug substance manufacturing process is described in sufficient detail to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process. The applicant includes specifications and manufacturing schemes for each of the regulatory starting materials as well as a detailed description (b) (4) and controls for all CQAs.

Polymorph screenings revealed (b) (4) of gilteritinib drug substance, however, (b) (4) were observed during the early stages of development. The applicant indicates that these forms are distinguishable by XRPD and IR. A summary of the results of the polymorphic studies is included in the drug substance review.

The drug substance will be packaged and stored in (b) (4) which are manufactured from (b) (4) which meet the requirements of 21 CFR 177.1520 and EU Regulation 10/2011. (b) (4)

The drug substance specification include tests and acceptance criteria for description, identification (IR, TLC and UV), assay, related substances, (b) (4) Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and were considered adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail

and are appropriate for their intended use. All validation parameters (i.e. system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions) are provided in the NDA.

Batch analyses data are included for fourteen batches of the drug substance. The batches range in size from (b) (4) kg and were manufactured at one of four different manufacturing sites. All results were acceptable and all batches were manufactured (b) (4)

Primary stability studies were conducted on 3 production scale batches (batches 2215T14K07, 2215T14K07 and 2215T14K07) of the drug substance manufactured at Astellas Pharma Tech Co., (b) (4) These batches were store under long term conditions (b) (4) for 24 months and under accelerated condition (b) (4) for 6 months. All batches were packaged in (b) (4)

In addition to the long term and accelerated data, the applicant provided up to 36 months of supportive stability data for three pilot scale batches of the drug substance. (b) (4) The stability data for the registration batches demonstrated no notable changes in any attribute tested after up to 24 months under long term storage condition. The applicant requested (b) (4) month retest for drug substance. The long term, accelerated stability data and supportive data (b) (4) support the proposed retest of (b) (4) months for the drug substance (b) (4)

NDA 211349 is recommended for approval from a drug substance perspective.

Drug Product

The drug product, XOSPATA (gilteritinib) tablets, 40 mg is an immediate release oral dosage. The drug product is presented as a light yellow, round, film-coated tablet debossed with the Astellas logo and '235' on the same side. Each tablet contains 40 mg of the active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate) mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol, titanium dioxide and ferric oxide.

The drug product has a recommended dose of 120 mg once-daily with or without food with a MDD of 200 mg.

The QTPP was defined and the CQAs were identified. CQAs for the drug product include assay, content uniformity and dissolution.

The drug product is manufactured by Astellas Pharma Tech Co., Ltd. at a commercial batch size (b) (4) kg which translates to (b) (4) tablets. The drug product has a high loading dose (i.e. (b) (4) %). The manufacturing process includes (b) (4)

(b) (4)

The drug product will be packaged in 90-count, 30-cc, white-opaque high density polyethylene (HDPE) bottles with child resistant (CR) polypropylene (PP) closures lined with induction seals.

The drug product specifications included description, identification, assay, content uniformity, related substances, dissolution, and microbial limits. (b) (4) The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232>. The results of the risk assessment were acceptable and therefore a test for an elemental impurity in the drug product release specifications was not proposed and is not required (See drug product review for details). The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 36 month expiry, the applicant provided 24 months of long-term primary stability data for three pilot scale batches of the drug products. All batches were manufactured according to (b) (4) packaged in the proposed commercial packaging. The samples were stored under the long-term (b) (4) and 6 months accelerated (b) (4)

(b) (4)

"keep in original container" is noted in the Package Insert and on primary and secondary containers.

The available stability data shows consistency over time and support the proposed expiry. Based on the 24 months of stability data included in this application for Gilteritinib Tablets 40 mg, Astellas Pharma proposed and the FDA accepts the expiration dating period of **36 months** for the drug products when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 211349 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 36-months.

Biopharmaceutics

The proposed formulation and manufacturing process used for the commercial product are the same as those used in the Phase 3 clinical studies. Accordingly, the biopharmaceutics review primarily focused on the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus II (Paddle) at 50 rpm in 900 mL of 0.1 mol/L HCl at 37ºC. The proposed dissolution acceptance criterion is Q= (b) (4)% in 30 minutes. (b) (4)

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing for the drug products.

This application is recommended for approval from a biopharmaceutics perspective.

Facilities

The applicant included 5 facilities in this application:

- All sites were listed as ready for inspection:
- **Astellas Pharma Tech Co., Ltd.** – Manufacture, (b) (4) release and stability testing of drug product
- (b) (4)
- **Astellas Pharma Europe B.V..** – Annual stability testing of finished product
- **Astellas Pharma Tech Co., Ltd.** - Manufacture, release testing, stability storage and stability testing of drug substance
- **Astellas Analytical Science Laboratories Inc.** - (b) (4)

All facilities listed in NDA 211349 were deemed acceptable for the responsibility listed in the application. Accordingly, this application is recommended for approval from a compliance perspective.

Environmental Assessment

The approval of this application will increase the use of (b) (4) however, the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb. The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Attached.

LABELING (NDA 211349)

R Regional Information

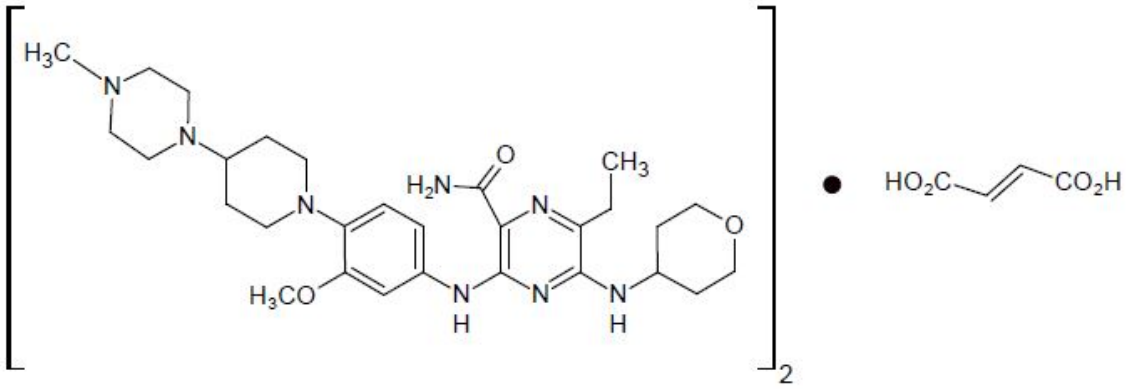
1.14 Labeling

Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

Gilteritinib is a [redacted] (b) (4) tyrosine kinase [redacted] (b) (4) inhibitor. The chemical name is 2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2*H*-pyran-4-yl) amino]-, (2*E*)-2-butenedioate (2:1). The molecular weight is 1221.50 and the molecular formula is $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$. The structural formula is:



Gilteritinib fumarate is [redacted] (b) (4) a light yellow to yellow powder or crystals that is sparingly soluble in water and very slightly soluble in anhydrous ethanol.

XOSPATA (gilteritinib) is provided as a tablet for oral administration. Each tablet contains 40 mg of gilteritinib active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate). The inactive ingredients are mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol, titanium dioxide and ferric oxide.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XOSPATA (gilteritinib) 40 mg tablets are supplied as light yellow, round-shaped film-coated tablets debossed with the Astellas logo and '235' on the same side. XOSPATA tablets are available in the following package size:

- Bottles with child resistant closure of 90 tablets (NDC 0469-1425-90)

16.2 Storage

Store XOSPATA tablets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Keep in original container.

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow *[see Clinical Studies (14)]*. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at http://www.fda.gov/CcompanionDiagnostics.

2.2 Recommended Dosage

The recommended starting dose of XOSPATA is 120 mg (b) (4) orally once-daily with or without food.

(b) (4)

Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Commercial packagings:

Immediate Container Label (90 tablets in bottle):

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reviewer's Assessment:

1. The labeling of the physician's and container labels is per labelling tool, guidances and CFR to have the most current information of the labels.

2. Child resistant closure statement per following guidance has been included in the physician's labeling (PI).

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM569607.pdf

3. Per 21 CFR 201.56 all relevant information pertaining to the each section of the labeling have been provided in the physician's labels.

4. Salt equivalency statement, per labelling tool, is provided in both container and physician's labels.

5. A final version of the agreed upon PI (with DMEPA's editorial chages) will be reviewed by the ATL and included in their memo.

The container and physician's lables are adequate.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 10-JUL-2018

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

Anamitro Banerjee, PhD, 15-JUL-2018

Rajiv Agarwal

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Anamitro Banerjee

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BIOPHARMACEUTICS

NDA: 211349
Drug Product Name/Strength: XOSPATA® (gilteritinib) Tablets 40 mg
Route of Administration: Oral
Applicant Name: Astellas Pharmaceuticals, Inc.
List of Reviewed Submissions:

eCTD # (SND #)	Received date	Document
0000 (1)	10/24/2016	Original submission
0010 (11)	3/20/2016	Information Amendment
0014 (15)	4/19/2017	Quality/Response to information request

Biopharmaceutics Review Team:
Primary Reviewer: Akm Khairuzzman, PhD
Secondary Reviewer: Banu Zolnik, PhD

RECOMMENDATION: ADEQUATE

Background: Astellas Pharmaceuticals, Inc. is seeking approval for XOSPATA ® (gilteritinib) Tablets 40 mg, to be administered orally for the treatment of Acute Myeloid Leukemia under the 505 (b)(1) regulatory path. The proposed drug product is an immediate release film coated tablet containing the active ingredient, gilteritinib and inactive ingredients namely, hydroxypropyl cellulose, low-substituted hydoroxypropyl cellulose, magnesium stearate (b) (4)

The primary clinical support of this NDA for treatment of Acute Myeloid Leukemia is supported by eight (8) Phase I studies (safety, efficacy, PK, PD), three (3) phase 1/2 studies (safety, efficacy & PK), one 2/3 study (efficacy, safety population PK) and two (2) Phase 3 studies.

REVIEW SUMMARY
The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the proposed dissolution method and acceptance criteria, **2)** bridging throughout product development, and **3)** Biowaiver request, if any.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution Method and Acceptance Criterion:*** The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 50 rpm; 900 mL of 0.1 mol/L HCl at 37°C*] was fully validated and is considered acceptable. The proposed acceptance criterion of Q= (b) (4) % at 30 min of the labeled amount of Gilteritinib is acceptable for release and on stability.

2) ***Bridging of Formulations:*** The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. Therefore, bridging between the clinical and commercial formulation/products is not needed.

3) Biowaiver Request: There is only one strength and the Applicant conducted a Phase 3 study (2215-CL-0301) under which the Applicant characterized plasma PK profile. Therefore, biowaiver request is not needed.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 211349 for Gilteritinib Tablets 40 mg, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzman, PhD ***7/5/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Banu Zolnik, PhD ***7/6/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ DRUG PRODUCT:

The proposed drug product is an immediate release film coated tablet containing the active ingredient, gilteritinib and inactive ingredients namely, hydroxypropyl cellulose, low-substituted hydoroxypropyl cellulose, magnesium stearate (b) (4)

➢ *BCS DESIGNATION*

The Applicant claimed that this drug belongs to BCS class IV category.

Solubility: The pH solubility profile of the drug given by the applicant is shown in the following table.

Table 1. pH solubility data

Attribute	Results	
Solubility Profile at 20 ± 5°C	Water	29 mg/mL (Sparingly soluble)
	Aqueous solution (pH 1) † (After dissolution: pH 5.8)	190 mg/mL (Freely soluble)
	Aqueous solution (pH 3) ‡ (After dissolution: pH 5.2)	130 mg/mL (Freely soluble)
	Aqueous solution (pH 5) ‡ (After dissolution: pH 5.3)	82 mg/mL (Soluble)
	Aqueous solution (pH 7) ‡ (After dissolution: pH 6.6)	0.087 mg/mL (Practically insoluble)

†0.1 mol/L hydrochloric acid was used. This pH value was measured before sample dissolution.
‡Carmody's buffer solutions (mixtures of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate) were used. This pH value was measured before dissolution.

Permeability: The permeability of gilteritinib was examined in Caco-2 cells (please refer to study # 2215-ME-0021). The apparent permeability coefficient (Papp) values of gilteritinib comparing the highly permeable model drugs were found to be low, suggesting the drug has low permeability. For details please see biopharmaceutics summary under the module 2.7.1[1].

***Reviewer's Assessment:* ADEQUATE**
Based on the solubility and dissolution data provided, it appears that the drug does not belong to BCS class IV, because the drug is considered soluble. Since Applicant's claimed designation of this drug as a BCS class IV does not impact any of the regulatory provision, or offer any regulatory flexibility, no further communication will be provided.

[1] \\cdsesub1\evsprod\NDA211349\0000\m2\27-clin-sum

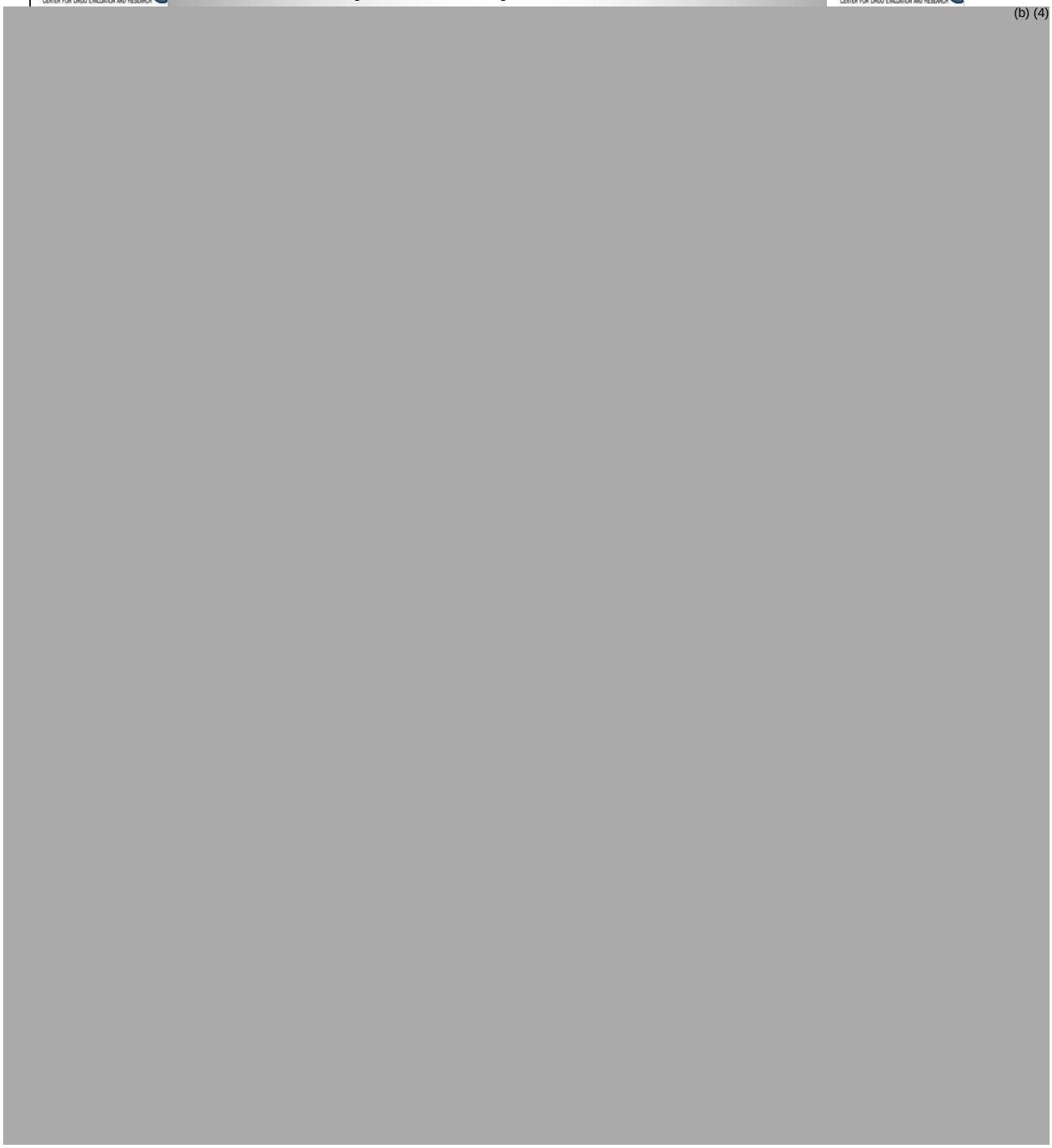
- ***DISSOLUTION INFORMATION:***

Proposed Dissolution Method and Acceptance Criterion: The dissolution method and dissolution

(b) (4)

[redacted]

(b) (4)



- ***Validation of Analytical Method used in the Dissolution Test:*** Refer to the Drug Product Review, for the evaluation of the adequacy of the validation of the analytical method (HPLC method used for dissolution testing).

Reviewer's Assessment: ***ADEQUATE***
Overall, the proposed dissolution method developed is fully validated and is considered adequate for the quality control purposes based on the availability of sufficient sink condition, as well as, discriminating ability of the method towards critical formulation and manufacturing variables.

- ***DISSOLUTION ACCEPTANCE CRITERION***

Based on the manufacturing experience, dissolution profile data of BE, pivotal clinical batches, and stability data, the Applicant proposed the following dissolution acceptance criteria for batch release and stability testing:

Q= (b) (4)% at 30 min

Reviewer's Assessment: ***ADEQUATE***
The dissolution profile data collected from all the clinical and registration batches at lot release are summarized in ***Figure 3****. Based on the provided dissolution data, high variability is observed at 15 min time points and thus proposed dissolution acceptance criteria of Q= (b) (4)% at 30 min is acceptable. No trend in dissolution from the stability samples were observed.*

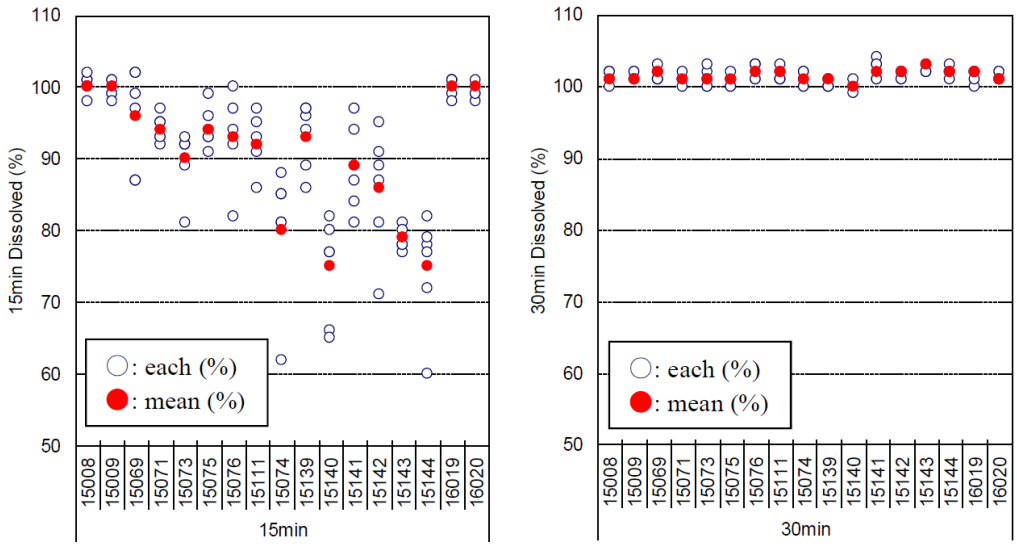


Figure 3: Dissolution Profiles of All the Clinical and Registration Batches at 15 min and 30 min Time Points

BRIDGING OF FORMULATIONS

Different formulations of Gilteritinib Tablets were studied at various stages of drug product development. Formulation was changed at Phase III stage (b) (4)

(b) (4)

The relative bioavailability study outcome provided by the applicant is as follows:

Table 2. Relative Bioavailability Study between Phase II (Treatment B) vs Phase III formulation (Treatment A)

Comparison	Parameter	Geometric LS Mean for Numerator	Geometric LS Mean for Denominator	Geometric LS Mean Ratio (%) †	90 % CI of the Ratio (%) †
Treatment A / Treatment B	AUC_{inf} (ng•h/mL)	1620	1810	89.33	(78.20, 102.04)
	AUC_{last} (ng•h/mL)	1580	1760	89.40	(78.23, 102.16)
	C_{max} (ng/mL)	29.5	31.7	93.21	(80.75, 107.60)

Table 3. In vitro dissolution data comparing the new and old formulation

Dissolution Medium	Dissolution (%, average)†			
	New Formulation (Gilteritinib Tablets 40 mg)		Reference Formulation (ASP2215 Tablets 40 mg)	
	15 min	30 min	15 min	30 min
0.1 mol/L hydrochloric acid	100	101	97	100
Acetate buffer (pH 4.5)	99	101	100	101
Phosphate buffer (pH 6.8)	92	96	92	94
Water	91	95	86	89

†Test condition: apparatus 2, 50 rpm, 0.1 mol/L hydrochloric acid, acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and water 900 mL, 6 vessels.

***Reviewer's Assessment*: ADEQUATE**

The assessment of the relative bioavailability is made by the Office of Clinical Pharmacology Reviewer who have found the study acceptable (refer to OCP review by Dr. Hisham Qosa). It is to be noted that the new formulation of the drug product was also used in the pivotal clinical studies (with a secondary objective of plasma PK characterization). The new formulation is as same as that of the commercial drug product. Therefore, no further bridging between the clinical and commercial formulation-products is needed. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site.

- ***BIOWAIVER REQUEST***

There is only one strength, the Applicant conducted Phase 3 study with a secondary objective of plasma PK characterization (study protocol # 2215-CL-0301).

***Reviewer's Assessment*: ADEQUATE**

OVERALL RECOMMENDATION: From a Biopharmaceutics perspective, NDA 211349 for XOSPATA® (gilteritinib) Tablets 40 mg, is recommended for **APPROVAL**.

Akm Khairuzzaman

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Banu Zolnik

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – **NDA 211349**

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	Controls are in place.
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	H		Acceptable	Controls are in place, continue stability monitoring post approval

(b) (4)

Rajiv Agarwal

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Anamitro Banerjee

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Sherita McLamore

Digitally signed by Sherita McLamore
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