

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210868Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval
NDA 210868
Review 1

Drug Name/Dosage Form	Lobrena (lorlatinib) film-coated tablets
Strength	25 mg and 100 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001 (1), Original Submission	12/05/2017	Drug Substance (DS), Drug Product (DP), Process, Facilities, Biopharmaceutics, and Microbiology
0008 (8), Response to IR	02/07/2018	DS, DP
0009 (9), Response to IR	02/12/2018	Biopharm
0014 (14), Response to IR	03/05/2018	DP
0017 (17), Response to IR	03/12/2018	Process
0027 (27), Response to IR	04/10/2018	DP, Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Charles Jewell	Ali Al Hakim
Drug Product	Olen Stephens	Anamitro Banerjee
Process	Steven Hertz	Rakhi Shah
Microbiology	Steven Hertz	Rakhi Shah
Facility	Steven Hertz	Zhihao Peter Qiu
Biopharmaceutics	Parnali Chatterjee	Okpo Eradiri
Regulatory Business Process Manager	Steven Kinsley	NA

Application Technical Lead	<i>Nina Ni</i>	<i>NA</i>
Laboratory (OTR)	<i>NA</i>	<i>NA</i>
ORA Lead	<i>Caryn McNab</i>	<i>NA</i>
Environmental	<i>Olen Stephens</i>	<i>Anamitro Banerjee</i>

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)	Adequate	Information provided in NDA	
	Type III			Adequate	Information provided in NDA	
	Type III			Closed by DMF holder 28-Dec-17	Information provided in NDA	
	Type III			Adequate	Information provided in NDA	
	Type III			Adequate	Information provided in NDA	
	Type III			Adequate	Information provided in	

					NDA	
(b) (4)	Type III	(b) (4)			Adequate	Information provided in NDA
	Type III				Adequate	Information provided in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	118296	Initial IND for PF-06463922, a small molecule inhibitor of the anaplastic lymphoma kinase (ALK) and ROS1 (c-ROS oncogene 1) receptor tyrosine kinases.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

* The liquid chromatography method for identification and purity was submitted to OPQ/OTR/DPA for method verification. DPA confirmed 29-Mar-18 in Panorama that this method is adequately verified.

Executive Summary

I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Based on the provided stability data, a 24-month expiration dating period is granted for Lobrena (lorlatinib) tablets in 25 mg and 100 mg strength when stored at 20 - 25°C (68 - 77°F); with excursions permitted to 15 - 30°C (59 - 86°F) [see USP controlled room temperature].

II. Summary of Quality Assessments

A. Product Overview

NDA 210868 was received on 12/05/2017 in the 505b(1) regulatory pathway with FDA orphan drug designation (ODD) on 06/23/2015 and breakthrough therapy designation (BTB) on 04/26/2017 to support Lobrena (lorlatinib) tablets, 25 mg and 100 mg marketing approval for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive, brain-penetrant, small molecule inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) receptor tyrosine kinases. The recommended dose is 100 mg taken orally once daily. Clinical development data is available in the cross-referenced IND 118296. The applicant requested priority review of the NDA which was granted.

Lorlatinib is a small molecule new molecular entity with the molecular formula of $C_{21}H_{19}FN_6O_2$ (anhydrous Form 7) and molecular weight of 406.41 Daltons. Lorlatinib has one asymmetric center, giving two possible stereoisomers. The absolute

stereochemistry at the chiral center is the R configuration. Lorlatinib meets the criteria of Class IV (low solubility and low permeability) compound, but the applicant is not claiming BCS classification or biowaivers. Lorlatinib is non-hygroscopic and more soluble at acidic pH (at pH 2.5 or below).

The drug substance is formulated into immediate release film-coated tablets for oral administration. Lorlatinib tablets will be marketed in 25 mg and 100 mg strengths.

(b) (4)

industry. The 25-mg tablet is presented as a round, tan film-coated tablet debossed with "Pfizer" on one side and "25" on the top and "LLN" on the bottom on the other side. The 100-mg tablet is presented as an oval, lavender film-coated tablet debossed with "Pfizer" on one side and "LLN 100" on the other side.

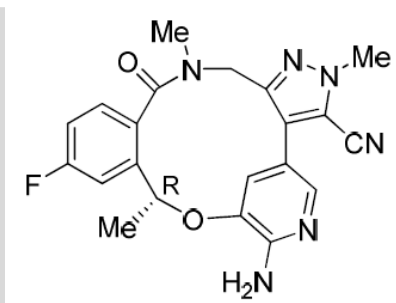
Proposed Indication(s) including Intended Patient Population	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	100 mg once daily
Alternative Methods of Administration	NA

B. Quality Assessment Overview

1. Drug Substance [Lorlatinib]

The drug substance lorlatinib has the following chemical name, structural formula, molecular formula, and molecular weight.

Structure Formula:



International Non-proprietary Name (INN): Lorlatinib

Chemical Name: (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile

CAS Registry Number: 1454846-35-5

Mol. Formula: C₂₁H₁₉FN₆O₂

Mol. Wt.: 406.41 Daltons

Lorlatinib is an orally bioavailable, small molecule inhibitor of tyrosine kinase. Lorlatinib is a lipophilic compound with a partition coefficient in the range of 2.4. It has low solubility in neutral water, with more solubility in acidic water. It demonstrates low membrane permeability but can penetrate the blood brain barrier.

(b) (4)

Adequate risk assessment for elemental impurities were provided and inclusion of elemental impurities testing is not considered necessary. Adequate risk assessment for mutagenic impurities was also provided with no significant risk identified. As per ICH S9 and ICH M7, any potential mutagenic impurities are treated as typical impurities due to the indication of advanced metastatic cancer.

The manufacture of 39 batches are described in the application, with analysis data; 24 of these batches utilized the commercial process, 3 registration batches are provided as manufactured at commercial scale and at commercial site. Stability data on the 3 registration batches supports a re-test period of (b) (4) months for lorlatinib. This includes 12 months' data at long term storage and 6 months' data at accelerated storage conditions.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturer (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

- PFIZER IRELAND PHARMACEUTICALS (FEI #: 3002807852) in Ireland

2. Drug Product [Lorlatinib Tablets, 25 mg and 100 mg]

The proposed commercial formulation for lorlatinib is immediate release (IR) tablets available in two strengths: a 25-mg tan film-coated tablet (b) (4) and a 100-mg lavender film-coated tablet (b) (4)

formulation for the lorlatinib 25 mg or 100 mg tablets. Both strengths are compounded using pharmaceutical excipients at levels used in previously approved US products. The excipients are all compendial quality (b) (4) (b) (4)

(b) (4) (b) (4). The tablet strengths are differentiated by size, shape, film-coat color, and debossing. The container closure systems selected for lorlatinib immediate release film-coated tablets are high-density polyethylene (HDPE) bottles containing desiccant and (b) (4) closure with heat induction seal liner; developmental data of the (b) (4)

Lorlatinib tablets are manufactured (b) (4) (b) (4). The applicant provided information regarding the equipment and process steps used in manufacturing the 25 mg and 100 mg strengths. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

There are no proposed changes to the commercial process when compared to the primary stability batches. The commercial manufacturing process has been executed at up to (b) (4) of the proposed commercial scale (b) (4) for the 25 mg film-coated tablet and (b) (4) of the proposed initial commercial scale (b) (4) for the 100 mg film-coated tablet using commercial scale equipment at Pfizer's manufacturing facility in Freiburg, Germany.

The application includes 40 batch analyses to support the proposed specifications. These batches spanned clinical development that used the (b) (4) form of the drug substance as well as the commercial Form 7 drug substance, formulation changes, and tablet presentation (shape and debossing). The batch data includes the registration stability batches and supportive stability batches. The data demonstrated robustness of the process to transfer between sites, stability of the drug substance, compatibility with the excipients, and consistency with content uniformity, dissolution performance, and assay.

The list of quality attributes in the release and stability specifications are consistent with other immediate release tablet formulations. The acceptance criteria for appearance is sufficient to distinguish dosage strengths. Identification determination is determined by two orthogonal methods as described in ICH Q6A. The assay acceptance criterion is a very typical (b) (4) % and this product is not a narrow therapeutic product, so this range is acceptable. The limits for specified degradation impurities, (b) (4) are supported by nonclinical data and similarity to the parent lorlatinib compound (b) (4). The unspecified degradation limit of NMT (b) (4)

(b) (4) Content uniformity testing complies with USP <905> and requirements. The applicant agreed to tighten the dissolution acceptance criterion to $Q = \frac{(b)(4)}{(4)}\%$ in 45 minutes (from in (b) (4) minutes) at batch release and for stability testing for lorlatinib tablets. The justification to omit microbial limits testing deems adequate. The justification is consistent with other solid oral dosage forms that are not overly hygroscopic. The lack of elemental impurities testing in the specification has been adequately justified and supported using data based on studies in line with the ICH Q3D Elemental Impurities Guidance.

In the original submission in section 3.2.P.5.1 and 3.2.P.8.1-2, the applicant argued that Identification, Assay, and Uniformity of Dosage Units testing are not necessary in the stability protocol. Only Dissolution, Degradation Products, and Appearance will be tested on stability. Note that identification is implicitly tested during the degradation products testing using method (b) (4), which is also one of

the two methods used to establish identity. Uniformity of Dosage Units is commonly not tested on stability as this is primarily a product release specification and would not be expected to change on stability. The analytical method for degradation products, (b) (4) does NOT determine the assay value of the sample. Rather, % degradation product is determined based on relative response factor compared to the average response factor for the lorlatinib peak in bracketing standards injections. Therefore, assay would not be directly reported by this stability protocol. This was deemed unacceptable and an information request was sent 17-Jan-18, instructing the applicant to include assay as part of the stability protocols. The applicant responded in the Amendment 0008 and the Amendment 0014 agreeing to the directive, though expressing disagreement with the criticality of assay monitoring on stability. (b) (4)

The sponsor provided detailed method validation data. Each method description is sufficiently detailed and the liquid chromatography method for identification and purity was submitted to OPQ/OTR/DPA for method verification. DPA confirmed 29-Mar-18 in Panorama that this method is adequately verified. The dissolution method for the proposed drug product was developed using USP Apparatus 2 at a paddle speed of 100 rpm in 900 mL pH 4.5 acetate buffer. The proposed dissolution method has the ability to detect certain changes in the formulation and manufacturing process, which deems acceptable.

A primary stability program for lorlatinib 25 mg and 100 mg immediate release film-coated tablets packaged in high-density polyethylene (HDPE) bottles (b) (4) desiccant and (b) (4) closures with heat induction seal liners (b) (4) has been completed through 12 months at the long term storage conditions of 25°C/60%RH and 30°C/75%RH and 6 months at the accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The primary stability batches were manufactured and packaged at the proposed commercial manufacturing site in Freiburg, Germany. All batches were manufactured at > (b) (4) % of the commercial scale using the commercial equipment. The commercial products will be only packaged in HDPE bottles for US market.

A bracketing design was implemented for each strength to reduce the samples placed on stability to only include the high and low count configurations for each strength. The stability protocol followed ICH Q1A testing intervals with an additional time point at 6 weeks. Testing at each point included appearance, assay, degradation products, dissolution, and (b) (4). Microbial enumeration was tested on release and annually thereafter. No quality attributes exceeded their acceptance criteria in the specification (b) (4)

(b) (4)

Photo-stability of one batch of each strength was evaluated in accordance with ICH guideline Q1B. No significant change was noted in the photo-stability study other than degradation product (b) (4) increasing from NMT (b) (4) % for the 25-mg tablet and up to (b) (4) % for the 100-mg tablet. Formation of this impurity is

controlled by the protective packaging configuration.

In-use stability studies were conducted for tablets packaged in HDPE bottles. The in-use stability protocol was conducted over 30 days when stored at 30°C/75%RH for the 30-count configuration with the desiccant removed. The bottles are subsequently opened and closed for 30 days to mimic how the product will be used by the patient followed by testing for appearance, assay, degradation products, dissolution, (b) (4) and microbial enumeration. Data is available for lots stored for 12 months, which show no change in quality attributes (b) (4)

The stability data through 12 months at long-term, intermediate, and accelerated (6 months) adequately supports a 24 months shelf life under USP Controlled Room Temperature at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) and packaged in either HDPE bottles (b) (4). The stress stability data indicates a stable formulation and drug substance such that no trends are anticipated on storage as shelf life is extended. This also justifies the reduced testing on the initial production batches. (b) (4)

The applicant's claim for categorical exclusion and request of a waiver from an environmental analysis is granted.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

- PFIZER MANUFACTURING DEUTSCHLAND GMBH (FEI #: 3002807097) in Germany
- PFIZER PHARMACEUTICALS LLC (FEI #: 2623619) in Puerto Rico

The drug product reviewer, Olen Stephens, recommended the following life cycle management considerations:

- (b) (4) (b) (4)

3. Special Product Quality Labeling Recommendations (NDA only)

NA

4. Final Risk Assessment (see Attachment below)

Attachment - Final Risk Assessment for Lorlatinib Tablets, 25 and 100 mg

From Initial Risk Identification			Final Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay Stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Low	(b) (4)	Acceptable	(b) (4)
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Medium		Acceptable	
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Acceptable	NA
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Medium		Acceptable	NA
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Low		Acceptable	NA
(b) (4)					



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NDA 210868
Table of Contents

Chapter	Page
Executive Summary.....	1
Drug Substance Review.....	14
Drug Product Review.....	42
Environmental Analysis.....	68
Labelling.....	72
Method Verification.....	79
Process/Micro Review.....	81
Facilities Review.....	102
Biopharmaceutics Review.....	110

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LABELING

Note that the proprietary name “Lorbrena” has been provisionally accepted as of the time of this review

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	Lorbrena (lorlatinib)
Dosage form, route of administration	Tablets, for oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Film-coated tablets: 25 mg and 100 mg

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)	Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

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	Film-coated tablets
Strengths: in metric system	25 mg and 100 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable – the drug substance is not a salt or solvate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	25 mg: 8 mm round, tan, immediate release film-coated tablet, debossed with “Pfizer” on one side and “25” and “LLN” on the other side 100 mg: oval (8.5 mm x 17 mm), lavender, immediate release film-coated tablet, debossed with “Pfizer” on one side and “LLN 100” on the other side

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	LOBRENA (lorlatinib)
Dosage form and route of administration	Tablets for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable. The drug substance is not a salt or solvate.
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>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Tyrosine kinase inhibitor
Chemical name, structural formula, molecular weight	(10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4,8-methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile; Structure provided; MW = 406.41 Daltons
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Lorlatinib is a white to off-white powder with a pKa of 4.92. The solubility of lorlatinib in aqueous media decreases over the range pH 2.55 to pH 8.02 from 32.38 mg/mL to 0.17 mg/mL. The log of the distribution coefficient (octanol/water) at pH 9 is 2.45.

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	25 mg and 100 mg
Available units (e.g., bottles of 100 tablets)	30 count bottle
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	25 mg: 8 mm round, tan, immediate release film-coated tablet, debossed with "Pfizer" on one side and "25" and "LLN" on the other side 100 mg: oval (8.5 mm x 17 mm), lavender, immediate release film-coated tablet, debossed with "Pfizer" on one side and "LLN 100" on the other side
Special handling (e.g., protect from light)	Not applicable
Storage conditions	Store 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].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Pfizer Labs, Division of Pfizer Inc, NY, NY 10017

Reviewer's Assessment of Package Insert: Adequate
All Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

(b) (4)

2. Carton Label: NA

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	LOBRENA (lorlatinib); font size of proprietary name, established name, and strength are the most prominent fonts.
Dosage strength	25 mg and 100 mg
Net contents	30 Tablets
“Rx only” displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0069-0227-01 and 0069-0231-01
Lot number and expiration date (21 CFR 201.17)	Space provided
Storage conditions	Store at 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) [see USP Controlled Room Temperature].
Bar code (21CFR 201.25)	Example provided
Name of manufacturer/distributor	Pfizer Labs, Division of Pfizer Inc, NY, NY 10017
And others, if space is available	Not applicable

Reviewer’s Assessment of Labels: Adequate

Labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies: The applicant’s SPL is inconsistent with the package insert (the SPL is not part of the review template) and an information request was sent to the applicant to correct these inconsistencies. The applicant made the requisite changes to the SPL and is now consistent with the product label.

Overall Assessment and Recommendation: Labels are adequate from a CMC perspective

Primary Labeling Reviewer Name and Date: Olen Stephens; 24-Apr-18

Secondary Reviewer Name and Date: Anamitro Banerjee; 24-Apr-18



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Anamitro
Banerjee

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**U.S. FOOD & DRUG
ADMINISTRATION**

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: March 28, 2018

To: Olen Stephens, Drug Product Reviewer
Steven Kinsley, RBPM

Through: Connie Ruzicka, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Jeffrey T. Woodruff, Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, Ph.D., Method Verification Coordinator,
CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 210868: Lorlatinib 25mg and 100mg Tablets

The following method was evaluated and is acceptable for quality control and regulatory purposes:

1. Identity and Purity Determination of Lorlatinib in Lorlatinib Immediate Release Tablets by Reversed-Phase Liquid Chromatography (b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the method:



Original analyst worksheets can be viewed using this ECMS link:
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f881a2979d>

Summary of Analysis

**Identity and Purity Determination of Lorlatinib in Lorlatinib Immediate Release Tablets
by Reversed-Phase Liquid Chromatography (b) (4)**

Identity 25mg and 100mg Tablets		
Identity Limit	25mg Sample Lorlatinib RT(min)	100mg Sample Lorlatinib RT(min)
(b) (4)	(b) (4)	(b) (4)
	Pass	Pass
%Degradation		
25mg Sample Lorlatinib	100mg Sample Lorlatinib	
No degradation	No degradation	

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BIOPHARMACEUTICS

NDA: 210868

Drug Product Name / Strength: Lorlatinib Film-Coated Tablet, 25 mg and 100 mg Strengths

Route of Administration: Oral

Applicant Name: Pfizer, Inc.

Background: Pfizer, Inc. is seeking approval for Lorlatinib immediate-release film-coated tablets, 25 mg and 100 mg, to be administered orally once daily for the treatment of anaplastic lymphoma kinase (ALK)-positive (b) (4) positive non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors *via* the 505 (b) (1) regulatory path.

In the current submission, the Applicant provided relative bioavailability (rBA) data from Study B7461005 that compared the rBA of tablets containing lorlatinib (b) (4) (Form 3) verses tablets containing lorlatinib Form 7. In addition, the current submission contains data from a Phase I/II safety and efficacy study (Study B7461001) that was conducted in patients with ALK-positive advanced NSCLC or patients with ROS1-positive advanced NSCLC using undebossed 25 mg drug product with (b) (4) % w/w lorlatinib Form 7 and a (b) (4) white film-coating .

The 25 mg strength TBM drug product is same as the 25 mg tablet used in the Phase II safety and efficacy study (Study B7461001) except for a tan film-coating and presence of debossing. The Applicant provided in vitro dissolution data to bridge the two formulations that will be discussed in later sections.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated the overall dissolution data supporting; **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, and **3)** the bridging of the formulations throughout the product development process due to formulation and manufacturing process changes.

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

- 1) Proposed Dissolution Method:** The dissolution method for the proposed drug product was developed using USP Apparatus 2 at a paddle speed of 100 rpm in 900 mL pH 4.5 acetate buffer. The proposed dissolution method has the ability to detect certain changes in the formulation and manufacturing process. The proposed dissolution method described below is acceptable for dissolution testing of the 25 mg and 100 mg strengths at batch release and for stability testing.

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 100 rpm
Media/Volume	pH 4.5 acetate buffer /900 mL
Bath temperature	37.0±0.5°C

- 2) **Proposed Dissolution Acceptance Criterion:** The dissolution acceptance criterion proposed by the Applicant for the Lorlatinib Tablets, 25 mg and 100 mg strength is permissive. The dissolution data for the three registration batches support the dissolution acceptance criterion of Q $\frac{(b)}{(4)}$ % in 45 minutes at batch release and for stability testing for each strength of the drug product. In response to an IR comment, the Applicant agreed to the recommended dissolution acceptance criterion of Q= $\frac{(b)}{(4)}$ in 45 minutes at batch release and for stability testing for 25 mg and 100 mg strength of Lorlatinib Tablets.

Recommended Dissolution Acceptance Criterion	Q $\frac{(b)}{(4)}$ % in 45 minutes for 25 mg and 100 mg Lorlatinib Film-Coated Tablets
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- 3) **Bridging of the Formulations:** The Applicant provided adequate in vitro dissolution data to support the bridge between the white, undebossed, film-coated 25 mg strength tablet used in the Phase II Study B7461001 and the tan, debossed, film-coated 25 mg strength TBM drug product; the similarity factor ' f_2 ' as calculated by this Reviewer was 76.98 ($f_2 > 50$), indicating that the dissolution profiles are similar. In addition, the similarity factor ' f_2 ' between the 25 mg strength TBM drug product (Lot N57273) and the 100 mg strength TBM drug product (Lot N68193) as calculated by this Reviewer was 63.44 ($f_2 > 50$), indicating that the dissolution profiles for the 25 mg and 100 mg strength TBM drug products are similar.

4) **Biopharmaceutics Risk Assessment:**

Lorlatinib is a basic drug substance that exhibits pH-dependent solubility with low solubility in water (0.17 mg/mL) and in buffer solutions at pH > 4.58. However, lorlatinib is highly soluble in 0.1 N HCl (pH 2.55) in line with its basic chemical structure. Because of its low solubility in water and basic pH, particle size distribution (PSD) of lorlatinib was considered a CQA during the product development process. In order to ensure batch-to-batch consistency in terms of in vitro and vivo performance, the Applicant proposed $D_{90} = \text{NMT } \frac{(b)}{(4)} \mu\text{m}$ as the particle size specification for lorlatinib drug substance to be used in the manufacture of all the clinical batches. The Applicant provided sufficient in vitro and in vivo data to support the proposed $D_{90} = \text{NMT } \frac{(b)}{(4)} \mu\text{m}$ as the particle size specification for lorlatinib drug substance. In addition, the Applicant manufactured 25 mg and 100 mg TBM variant formulations with $D_{90} = \frac{(b)}{(4)} \mu\text{m}$ for the drug substance. The dissolution profile of the 25 mg TBM variant formulation was not impacted by the change in particle size of the drug substance. However, the release of lorlatinib from the 100 mg strength containing drug substance with particle size = $\frac{(b)}{(4)} \mu\text{m}$ was attenuated, with $\frac{(b)}{(4)}\%$ release of lorlatinib within $\frac{(b)}{(4)}$ minutes. The CMC information related to the control strategy(ies) regarding the PSD will be reviewed by the CMC Reviewer(s).



QUALITY ASSESSMENT Chapter VII-Biopharmaceutics



➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 210868 for Lorlatinib Film-Coated Tablet, 25 mg and 100 mg Strengths is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD **04/17/2018**

Secondary Biopharmaceutics Reviewer Name and Date:

Okpo Eradiri, PhD **04/23/2018**

OVERALL BIOPHARMACEUTICS RECOMMENDATION:

Based on the review of the overall information, from the Biopharmaceutics perspective NDA 210868 for Lorlatinib Film-Coated Tablet, 25 mg and 100 mg is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
Original NDA Submission 210868	\\cdsesub1\evsprod\nda210868\0001\m1\us\cover.pdf , 12/05/2017, SDN 1
Response to Information Request Comment #1	\\cdsesub1\evsprod\nda210868\0009\m1\us\ir-response.pdf , 02/12/2018, SDN 9
Response to Information Request Comment #2	\\cdsesub1\evsprod\nda210868\0027\m1\us\ir-response-27mar2018-qqr1.pdf , 04/10/2018, SDN 27

➤ **DRUG PRODUCT:**

The proposed drug product will be available as immediate-release, round, debossed, film-coated 25 mg strength tablets, and as oval, debossed, film-coated 100 mg strength tablets containing lorlatinib, a small-molecule, selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK or ROS -1 receptor tyrosine kinase for the treatment of adult patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK-tyrosine kinase inhibitors (TKI). The recommended dose is 100 mg to be taken orally once daily.

The two strengths of the drug product (b) (4) The qualitative and quantitative composition of the 25 mg and 100 mg strength proposed TBM drug product are provided in **Table IIa-Table IIc**.

**Table IIa . Qualitative and Quantitative Composition of the
TBM Lorlatinib Film-coated Tablet, 25 mg Strength**

Name of Ingredients	Function	Reference to Standard	Unit Formula mg/tablet
Lorlatinib	Active	Pfizer	25.000 ^a
Microcrystalline Cellulose	(b) (4)	NF/Ph. Eur./JP	(b) (4)
Dibasic Calcium Phosphate Anhydrous		USP/Ph. Eur./JP	
Sodium Starch Glycolate		NF/Ph. Eur./JP	
Magnesium Stearate		NF/Ph. Eur./JP	
(b) (4)			
		Pfizer	
		USP/Ph. Eur./JP	
Total Finished Tablet Weight			

Note: NF = National Formulary; USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopeia; JP = Japanese Pharmacopeia

^a (b) (4)
(u) (4)

**Table IIb . Qualitative and Quantitative Composition of the
TBM Lorlatinib Film-coated Tablet, 100 mg Strength**

Name of Ingredients	Function	Reference to Standard	Unit Formula mg/tablet
Lorlatinib	Active	Pfizer	100.000 ^a
Microcrystalline Cellulose	(b) (4)	NF/Ph. Eur./JP	(b) (4)
Dibasic Calcium Phosphate Anhydrous		USP/Ph. Eur./JP	
Sodium Starch Glycolate		NF/Ph. Eur./JP	
Magnesium Stearate		NF/Ph. Eur./JP	
		Pfizer	
		USP/Ph. Eur./JP	
Total Finished Tablet Weight			

Note: NF = National Formulary; USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopeia; JP = Japanese Pharmacopeia

^a

(b) (4)

(b) (4)

**Table IIc . Qualitative and Quantitative Composition of the
Film-Coating (b) (4) for the TBM Lorlatinib Film-coated Tablet**

Name of Ingredients	Reference to Standard	(b) (4)	
		Tan Formula % w/w (for 25 mg Tablet)	Lavender Formula % w/w (for 100 mg Tablet)
HPMC 2910/Hypromellose	USP, Ph. Eur., JP	(b) (4)	(b) (4)
Lactose Monohydrate	NF, Ph. Eur., JP		
Macrogol (b) (4)/PEG 3350	NF, FCC, Ph. Eur., JECFA, JP		
Triacetin	USP, FCC, Ph. Eur., JPE		
Titanium Dioxide	USP, FCC, Ph. Eur., JP		
Ferrosoferric Oxide/Black Iron Oxide	NF/JPE		
Iron Oxide Red	NF, JPE		

Note: NF = National Formulary; USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopeia; FCC = Food Chemicals Codex; JECFA = Joint FAO/WHO Expert Committee on Food Additives; JP = Japanese Pharmacopeia; JPE = Japanese Pharmaceutical Excipients

The 25 mg strength product is an 8 mm diameter round (b) (4) tablet that contains (b) (4) % w/w lorlatinib. On the other hand, the 100 mg strength TBM product is an 8.5 mm × 17 mm diameter oval tablet containing (b) (4) % w/w lorlatinib. The drug product is composed of microcrystalline cellulose, sodium starch glycolate, dibasic calcium phosphate, and magnesium stearate. (b) (4)

(b) (4)

(b) (4)

Applicant provided in vitro dissolution data and in vivo BA/BE data for the 25 mg drug product that was used in the Phase II safety and efficacy study and the TBM drug product which will be reviewed in later sections.

A variety of formulations were manufactured for Phase I, Phase II, and Phase III clinical studies that included immediate-release tablets, extemporaneously prepared tablets, intravenous solution, and extemporaneously prepared oral solutions. (b) (4)

Formulations containing the (b) (4) (Form 1), (b) (4) (Form 3), and Form 7 were manufactured and used for Phase I, Phase II, and Phase III clinical studies.

In the Phase I clinical study B7461001, (b) (4) Form 3 was evaluated. (b) (4)
On further (b) (4) screening, (b) (4) (Form 1) and Form 7 were selected. A BA Study B7461005 was conducted that compared the relative BA of tablets containing lorlatinib (b) (4) (Form 1), (b) (4) (Form 3), and Form 7. According to the Applicant, all three forms exhibited comparable bioavailability in the rBA Study B7461005. Form 7 was found to exhibit optimal physicochemical properties as compared to Form 1 and Form 3. Form 7 was therefore selected as the solid-state Form for the TBM drug product and in the Phase II study B7461001.

The Phase II clinical study (Study B7461001) was also conducted with undebossed 25 mg drug product with (b) (4)% w/w lorlatinib Form 7 and a (b) (4) white film-coating. However, the 25 mg TBM product will be a debossed tablet with a tan (b) (4) film-coating containing (b) (4)% w/w lorlatinib Form 7. Dissolution data to bridge the 25 mg and 100 mg Form 7 drug product will be evaluated in the later sections.

Manufacturing Sites for the Proposed Drug Product

Formulations that were used in the Phase I, Phase II, and Phase III clinical studies were manufactured at Pfizer facilities in Groton (USA), Sandwich (UK), and in Freiburg (DE). The bio-batches used in the BA Study B7461016 and the registered stability batches for the 25 mg (Lot N57273) and the 100 mg (Lot N68193) Form 7 TBM drug product were manufactured in Freiburg, Germany. Therefore no bridging is warranted as a single manufacturing site was used for the production of clinical and stability batches for both the 25 mg and the 100 mg Form 7 TBM drug product.

➤ **BCS DESIGNATION**

Reviewer's Assessment: Adequate

The active ingredient in the proposed product is lorlatinib ($C_{21}H_{19}FN_6O_2$) which is a crystalline, non-hygroscopic, and a basic drug that exhibits pH-dependent solubility profile (see **Table 1**).

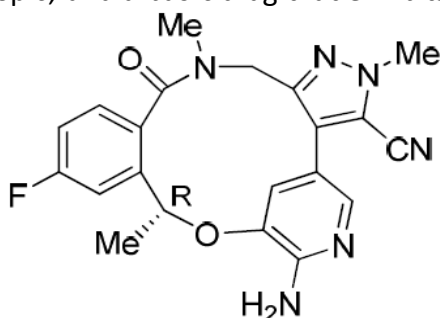


Figure I: Chemical structure of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4,8-methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile

The molecular weight of the drug substance is 406.41 Da. Lorlatinib has one asymmetric center and therefore exhibits two possible stereoisomers. The pKa of lorlatinib is 4.92 due to the pyridinyl nitrogen. The LogP and LogD of lorlatinib is 2.45 at pH 9.0. (b) (4)

(b) (4) Lorlatinib Form 1 is the (b) (4), Form 3 is the (b) (4), whereas Form 7 which is the anhydrous free base is the most stable (b) (4)

(b) (4) All three forms exhibit similar bioavailability (BA) profile in the relative BA Study B7461005 that will be reviewed by the Office of Clinical Pharmacology. In addition, the Applicant indicates that there is no change in the solid state Form 7 (b) (4) therefore Form 7 was used in the manufacture of the TBM drug product. (b) (4)

• **Solubility:**

The drug substance exhibits pH-dependent solubility, with highest solubility at low pH values. The solubility profile of the drug substance Form 7 (batch E010016161) was determined in water and in buffer solutions across the physiological pH range of 2.55-8.02 (b) (4) (see **Table I**). From **Table 1**, it can be concluded that the drug substance exhibits low solubility in water (0.17 mg/mL) and in buffer solutions at pH>4.58. However, Lorlatinib is highly soluble in 0.1 N HCl (pH 2.55) in line with its basic chemical structure.

According to the Applicant, the highest dose ie. 100 mg is not soluble in 250 mL buffer solutions at pH>4.58. However, 100 mg dose is completely soluble in 250 mL buffer solutions at pH<4.58.

Table 1. Thermodynamic Solubility Profile of Lorlatinib Form 7 (Batch E010016161) in Water and Buffer Solutions Across Physiological pH Range 2.55-8.02

Aqueous solubility	Solubility (mg/mL)
Water (pH 8.02)	0.17
0.1N HCl (pH 2.55)	32.38
0.05M Acetate buffer (pH 4.58)	0.37
0.05M Phosphate buffer (pH 6.86)	0.1

Reviewer's Assessment of Lorlatinib Drug Substance and Drug Product Solubility:

From **Table I**, it can be concluded that lorlatinib exhibits pH-dependent low solubility profile in basic pH>4.58. However, the basic drug substance exhibits high solubility profile in acidic pH=2.55. The 25 mg strength drug product would be classied as a highly soluble drug product across the physiological pH range. However, the 100 mg strength drug product would be classied as a low soluble drug product at pH≥4.58.

- **Permeability:**

According to the Applicant, lorlatinib exhibits low permeability profile that was inferred based on the data from two clinical studies.

In the first study, the absorption profile of lorlatinib was determined in the ADME (Absorption, Distribution, Metabolism, and Excretion) Study B7461004 conducted in healthy subjects with a single oral dose of 100 mg lorlatinib (b) (4) (Form 3) tablets spiked with 100 µCi ¹⁴C-labeled lorlatinib. According to the Applicant, approximately 47.73% of the administered radioactive dose was recovered in the urine and 40.91% was recovered in the feces unchanged over 288 hours.

In the second study, the absolute bioavailability of lorlatinib Form 7 tablets was determined under fasted conditions in Study B7461007 following oral administration of 4×25 mg tablets in comparison to a single 50 mg intravenous (IV) dose. The absolute bioavailability of lorlatinib Form 7 tablets was determined to approximately 80.78%.

Reviewer's Assessment of Lorlatinib Absorption:

Based on the information provided in the mass balance study (# B7461004) and the absolute bioavailability Study B7461007, it can be concluded that 25 mg and 100 mg strength lorlatinib Form 7 and Form 3 tablets exhibit low gastro-intestinal permeability.

➤ **DISSOLUTION INFORMATION:**

Because the drug substance exhibits low aqueous solubility, dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product. The Applicant utilized the dissolution test throughout the proposed drug product development process across the different manufacturing processes, for the batches used in the pivotal clinical PK studies, and for batches on stability. The dissolution method was also used to select the final drug product formulation and final manufacturing process.

➤ **PROPOSED DISSOLUTION METHOD:**

Based on the overall dissolution data provided by the Applicant to optimize the release of lorlatinib from the proposed drug product, 100 rpm paddle speed using standard USP II apparatus in 900 mL pH 4.5 acetate buffer provides the optimal release characteristics of lorlatinib from the 25 mg and 100 mg drug product. Therefore, the Applicant's selection of 100 rpm as the paddle speed using standard USP II apparatus in 900 mL pH 4.5 acetate buffer for the dissolution testing of the proposed drug product is justified and acceptable.

4. Discriminating Power of the Proposed Dissolution Method:

The discriminating power of the proposed dissolution method was evaluated to ascertain that the developed dissolution method could detect manufacturing and/or process changes. The Applicant assessed a number of critical quality attributes (CQA) that could have an impact on the quality of the proposed drug product. The tablet hardness, (b) (4) (b) (4) film-coating levels, (b) (4) and particle size distribution (PSD) of the drug substance were identified as CQAs that could alter the dissolution profile of the drug product as lorlatinib exhibits low aqueous solubility. The Applicant manufactured 25 mg and 100 mg strength drug product with the variations in the manufacturing process as noted in **Table III**.

Table III. Variations in Manufacturing Process of the 25 mg and 100 mg Strength Drug Product to Evaluate the Discriminatory Power of the Proposed Dissolution Method

	25 mg TBM Drug Product	100 mg TBM Drug Product
Tablet Hardness	(b) (4)	
Film-coating Levels		

D ₉₀ PSD	(b) (4)	
Composite Abberation (All variations)	+	+

The dissolution profile for the 25 mg and 100 mg strengths manufactured with the variations in tablet hardness, (b) (4), film-coating levels, (b) (4) and particle size distribution (PSD) of the drug substance using the proposed dissolution method are shown in **Figure IV: Panel A** and **Panel B**, respectively. The dissolution profile for the 25 mg and 100 mg strength drug product manufactured with all the variations in the manufacturing process and labeled as 'composite aberrant' is also provided in **Figure IV: Panel A** and **Panel B**, respectively.

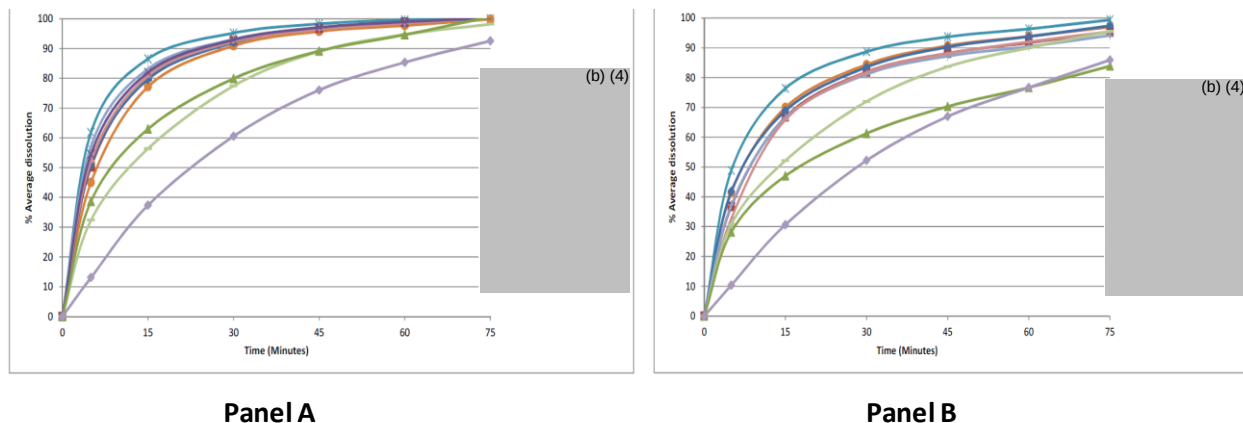


Figure IV. Dissolution Profile for Variations in the Manufacturing Process of the 25 mg and 100 mg Strength Drug Product to Evaluate the Discriminatory Power of the Proposed Dissolution Method

From **Figure IV**, Panel A and Panel B, it can be concluded that for both 25 mg and 100 mg strengths, variations in tablet hardness, (b) (4), film-coating levels, (b) (4) did not have an impact on the dissolution profile, (b) (4)

Though the dissolution rate for the 25 mg drug product manufactured with lorlatinib drug substance with particle size (D₉₀) (b) (4) μm and (b) (4) μm and the composite aberrant drug product was significantly slower as compared to the control drug product, > (b) (4)% release of lorlatinib was reached within (b) (4) minutes for the 25 mg product and the composite aberrant drug product. Lorlatinib is a basic drug substance that exhibits pH-dependent solubility with low solubility in water (0.17 mg/mL) and in buffer solutions at pH>4.58. However, it is highly soluble in 0.1 N HCl (pH 2.55) in line with its basic chemical structure. Because of its low solubility in water and basic

pH, the Applicant proposed $D_{90} = \text{NMT } (b)(4) \mu\text{m}$ as the particle size specification for lorlatinib drug substance to be used in the manufacture of the 25 mg and 100 mg clinical batches. The Applicant provided sufficient in vitro and in vivo data to support the proposed $D_{90} = \text{NMT } (b)(4) \mu\text{m}$ as the particle size specification for lorlatinib drug substance. Because the 25 mg drug substance shows high aqueous solubility, particle size would not have a significant impact on the dissolution rate of the 25 mg drug product.

Similar dissolution profile was obtained for the 100 mg drug product manufactured with lorlatinib drug substance of particle size (D_{90}) = $(b)(4) \mu\text{m}$ as the 25 mg drug product. However, for the 100 mg drug product manufactured with lorlatinib drug substance of particle size (D_{90}) $(b)(4) \mu\text{m}$, $(b)(4)\%$ release of lorlatinib is observed within $(b)(4)$ minutes. Lorlatinib release profile from 100 mg drug product manufactured with lorlatinib drug substance of particle size (D_{90}) = $(b)(4) \mu\text{m}$ was similar to that of the composite aberrant drug product. Because the 100 mg drug substance exhibits low aqueous solubility, particle size (D_{90}) $(b)(4) \mu\text{m}$ would have an impact on the dissolution rate of the 100 mg drug product as supported by the provided dissolution data. This study highlights the negative influence of higher particle size ($D_{90} (b)(4) \mu\text{m}$) on the dissolution rate of the 100 mg drug product and can be used to support the discriminating ability of the proposed dissolution method.

Reviewer's Assessment:**Overall Reviewer's Assessment of the Proposed Dissolution Method:**

The Applicant proposed USP Apparatus II at 100 rpm paddle speed in pH 4.5 acetate buffer at 37°C as the dissolution method for the dissolution testing of the 25 mg and 100 mg drug product. The proposed dissolution method has the ability to detect limited changes in the formulation and manufacturing process based on the information provided in the current submission. The proposed dissolution method has not been shown to reject batches with unacceptable tablet hardness, $(b)(4)$, film-coating levels, and $(b)(4)$ for the 25 mg drug product as 25 mg drug substance shows high aqueous solubility. However, the proposed dissolution method can reject batches of 100 mg drug product with particle size (D_{90}) $(b)(4) \mu\text{m}$.

From a Biopharmaceutics perspective, the proposed dissolution method is adequate for batch release and stability testing of the produced FDC drug product. The analytical method (HPLC/UV) associated with the proposed dissolution method will be evaluated by the CMC Reviewer.

➤ PROPOSED DISSOLUTION ACCEPTANCE CRITERION:

The Applicant proposed 'Q = $(b)(4)\%$ in $(b)(4)$ minutes' as the dissolution acceptance criterion for batch release and stability testing of the 25 mg and 100 mg strength Lorlatinib Film-Coated Tablets

Reviewer's Assessment of the Proposed Dissolution Acceptance Criterion:

A review of the dissolution data for the 25 mg and 100 mg strength clinical batch used in the Phase II study (shown in **Table IV** and **Figure Va**) indicates that the dissolution data support the dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 45 minutes for both strengths of the drug product. Based on the dissolution data presented in **Table IV**, the following dissolution acceptance criterion is recommended for the drug product:

Recommended Dissolution Acceptance Criterion Lorlatinib Film-Coated Tablets, 25 mg and 100 mg	$Q = \frac{(b)}{(4)}\%$ in 45 minutes
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Table IV. Dissolution Profile Data for the TBM 25 mg and 100 mg Products Used in the Phase II Clinical Study using the Proposed Dissolution Method

4 x 25 mg Phase 2 Clinical Tablet – Lot 15-004850

Time (mins)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	Min	Max	Standard Deviation	%RSD
0	(b) (4)												0	(b) (4)		0.0	
5													39			1.7	4.5
15													70			1.2	1.7
30													84			1.0	1.2
45													89			1.1	1.3
60													92			0.9	0.9

4 x 25 mg Proposed Commercial Tablet – Lot N57273

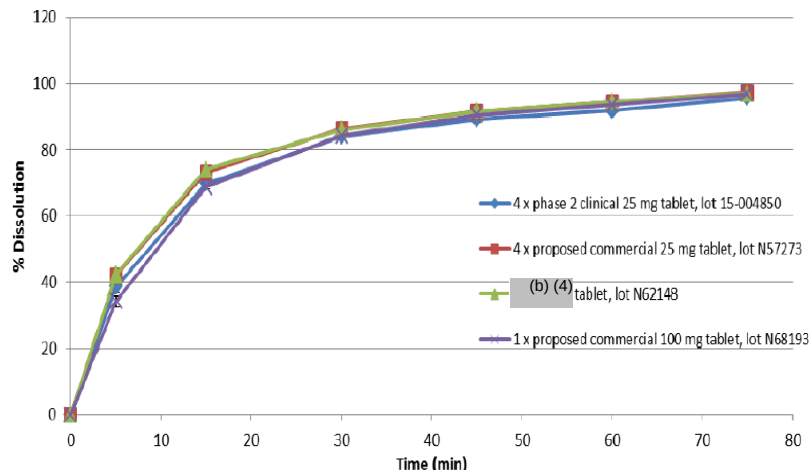
Time (mins)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	Min	Max	Standard Deviation	%RSD
0	(b) (4)												0	(b) (4)		0.0	
5													42			1.9	4.5
15													73			0.8	1.1
30													86			0.6	0.7
45													91			0.8	0.9
60													94			0.8	0.8

1 x 100 mg Proposed Commercial Tablet – Lot N68193

Time (mins)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	Min	Max	Standard Deviation	%RSD
0	(b) (4)												0	(b) (4)		0.0	
5													34			1.7	4.8
15													69			0.6	0.9
30													84			0.5	0.5
45													90			0.5	0.6
60													94			0.7	0.7

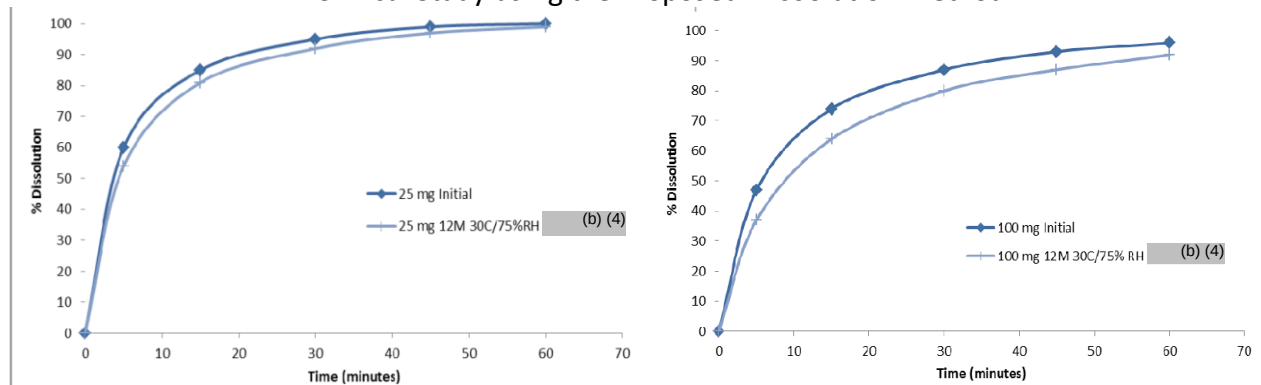
An Information Request was conveyed to the Applicant on 04/10/2018 recommending a dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 45 minutes for 25 mg and 100 mg strength of the drug product.

Figure Va . Dissolution Data at Release for TBM 25 mg and 100 mg Products Used in the Phase II Clinical Study using the Proposed Dissolution Method



The recommended dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 45 minutes for the 25 mg and 100 mg strength TBM drug product is also supported by the dissolution data provided in the batch analyses record and 12 month stability data at 30°C/75% RH for 25 mg and 100 mg strength TBM drug product in $\frac{(b)}{(4)}$ count bottles as shown in **Figure Vb** and **Table V**.

Figure Vb. Dissolution Data on Stability for TBM 25 mg and 100 mg Products Used in the Phase II Clinical Study using the Proposed Dissolution Method



From **Figure Vb**, it can be concluded that for the 25 mg drug product there is no change in the dissolution data on stability at 30°C/75% RH for 12 months. However, for the 100 mg drug product, there is a slight downward trend in the release of lorlatinib on stability at 30°C/75% RH for 12 months using the proposed dissolution method (see **Table V**). The Applicant attributes this downward trend to the $\frac{(b)}{(4)}$

Due to the low solubility of the drug substance at pH>4.5 and insoluble excipients, (b) (4) is more pronounced for the 100 mg strength (**eCTD Module 3.2.P.2.2**). The dissolution profile for the 25 mg drug product manufactured with drug substance of particle size range (D_{90}) between (b) (4) (b) (4) μm exhibits (b) (4) % release of the drug substance within (b) (4) minutes. However, similar trend is not observed in the dissolution profile of the 100 mg drug product with drug substance of particle size= (b) (4) μm (**eCTD Module Figure 3.2.P.2.2-19**). According to this Reviewer, the (b) (4) effect for the 100 mg drug product is probably because (b) (4) (b) (4) μm and (b) (4) μm in diameter. This could also contribute to the slower dissolution rate observed for the 100 mg drug product.

In response to the Information Request (04/10/2018), the Applicant agreed to the recommended dissolution acceptance criterion of 'Q= (b) (4) % in 45 minutes' for 25 mg and 100 mg strengths of the drug product. In addition, the Applicant updated the final drug product specification table in eCTD modules 2.3.P.5 and 8, and stability specification table in eCTD modules 3.2.P.5.1, 5.6, 8.1, and 8.3 accordingly to reflect the updated dissolution acceptance criterion of 'Q (b) (4) % in 45 minutes' for the dissolution testing of 25 mg and 100 mg strengths of Lorlatinib Tablets.

➤ **IN VITRO DISSOLUTION DATA TO BRIDGE THE 25 MG AND 100 MG TBM DRUG PRODUCTS**

The 25 mg strength Form 7 drug product used in the Phase II safety and efficacy study (Study B7461001) was a white, undebossed, film-coated tablet. However, the 25 mg strength Form 7 TBM drug product will be a tan, debossed, film-coated tablet. In order to bridge the two formulations, the Applicant provided in vitro dissolution data as shown in **Table IV**. The similarity

factor 'f2' value as calculated by this Reviewer was 76.98 ($f2 > 50$), indicating that the dissolution profiles are similar. In addition, the Applicant provided dissolution profile data for the 100 mg strength Form 7 TBM drug product (Lot N68193) as shown in **Table IV**. The similarity factor 'f2' value between the dissolution profile data for the 25 mg strength TBM drug product (Lot N57273) and the 100 mg strength TBM drug product (Lot N68193) as calculated by this Reviewer is 63.44 ($f2 > 50$), indicating that the dissolution profiles are similar.

➤ **IN VIVO BIOEQUIVALENCE STUDY TO ASSESS THE EFFECT OF FORMULATION CHANGES ON THE PHARMACOKINETICS OF the Proposed Drug Product:**

In order to bridge the white, undebossed, 25 mg strength Form 7 drug product used in the Phase II safety and efficacy study (Study B7461001) with the tan, debossed, film-coated tablet 25 mg strength Form 7 TBM drug product, the Applicant conducted a bioavailability (BA) study B7461016 under fasted conditions. In addition, the Applicant conducted BE studies to bridge the 25 mg TBM drug product with the 100 mg TBM drug product. The pharmacokinetic (PK) parameters following single oral doses of 4×25 mg white, undebossed, film-coated tablet 25 mg strength Form 7 drug product, 4×25 mg tan, debossed, film-coated tablet 25 mg strength Form 7 TBM drug product, and 1×100 mg TBM drug product is shown in **Table VI a**. The statistical analysis of the PK data is shown in **Table VI b**.

Table VI a. Pharmacokinetic (PK) Parameters following Single Oral Doses of Phase II and TBM 25 mg and 100 mg Drug Products

Parameter (Units)	PF-06463922 Clinical 4 x 25 mg Tablets	PF-06463922 Commercial 4 x 25 mg Tablets	PF-06463922 Commercial 1 x 100 mg Tablet
N, n	20,20	20,20	20,20
AUC _{inf} (ng*hr/mL)	7683 (18)	7769 (21)	8054 (19)
AUC _{last} (ng*hr/mL)	7482 (18)	7526 (21)	7785 (19)
C _{max} (ng/mL)	532.0 (25)	567.3 (28)	569.3 (34)
T _{max} (hr)	1.50 (0.500 – 2.00)	1.04 (0.500 – 4.00)	1.50 (1.00 – 4.00)
T _{1/2} (hr)	22.36 ± 4.68	23.28 ± 6.04	24.05 ± 5.98

Note: The dissolution data for the drug product batches used in study B7461016 are presented in [Figure 3.2.P.2.2-4](#).

Table VI b. Statistical Analysis of the Pharmacokinetic (PK) Parameters following Single Oral Doses of Phase II and TBM 25 mg and 100 mg Drug Products

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio
	Test	Reference		
PF-06463922 Commercial 4 × 25-mg Tablets (Test 1) Versus PF-06463922 Clinical 4 × 25-mg Tablets (Reference)				
AUC _{inf} (ng•hr/mL)	7769	7683	101.12	(97.530, 104.84)
AUC _{last} (ng•hr/mL)	7526	7482	100.59	(97.194, 104.10)
C _{max} (ng/mL)	567.3	532.0	106.64	(96.416, 117.95)
PF-06463922 Commercial ^{(b) (4)} Tablets (Test 2) Versus PF-06463922 Clinical 4 × 25-mg Tablets (Reference)				
AUC _{inf} (ng•hr/mL)	7770	7683	101.14	(97.554, 104.87)
AUC _{last} (ng•hr/mL)	7539	7482	100.76	(97.366, 104.28)
C _{max} (ng/mL)	539.8	532.0	101.47	(91.742, 112.23)
PF-06463922 Commercial 1 × 100-mg Tablet (Test 3) Versus PF-06463922 Clinical 4 × 25-mg Tablets (Reference)				
AUC _{inf} (ng•hr/mL)	8054	7683	104.84	(101.12, 108.70)
AUC _{last} (ng•hr/mL)	7785	7482	104.05	(100.54, 107.68)
C _{max} (ng/mL)	569.3	532.0	107.02	(96.758, 118.37)

Abbreviation: CI = confidence interval.

a. The ratios (and 90% CIs) are expressed as percentages.

From **Table VI a** and **Table VI b**, it can be seen that following single oral doses of 100 mg Phase II and TBM 25 mg and 100 mg drug products, the C_{max} (ng/mL) are 532-569 ng/mL, AUC_{inf} (ng.hr/mL) are 7482-7785 ng.hr/mL, T_{max} are 1.04-1.50 hours, with long terminal half-life (T_{1/2}) of 22.36-24.05 hours for the three formulations. The 25 mg Phase II and TBM formulations were bioequivalent with geometric mean ratios (90% confidence interval) for the C_{max} (ng/mL) and AUC_{inf} (ng.hr/mL) between 96.416%-117.95% and 97.530%-104.84%, respectively. The 25 mg and 100 mg TBM formulations were bioequivalent with geometric mean ratios (90% confidence interval) for the C_{max} (ng/mL) and AUC_{inf} (ng.hr/mL) between 96.758%-118.37% and 101.12%-108.70%, respectively.

➤ **BIOPHARMACEUTICS RISK ASSESSMENT:**

• *Effect of Particle Size on the Drug Product Performance*

Lorlatinib is a basic drug substance that exhibits pH-dependent solubility profile with low solubility in water (0.17 mg/mL) and in buffer solutions at pH>4.58 (see **Table 1**). However, lorlatinib is highly soluble in 0.1 N HCl (pH 2.55) in line with its basic chemical structure. Because of its low solubility profile in water and basic pH, particle size distribution (PSD) of lorlatinib was considered a CQA during the product development process. In order to ensure batch-to-batch consistency in terms of in vitro and vivo performance, the Applicant controlled the PSD of the drug substance, Form 7, used in the manufacture of all the clinical batches (see **Table VII**).

Table VII. Particle Size Distribution of the Lorlatinib Form 7 used in the Manufacture of Clinical Batches of the TBM Drug Product

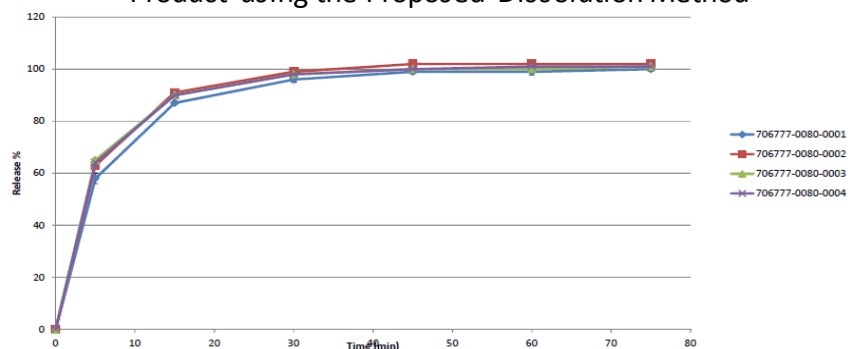
Lot Number	D[v,0.9] (µm)
E010016159	(b) (4)
E010016161	
E010016420	
E010016426	
E010016714	
E010016728	
E010016887	
E010016913	
E010016921	
E010017344	
E010017548	
E010017652	
E010017657	
E010017668	

The D₉₀ of the drug substance, Form 7, used in all the clinical batches manufactured were between (b) (4) µm (see **Table VII**). In order to evaluate the impact of PSD on the in vitro dissolution profile of the drug product, two Lots of 25 mg TBM drug product were manufactured with particle size of D₉₀ (b) (4) µm and (b) (4) µm (see **Table VIII**). The in vitro dissolution profile for the four lots of the 25 mg TBM drug product with drug substance PSD between (b) (4) µm and (b) (4) µm is shown in **Figure VI**.

Table VIII. Particle Size Distribution of the Lorlatinib Form 7 used in the Evaluation of the Effect of Particle Size on the Dissolution Profile of the Drug Product

Tablet Core Lot Number	Drug Substance Lot	D[v, 0.9] (µm)
00706777-0080-0001 00706777-0080-0003	E010016426	(b) (4)
00706777-0080-0002 00706777-0080-0004	E010017548 ^a	

^a Lot E010017548 was a development lot of drug substance which was reprocessed during manufacturing, resulting in a smaller particle size distribution compared to other lots

Figure VI. Effect of Particle Size Distribution on the Dissolution Profile of the 25 mg TBM Product using the Proposed Dissolution Method

From **Figure VI**, it can be concluded that the PSD of the drug substance between (b) (4) μm and (b) (4) μm has no impact on the dissolution profile of the 25 mg TBM product. Therefore, the Applicant proposed $D_{90}=\text{NMT}$ (b) (4) μm as the particle size specification for lorlatinib drug substance.

In addition to the in vitro dissolution data, the Applicant provided in vivo BA data for lot E010016426 with PSD D_{90} (b) (4) μm from the relative BA Study B7461008. According to the Applicant, the geometric mean ratios of AUC_{inf} (ng.hr/mL) for the 100 mg oral solution of lorlatinib drug substance Form 7 was comparable to the reference 4x25 mg tablets for lot E010016426 containing lorlatinib with PSD $D_{90}=\text{NMT}$ (b) (4) μm (90% CI=104.38%-111.50%) as shown in **Table IX a** and **Table IX b**.

Table IX a. Pharmacokinetic Parameters for the Relative BA Study B7461008 to Evaluate the Effect of Particle Size on the In Vivo Performance of the 25 mg TBM Drug Product

Parameter (Units)	Parameter Summary Statistics ^a by Treatment		
	Lorlatinib 100 mg Tablets With Overnight Fasting	Lorlatinib 100 mg Tablets With High-Fat Meal	Lorlatinib 100 mg Oral Solution
AUC_{last} (ng•hr/mL)	8191 (21)	8262 (22)	8789 (21)
C_{max} (ng/mL)	547.8 (20)	488.5 (26)	704.7 (22)
T_{max} (hr)	1.50 (0.500-2.02)	2.00 (1.00-6.00)	1.00 (0.500-1.50)
$t_{1/2}$ (hr)	24.2 (22)	23.7 (25)	24.1 (22)
CL/F (L/hr)	11.48 (24)	11.40 (24)	10.69 (24)
V_z/F (L)	390.6 (20)	378.2 (22)	361.1 (19)

Source: Module 5, Section 5.3.1.1, Study 1008 CSR In-text Table 12.

%CV=percent coefficient of variation; AUC_{inf} =area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} =area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; CL/F=apparent clearance; C_{max} =maximum-observed plasma concentration; CSR=clinical study report; hr=hour(s); N=number of subjects in the treatment group; n=number of subjects contributing to the summary statistics; $t_{1/2}$ =terminal half-life; T_{max} =time for C_{max} ; V_z/F =apparent volume of distribution.

^aGeometric mean (geometric %CV) for all except: median (range) for T_{max} ; arithmetic mean (%CV) for $t_{1/2}$.

Table IX b. Statistical Analysis of Pharmacokinetic Parameters for the Relative BA Study B7461008 to Evaluate the Effect of Particle Size on the In Vivo Performance of the 25 mg TBM Drug Product

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio
	Test	Reference		
Lorlatinib 100 mg Oral Solution (Test) vs Lorlatinib 100 mg Tablets (Reference)				
AUC _{inf} (ng•hr/mL)	9141	8473	107.88	(104.38, 111.50)
AUC _{last} (ng•hr/mL)	8602	7980	107.80	(104.40, 111.30)
C _{max} (ng/mL)	691.5	533.1	129.72	(121.18, 138.86)
Lorlatinib 100 mg Tablets With High-Fat Meal (Test) vs Lorlatinib 100 mg Tablets (Reference)				
AUC _{inf} (ng•hr/mL)	8874	8473	104.73	(101.28, 108.30)
AUC _{last} (ng•hr/mL)	8347	7980	104.61	(101.26, 108.06)
C _{max} (ng/mL)	484.5	533.1	90.89	(84.82, 97.40)

Source: Module 5, Section 5.3.1.1, Study 1008 CSR In-text Table 13.

AUC_{inf} =area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} =area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; CI=confidence interval; C_{max} =maximum-observed plasma concentration; CSR=clinical study report; hr=hour(s); vs=versus.

^aThe ratios (and 90% CIs) are expressed as percentages.

However, the geometric mean ratios of C_{max} (ng /mL) for the 100 mg oral solution of lorlatinib drug substance Form 7 was higher than the reference 4x25 mg tablets for lot E010016426 containing lorlatinib with PSD D₉₀= (b) (4) μm (90% CI=121.18%-138.86%) as shown in **Table IX a** and **Table IX b**. Therefore, the two formulations would be considered not bioequivalent. However, the OCP Reviewer (E. Chow) notes that the 100 mg oral solution and the 4x25 mg tablets of lorlatinib are bioequivalent.

On the other hand, the geometric mean ratios of C_{max} (ng /mL) for the 25 mg and 100 mg TBM formulations that were evaluated in BA Study B7461016 were between 96.758%-118.37%, respectively (see **Table VI b** of this Review) with C_{max} in the range of 532.0-569.3 ng/mL, which is similar to that obtained in the rBA Study B7461008. Taken together, it can be concluded that 25 mg TBM drug product containing lorlatinib with PSD D₉₀ (b) (4) μm shows comparable in vitro and in vivo performance. Therefore, the Applicant has provided sufficient in vitro and in vivo data to support the proposed D₉₀=NMT (b) (4) μm as the particle size specification for lorlatinib drug substance.

In addition, the Applicant manufactured 25 mg and 100 mg TBM aberrant formulations with (b) (4) μm for the drug substance as discussed under “**Discriminatory Power of the Proposed Dissolution Method**”. The dissolution profile data for the 25 mg TBM aberrant formulation indicates that the D₉₀= (b) (4) μm for the drug substance would have minimal impact on the release of lorlatinib from the 25 mg drug product. However, the release of lorlatinib from the 100 mg drug product containing drug substance of particle size = (b) (4) μm would be attenuated, with (b) (4) % release of lorlatinib within (b) (4) minutes. The CMC information related to the control strategy(ies) regarding the PSD will be reviewed by the CMC Reviewer(s). In addition the pharmacokinetic data for the BA Study B7461008 and B7461016 will be reviewed by the Clinical Pharmacology Reviewers.

➤ **POST-APPROVAL COMMITMENTS:** None

➤ **LIST OF DEFICIENCIES:** None

➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 210868 for Lorlatinib Film-Coated Tablet, 25 mg and 100 mg Strengths is recommended for **APPROVAL**.

➤ **SIGNATURES**

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD **04/10/2018**

Secondary Reviewer Name and Date:

Okpo Eradiri, PhD **04/23/2018**

APPENDIX I

Qualitative and Quantitative Composition of the Formulations used in the Relative Bioavailability Study B7461005

Drug Substance Form	(b) (4)	Form 7	(b) (4)
Drug Loading (% w/w)		(b) (4)	
Strength (mg)			
Shape			
Debossing	none	none	none
Component	Unit Composition (mg)		
Lorlatinib (b) (4) ^a	(b) (4)		
Lorlatinib (Form 7) ^b			
Lorlatinib (b) (4) ^c			
Microcrystalline Cellulose ^d			
Dibasic Calcium Phosphate Anhydrous			
Sodium Starch Glycolate			
Magnesium Stearate			
Total Tablet Weight			
	(b) (4)		

^b Based on the potency factor of 1.00 for lorlatinib (Form 7)

(b) (4)

Qualitative and Quantitative Composition of the Phase II and TBM Lorlatinib Formulations, 25 mg and 100 mg

Formulation Description	Phase 2 White Film-Coated	Proposed Commercial Tan Film-Coated	Lavender Film-Coated	Proposed Commercial Lavender Film-Coated
Drug Loading (% w/w)	(b) (4)			
Formulation ID number				
Strength				
Shape & dimensions				
Debossing				
Component				
Lorlatinib (Form 7) ^c				
Microcrystalline Cellulose ^d				
Dibasic Calcium Phosphate Anhydrous				
Sodium Starch Glycolate				
Magnesium Stearate				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
^c Based on a theoretical potency of 100%				
(b) (4)				

Table 3.2.P.2.2-6. Comparison of Phase 1 Acetic Acid Solvate Tablet Formulations, Phase 2 White Film-Coated, and Proposed Commercial Tablet Formulations

		Phase 1		(b) (4) Tablet Non	Phase 2 25 mg White Film- Coated Tablet	Proposed Commercial Debossed Tan 25 mg Film-Coated Tablets	(b) (4)	Proposed Commercial Debossed Lavender 100 mg Film-Coated Tablets
		Film-Coated Tablets		(b) (4) 25 mg			100 mg	
Composition	Drug Substance Form	(b) (4)				Form 7		
	(b) (4)					(b) (4) % w/w		(b) (4) % w/w
		(b) (4)						
	Film- Coating	Not used		(b) (4)	(b) (4) Tan	(b) (4)	(b) (4) Lavender	
			(b) (4)	(b) (4) 8.0 mm diameter Debossed "Pfizer" and "25" "LLN"		(b) (4) oval 8.5 mm x 17 mm Debossed "Pfizer" and "LLN 100"		
		(b) (4)						

Manufacturing Sites for the 25 mg and 100 mg TBM Lorlatinib Drug Product

Protocol Number	Drug Product Batch #	Drug Substance Batch #	Formulation Description	Formulation ID	Drug Substance Form	Drug Product Manufacturing Site
B7461001	13-109240 (CM-07613)	GR07117	(b) (4)	D1306523	(b) (4)	Groton
	13-109241 (CM-07713)	GR07117		D1306524		Groton
	13-108959 (CM-07813)	GR07117		D1306525		Groton
	14-003016	GR07970		D1306525		Groton
	14-004521	GR07970		D1306524		Groton
	14-003438	GR07970		D1306525		Groton
	15-001079	GR08852		D1306523		Groton
	14-005711	GR08852		D1306524		Groton
	15-001081	GR08852		D1306525		Groton
	15-002606	E010016159	PF-06463922 25mg round white film-coated tablet	D1500005	Form 7	Sandwich
	15-004169	E010016161	PF-06463922 25mg round white film-coated tablet	D1500005	Form 7	Sandwich
	15-005956	E010016420	PF-06463922 25mg round white film-coated tablet	D1500005	Form 7	Sandwich
	15-007274 (M60859) (H000010592)	E010016426	PF-06463922 25mg round white film-coated tablet	D1500005	Form 7	Freiburg

Manufacturing Sites for the 25 mg and 100 mg TBM Lorlatinib Drug Product, contd..

Protocol Number	Drug Product Batch #	Drug Substance Batch #	Formulation Description	Formulation ID	Drug Substance Form	Drug Product Manufacturing Site
B7461004	N/A (drug substance only)	PFX000229	(b) (4)			
B7461005	14-003438	GR07970				
	N/A (drug substance only)	GR08920	(b) (4)	N/A	Form 7	N/A
	N/A (drug substance only)	GR08927		N/A	(b) (4)	N/A
B7461007	16-001522 (P01716 - sub lot B)	E010016161		D1500212	Form 7	(b) (4)
	15-004850	E010016426		D1500005	Form 7	Sandwich
B7461008	15-004850	E010016426	PF-06463922 25 mg round white film-coated tablet	D1500005	Form 7	Sandwich
	N/A (drug substance only)	E010016159	(b) (4)	N/A	Form 7	N/A
B7461011	15-002606	E010016159	PF-06463922 25 mg round white film-coated tablet	D1500005	Form 7	Sandwich
B7461012	15-002606	E010016159	PF-06463922 25 mg round white film-coated tablet	D1500005	Form 7	Sandwich
	15-004850	E010016426	PF-06463922 25 mg round white film-coated tablet	D1500005	Form 7	Sandwich

Manufacturing Sites for the 25 mg and 100 mg TBM Lorlatinib Drug Product, contd..

Protocol Number	Drug Product Batch #	Drug Substance Batch #	Formulation Description	Formulation ID	Drug Substance Form	Drug Product Manufacturing Site
B7461016	15-004850	E010016426	PF-06463922 25 mg round white film-coated tablet	D1500005	Form 7	Sandwich
	16-003357 (N57273) (H000011600)	E010016921	PF-06463922 25 mg round tan film-coated tablet	D1500204	Form 7	Freiburg
	(b) (4)					
	16-003363 (N68193) (H000011702)	E010016921	PF-06463922 100 mg oval lavender film-coated tablet	D1600014	Form 7	Freiburg
(b) (4)						



Parnali
Chatterjee

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