

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213721Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213721 Assessment #1

Drug Product Name	GAVRETO (pralsetinib)	
Dosage Form	Capsule	
Strength	100 mg	
Route of Administration	Oral	
Rx/OTC Dispensed	Rx	
Applicant	Blueprint Medicines Corporation	
US agent, if applicable	N/A	
Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	03/23/20220	CMC
Quality Amendment	04/22/2020	DS, DP
Quality Amendment	05/07/2020	DP
Quality Amendment	05/14/2020	Biopharm
Quality Amendment	05/19/2020	DP
Quality Amendment	06/03/2020	OPMA
Quality Amendment	06/05/2020	OPMA
Quality Amendment	06/08/2020	DP
Quality Amendment	06/15/2020	DP
Quality Amendment	06/16/2020	EA
Labeling Amendment	06/23/2020	DP
Quality Amendment	06/29/2020	DP
Quality Amendment	07/07/2020	DP
Labeling Amendment	07/10/2020	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali Al Hakim
Drug Product	Yang Nan	Anamitro Banerjee
Biopharm	Mei Ou	Banu Zolnik
Manufacturing	Quamrul Majumder	Bogdan Kurtyka
Environmental Analysis	Jim Laurenson	
RBPM	Kristine Leahy	
ATL	Xing Wang	



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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted to NDA 213721 and found to be adequate upon completion of the review. All facilities are approvable based on acceptable compliance history.

OPQ recommends **APPROVAL** of NDA 213721 for GAVRETO (pralsetinib) capsules, 100 mg. OPQ grants an **18-month expiration period** for pralsetinib capsules 100 mg in the commercial packaging configuration (b) (4)

(b) (4) The storage conditions for the drug product are USP Controlled Room Temperature 20 - 25 °C (68 - 77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F). (b) (4)

(b) (4) OPQ grants a retest period of (b) (4)-month for pralsetinib drug substance when stored (b) (4) (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

GAVRETO (pralsetinib) is a kinase inhibitor indicated for the treatment of patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

The drug substance (DS), Pralsetinib, is claimed as a BCS 2 compound with low solubility and high permeability. (b) (4) (b) (4)

(b) (4) The drug product GAVRETO (pralsetinib) capsules contain 100 mg pralsetinib. The capsules also contain inactive ingredients: hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC), pregelatinized starch, sodium bicarbonate, citric acid, magnesium stearate. The capsules are size 0 light blue opaque HPMC capsules, with “BLU-667” printed in white ink on the capsule shell body and “100 mg” printed in white ink on the capsule shell cap. The recommended dose is 400 mg orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal.

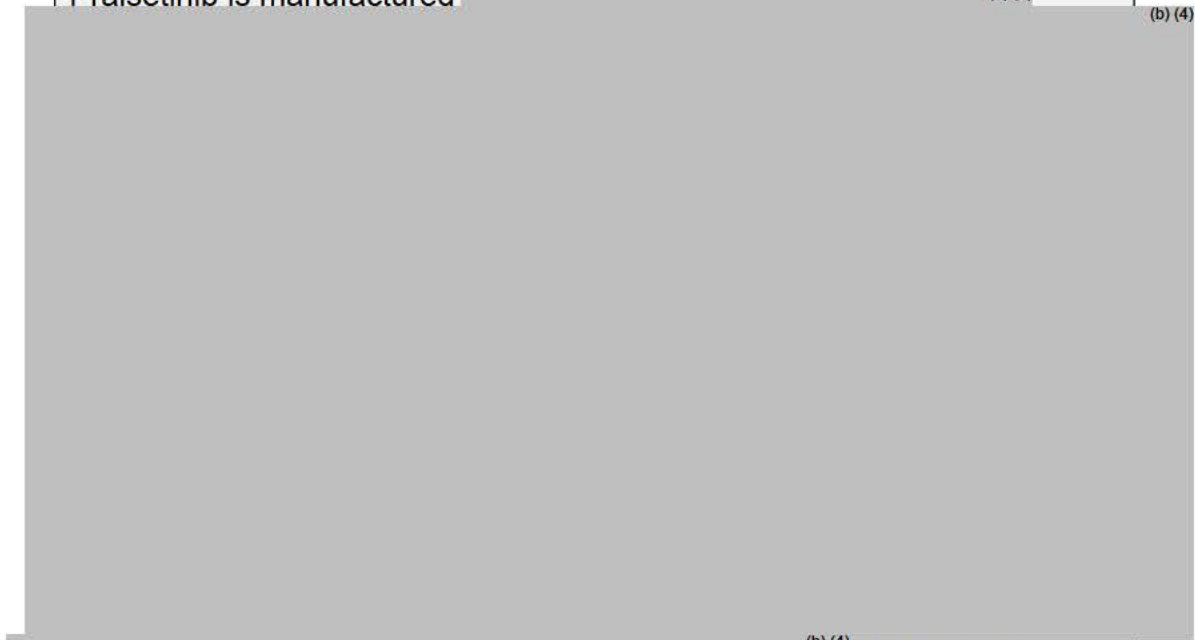
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Proposed Indication(s) including Intended Patient Population	GAVRETO is a kinase inhibitor indicated for the treatment of patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	400 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Pralsetinib drug substance is white to off-white yellow solid and exhibits polymorphism. It is an optically active compound and has 1 stereocenter with S configuration and one geometric center with cis configuration. Pralsetinib is manufactured (b) (4)



(b) (4) The proposed drug substance specifications are adequate and include controls for the specified impurities, residual solvents and elemental impurities. The applicants manufacturing process, in-process controls, control of critical steps and the manufacturing process development data ensure that the specified impurities are maintained as per the proposed control threshold. From CMC perspective, the applicant controlled the impurities appropriately (b) (4)

(b) (4) The proposed threshold levels for specified impurities were discussed with the P/T

reviewer Dr. Emily Wearne (Fox) and from toxicology perspective the proposed impurity acceptance criteria are adequate. The applicant provided batch analyses data for the registration stability batches manufactured at the proposed commercial site and the batch analyses data further supports the proposed risk-based drug substance specification. Pralsetinib drug substance is packaged in a (b) (4) (b) (4) (b) (4) No out of specification results or undesirable trends were noted in any of the test parameters under both long-term and accelerated stability studies. The applicant proposed a retest period of (b) (4) months based on the stability data when stored (b) (4) (b) (4) and based on the provided that this retest period is acceptable.

Drug Product: Adequate

GAVRETO (pralsetinib) drug product is solid oral immediate release hard hydroxypropyl methylcellulose (HPMC) capsule available as a 100 mg strength. The capsules are light blue opaque, with "BLU-667" printed in white ink on the capsule shell body and "100 mg" printed in white ink on the capsule shell cap. All excipients used in the formulation are adequately qualified. The drug product specifications include controls of critical quality attributes for immediate release capsules such as appearance, identity, assay, control of degradation products, content uniformity, dissolution, (b) (4) and drug substance physical form. Elemental impurity risk assessment was performed on five lots of commercial scale BLU-667 capsules that were analyzed for Class 1 and 2a (b) (4) Levels for Class 1 and 2a (b) (4) and (b) (4) in all capsules lots were found below (b) (4) % of PDE values per option 1 of ICH Q3D. The main stability studies of the drug product (b) (4) (b) (4) and drug product capsules are summarized as follows:

- Three primary (registration) capsules lots are placed on long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions. The capsules registration lots are manufactured at commercial site (b) (4) (b) (4) with commercial process (Process III) and packaged in commercial container closure system. Up to 9-month long term stability data is available. An acceptable 18-month shelf life for pralsetinib capsules, 100 mg is established in the commercial packaging configuration (b) (4) (b) (4)

The storage conditions for the drug product are USP Controlled Room

Temperature 20 - 25 °C (68 - 77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F).

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Biopharmaceutics: Adequate

The drug substance (DS), Pralsetinib, is claimed as a BCS 2 compound with low solubility and high permeability. (b) (4)

(b) (4) The proposed drug product (DP), Pralsetinib Capsule, is a solid oral immediate release hard hydroxypropyl methylcellulose (HPMC) capsule available in a 100 mg strength. The recommended dose is 400 mg orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal. In vitro dissolution method and acceptance criterion are found acceptable as a quality control (QC) test for the proposed drug product. The drug product composition and formulation remained unchanged during the pharmaceutical development; however, there were 3 manufacturing processes (I, II, and III) that were implemented for producing the drug product (refer to Process and Facility review for details). All drug product registration batches are manufactured using Process III, which is the commercial manufacturing process. The Applicant collected the PK information of the capsules manufactured with these three processes, therefore, the PK data will support the bridging the process I, II and III capsules, the PK studies is assessed and will be determined by the Office of Clinical Pharmacology. From Biopharmaceutics perspective, bridging is established.

Manufacturing: Adequate

The drug product manufacturing process encompasses (b) (4)

(b) (4) OMIR is approval.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	(b) (4)	L	
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Dissolution – BCS Class II	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	

Application Technical Lead Name and Date:

Xing Wang



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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	Adequate	07/07/2020	MAPP 5015.5 (Rev.1)
	III		Adequate	07/07/2020		
	III		Adequate	07/07/2020		
	III		Adequate	07/07/2020		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	(b) (4)	Drug development
IND	143094	Drug development

2. **CONSULTS** None



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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	GAVRETO™	Adequate
Established name(s)		
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 100 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

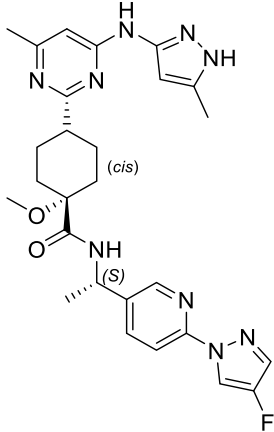
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	None	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsule	Adequate
Strength(s) in metric system	100 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Light blue, opaque hard hydroxypropyl methylcellulose (HPMC) capsule printed with "BLU-667" on the capsule shell body and "100 mg" on the capsule shell cap.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	GAVRETO	Adequate
Dosage form(s) and route(s) of administration	GAVRETO (pralsetinib) is supplied for oral use as immediate release hydroxypropyl methylcellulose (HPMC) hard capsules containing 100 mg pralsetinib.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The capsules also contain inactive ingredients: hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC), pregelatinized starch, sodium bicarbonate, citric acid, magnesium stearate. The capsule shell consists of hypromellose, titanium dioxide, and FD&C Blue #1 (Brilliant Blue FCF). The white printing ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, purified water, potassium hydroxide, and titanium dioxide	Recommendation: Re-order the list of excipient names alphabetically.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	Pralsetinib is an oral receptor tyrosine kinase inhibitor.	Adequate
Chemical name, structural formula, molecular weight	(<i>cis</i>)-<i>N</i>-((<i>S</i>)-1-(6-(4-fluoro-1<i>H</i>-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1<i>H</i>-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide.  The chemical structure shows a central cyclohexane ring in a chair conformation. A methyl group is attached to the ring with a dashed bond. A carboxamide group is attached to the ring with a wedged bond. The nitrogen of the carboxamide group is bonded to a chiral center marked with a dashed bond and labeled '(S)'. This chiral center is bonded to an ethyl chain, which is further substituted with a 6-(4-fluoro-1<i>H</i>-pyrazol-1-yl)pyridin-3-yl group. The pyridine ring is substituted at the 4-position with a 5-methyl-1<i>H</i>-pyrazol-3-ylamino group. $C_{27}H_{32}FN_9O_2$ molecular weight is 533.61 g/mol	Specific letters for elements and affix should be italic. Comment: The symbols for elements and affix in the chemical name should be italic to be in line with IUPAC naming convention, so the chemical name should read: <i>(cis)-N-((S)-1-(6-(4-fluoro-1<i>H</i>-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1<i>H</i>-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide</i>
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	The solubility of pralsetinib in aqueous media decreases over the range pH 1.99 to pH 7.64 from 0.880 mg/mL to <0.001 mg/mL, indicating a decrease in solubility with increasing pH	Acceptable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsule	Adequate
Strength(s) in metric system	100 mg	Adequate
Available units (e.g., bottles of 100 tablets)	GAVRETO (pralsetinib) capsules are supplied as follows (not all pack sizes may be marketed): • 100 mg, light blue opaque immediate release hydroxypropyl methylcellulose (HPMC) hard capsule, printed with "BLU-667" on the body and "100 mg" on the cap, available in bottles of 60 capsules (NDC 72064-210-60). • 100 mg, light blue opaque immediate release hydroxypropyl methylcellulose (HPMC) hard capsule, printed with "BLU-667" on the body and "100 mg" on the cap, available in bottles of 90 capsules (NDC 72064-210-90). • 100 mg, light blue opaque immediate release hydroxypropyl methylcellulose (HPMC) hard capsule, printed with "BLU-667" on the body and "100 mg" on the cap, available in bottles of 120 capsules (NDC 72064-210-12).	DMEPA reviewer Janine Stewart suggested revision of the description to reduce redundancy and to improve readability, refer to her review for details.

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."		According to the referenced Type III DMF (b) (4) for the (b) (4)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F) in original bottle (b) (4) protect from moisture; excursions are	(b) (4)

	permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	(b) (4) Comment: In Section 16, revise the storage conditions as follows: Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging		(b) (4)

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Blueprint Medicines Corporation, 45 Sidney Street, Cambridge, MA 02139, USA	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

The patient labeling (Patient Information) contains CMC related information such as storage conditions and ingredients in GAVRETO. The storage conditions should be revised. Also, the names of inactive ingredients should be organized alphabetically.

Comment:

In PATIENT INFORMATION under 2.0 PATIENT LABELING, revise the following sections:

1. Add "Protect from moisture" in the storage conditions so that the storage conditions read:

Store GAVRETO at room temperature between 68°F to 77°F (20°C to 25°C).
Protect from moisture.

2. Re-order list of excipient names alphabetically as follows:

Inactive ingredients: citric acid, hydroxypropyl methylcellulose (HPMC), magnesium stearate, microcrystalline cellulose (MCC), pregelatinized starch, sodium bicarbonate.

Capsule shell: FD&C Blue #1 (Brilliant Blue FCF), hypromellose and titanium dioxide.

White printing ink: butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Gavreto 120 CT capsules:



3.2 Carton Labeling

The same container labeling will be used for carton. See the above labeling.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	GAVRETO™ (pralsetinib) capsules	Acceptable
Dosage strength	100 mg	Acceptable
Route of administration	Oral	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	120 Capsules	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	NDC 72064-210-12	Acceptable
Lot number and expiration date	Yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature). (b) (4) (b) (4) protect from moisture. KEEP AWAY FROM CHILDREN	The storage conditions should be revised. Comment: Revise the storage conditions on carton labeling to include "Protect from moisture".
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	provided	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Blueprint Medicines Corp. Cambridge, MA 02139	Acceptable
Medication Guide (if applicable)	Recommended Dosage: see Prescribing Information	Acceptable
No text on Ferrule and Cap over seal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Comments:

1. *In section 11, suggest the following revisions:*
 - 1) *Re-order the excipient names alphabetically as follows:
The capsules also contain inactive ingredients: citric acid, hydroxypropyl methylcellulose (HPMC), magnesium stearate, microcrystalline cellulose (MCC), pregelatinized starch and sodium bicarbonate. The capsule shell consists of FD&C Blue #1 (Brilliant Blue FCF), hypromellose and titanium dioxide. The white printing ink contains butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.*

- 2) *The symbols for elements and affix in the chemical name should be italic to be in line with IUPAC naming convention, so the chemical name should read: (cis)-N-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide.*
2. *In Section 16, revise the storage conditions as follows:
Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Protect from moisture.*
3. *In PATIENT INFORMATION under 2.0 PATIENT LABELING, suggest the following revisions:*
 - 1) *Add “Protect from moisture” in the storage conditions so that the storage conditions read:
Store GAVRETO at room temperature between 68°F to 77°F (20°C to 25°C). Protect from moisture.*
 - 2) *Re-order list of excipient names alphabetically as follows:*

Inactive ingredients: *citric acid, hydroxypropyl methylcellulose (HPMC), magnesium stearate, microcrystalline cellulose (MCC), pregelatinized starch, sodium bicarbonate. Capsule shell: FD&C Blue #1 (Brilliant Blue FCF), hypromellose and titanium dioxide. White printing ink: butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.*
4. *Revise the storage conditions on carton labeling to include “Protect from moisture”.*

Overall Assessment and Recommendation:

The labeling should be adequate if the Applicant can address the above comments successfully.

Primary Labeling Assessor Name and Date: Yang Nan, Ph.D.

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Anamitro Banerjee, Ph.D., Branch Chief*



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CHAPTER VI: BIOPHARMACEUTICS**NDA: 213721 [505(b)(1)]****Drug Product Name/Strength:** GAVRETO™ (Pralsetinib) Capsules, 100 mg**Route of Administration:** Oral**Proposed Indication:** Pralsetinib is a kinase inhibitor indicated for the treatment of patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) as detected by an FDA approved test.**Applicant Name:** Blueprint Medicines Corporation**Submission Date:** 03/23/2020, 04/22/2020, 05/14/2020**Primary Reviewer:** Mei Ou, Ph.D.**Secondary Reviewer:** Banu Zolnik, Ph.D.**EXECUTIVE SUMMARY**

Pralsetinib (known as BLU-667) is a highly potent and selective rearranged during transfection (RET) inhibitor, activates RET mutants (including gatekeeper mutants) and shows potent antitumor activity in RET-driven tumor models, so that it is indicated for the treatment of patients with RET fusion-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

The drug substance (DS), Pralsetinib, is claimed as a BCS 2 compound with low solubility and high permeability. (b) (4)

(b) (4) The proposed drug product (DP), Pralsetinib Capsule, is a solid oral immediate release hard hydroxypropyl methylcellulose (HPMC) capsule available in a 100 mg strength. The capsules are size 0 light blue opaque HPMC capsules, with “BLU-667” printed in white ink on the capsule shell body and “100 mg” printed in white ink on the capsule shell cap. The recommended dose is 400 mg orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal. (b) (4)

The Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Pralsetinib Capsule, 100 mg; (ii) the in vitro formulation bridging during the manufacturing process optimization.

In Vitro Dissolution Testing of the Finished Product:

The proposed dissolution method (Method-3) is reviewed and found acceptable as a quality control (QC) test for the proposed Pralsetinib Capsules, 100 mg, for batch release and stability testing based on the totality information submitted. The proposed dissolution method showed acceptable discriminating ability with regards to critical material attributes (b) (4) but not for critical in process parameters (b) (4) The overall

dissolution data also support the proposed acceptance criterion of “Q= (b) (4) % in 45 minutes”.

The acceptable in vitro dissolution method and acceptance criterion for the proposed Pralsetinib Capsules, 100 mg, are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Sinker	XL Sotax Helical Sinkers, QLA PN CAPWST-31
Dissolution Medium	900 mL of 50 mM sodium phosphate buffer at pH 6.8 containing 0.4% w/v CTAB
Temperature	37°C±0.5°C
Acceptance Criterion	Q= (b) (4) % in 45 minutes

The In Vitro Formulation Bridging:

The drug product composition and formulation remained unchanged during the pharmaceutical development; however, there were 3 manufacturing processes (I, II, and III) that were implemented for producing the drug product (refer to Process and Facility review for details). All drug product registration batches are manufactured using Process III, which is the commercial manufacturing process. The Applicant collected the PK information of the capsules manufactured with these three processes, therefore, the PK data will support the bridging the process I, II and III capsules, the PK studies is assessed and will determined by the Office of Clinical Pharmacology (OCP).

Process I and Process II capsules bridging:

The dissolution data showed that process I capsules had slower dissolution than process II capsules, which is aligned with the in vivo results that process I capsules had lower exposure than process II capsules. Per our communication with the OCP reviewers, Dr. Amal Ayyoub and Dr. Hong Zhao, OCP assessment will address the impact of lower exposure observed with Process 1 capsules. From Biopharmaceutics perspective, bridging is established as the Applicant conducted the PK studies with Process I and Process II capsules.

Process II and Process III capsules bridging:

The dissolution data showed process II and III capsules had comparable dissolution profiles. It appears that process II and III capsules have similar in vivo performances, however, the final assessment will be determined by the OCP reviewers, Dr. Amal Ayyoub and Dr. Hong Zhao. From Biopharmaceutics perspective, bridging is established as the Applicant conducted the PK studies with Process II and Process III capsules.

Bridging Pralsetinib (b) (4) manufacturing sites: clinical site (b) (4) vs. commercial site (b) (4)

The dissolution profiles of capsules produced from same commercial manufacturing process III but using Pralsetinib (b) (4) from different manufacturing sites (clinical site (b) (4) vs. commercial site (b) (4) are comparable, indicating the change in Pralsetinib (b) (4) manufacturing sites had no impact on the in

vitro dissolution of final drug product. Therefore, in vitro bridging has been established, and no additional in vivo and in vitro bridging studies are needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213721 for the proposed GAVRETO™ (Pralsetinib) Capsules, 100 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS REVIEW

1. In Vitro Dissolution Method

Dissolution is one of the critical quality attributes (CQAs) of the proposed drug product. The information regarding the in vitro dissolution method development was conveyed to the Applicant cross referenced to IND (b) (4) on 05/23/2019 and to IND 143094² on 11/25/2019. The complete dissolution method development report is submitted in M.3.2.P.2 (Report TECH-00800) of this NDA.

(1) Pralsetinib crystalline solubility and permeability

Per the Applicant, the crystalline DS is a BCS 2 compound. The DS has low solubility in neutral pH media (pH 5~7), but relatively higher solubility in acidic pH media (pH 1~3), as data presented in Table 1 below.

Tablet 1: The aqueous solubility of pralsetinib
(data from M.3.2.P.2)

Target pH	Final pH (168 h)	Solubility mg/mL (USP Definition) (24 h)	Solubility mg/mL (USP Definition) (168 h)
~50 mM HCl/KCl	1.99	0.880 (Very Slightly Soluble)	0.736 (Very Slightly Soluble)
~50 mM citric acid/NaOH	2.84	>1.830 (Slightly Soluble)	>1.920 (Slightly Soluble)
~50 mM citric acid/NaOH	3.87	0.387 (Very Slightly Soluble)	0.368 (Very Slightly Soluble)
~50 mM citric acid/NaOH	5.06	0.026 (Practically Insoluble)	0.024 (Practically Insoluble)
~50 mM K ₂ HPO ₄ /NaOH	6.11	0.003 (Practically Insoluble)	0.002 (Practically Insoluble)
~50 mM K ₂ HPO ₄ /NaOH	7.64	<0.001 (Practically Insoluble)	<0.001 (Practically Insoluble)
Water	7.36	<0.001 (Practically Insoluble)	<0.001 (Practically Insoluble)

USP solubility definitions: < 0.1 mg/mL: practically insoluble, 0.1-1 mg/mL: very slightly soluble, 1-10 mg/mL: slightly soluble, 10-33 mg/mL: sparingly soluble, 33-100 mg/mL: soluble, 100-1000 mg/mL: freely soluble

The reported apparent permeability coefficients (P_{app} A->B) of the DS is ranged from 8.81 to 21.2 x10⁻⁶ cm/s at 0.1 to 10 μM in C2BBel monolayers (a clone of Caco-2 cell line) (Data from Study Report 19BLUPP1R1, M.4.2.2.6. Please note that no moderate or high permeability compounds/comparators were included or reported in the study).

(2) Dissolution method development

Three dissolution methods had been evaluated during method development and listed in Table 2 below.

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

¹ https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804f700d&_afRedirect=5152005143818543

² https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8052a70b&_afRedirect=5152082083984157

Overall, this Reviewer considers that the proposed dissolution Method-3 (USP Apparatus II Paddle, 50 rpm, 900 mL of 50 mM sodium phosphate buffer at pH 6.8 containing 0.4% w/v CTAB, with XL Sotax Helical Sinkers, QLA PN CAPWST-31) is deemed acceptable. The proposed dissolution method showed acceptable discriminating ability with regards to critical material attributes [REDACTED] (b) (4), but not to critical in process parameters [REDACTED] (b) (4). However, the proposed commercial dissolution method is still acceptable as a quality control (QC) test for the proposed drug product based on the totality information submitted.

2. Dissolution Data and Acceptance Criterion

The dissolution data profiles of three registration batches (lot 3722135, 3722141, 3722146) are provided, as illustrated in the Figure 12 below.

Figure 12: Dissolution of 100 mg capsule registration batches
(lot 3722135, lot 3722141, and lot 3722146)
(from Figure 9 in dissolution method development report)

(b) (4)

Per the Applicant, the dissolution testing for initial time points of registration stability samples were performed with dissolution Method-2. The commercial dissolution method

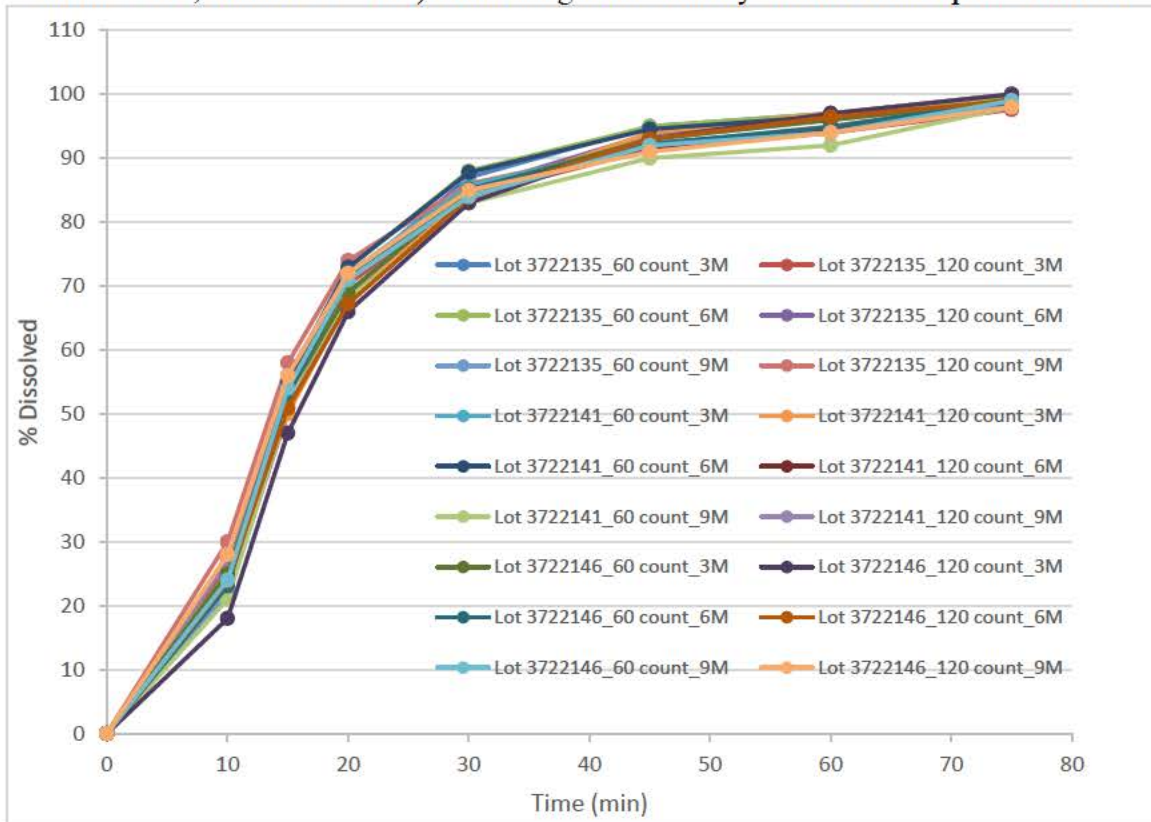
(Method-3) was implemented from the 3 months testing of registration stability samples. From the submitted data, the 3 months and 6 months long-term stability (25°C/60% RH) registration batches were tested by both dissolution Method-2 and Method-3. This Reviewer summarized the mean dissolution data profiles of the registration batches generated by the proposed dissolution method (Method-3) in the following Tables 6, 7 and Figures 13, 14.

Table 6: Mean dissolution data of 100 mg capsule registration batches (lot 3722135, lot 3722141, and lot 3722146) under long-term stability condition for 3 and 6 months (from 3/23/2020 submission) and 9 months (from 4/22/2020 submissions)

Lot Numbers		Time (min)							
		0	10	15	20	30	45	60	75
Lot 3722135_60 count_3M	mean	0	26	54	71	87	95	97	100
	%RSD	0	26	11	8	4	2	1	1
Lot 3722135_120 count_3M	mean	0	26	54	70	84	91	94	98
	%RSD	0	40	19	13	8	6	4	2
Lot 3722135_60 count_6M	mean	0	25	55	73	88	95	97	99
	%RSD	0	27	6	4	2	1	1	1
Lot 3722135_120 count_6M	mean	0	22	50	68	85	94	97	98
	%RSD	0	41	11	6	3	1	1	1
Lot 3722135_60 count_9M	mean	0	22	51	69	85	93	96	99
	%RSD	0	42	10	6	4	3	2	1
Lot 3722135_120 count_9M	mean	0	30	58	74	86	92	95	99
	%RSD	0	33	12	8	4	2	2	1
Lot 3722141_60 count_3M	mean	0	24	54	72	86	92	95	99
	%RSD	0	43	18	12	7	5	4	3
Lot 3722141_120 count_3M	mean	0	24	50	68	84	94	97	100
	%RSD	0	26	12	9	6	3	2	2
Lot 3722141_60 count_6M	mean	0	24	55	73	88	95	97	99
	%RSD	0	43	14	8	4	2	2	1
Lot 3722141_120 count_6M	mean	0	24	54	72	85	92	95	99
	%RSD	0	41	13	7	4	3	3	2
Lot 3722141_60 count_9M	mean	0	21	51	68	83	90	92	98
	%RSD	0	50	16	10	6	4	3	2
Lot 3722141_120 count_9M	mean	0	27	56	72	85	92	94	98
	%RSD	0	36	13	8	5	3	3	2
Lot 3722146_60 count_3M	mean	0	25	53	69	85	93	96	99
	%RSD	0	36	10	5	3	2	2	1
Lot 3722146_120 count_3M	mean	0	18	47	66	83	93	97	100
	%RSD	0	51	12	6	3	2	2	1
Lot 3722146_60 count_6M	mean	0	23	53	71	85	92	95	99
	%RSD	0	42	13	7	4	2	2	1

Lot 3722146_120 count_6M	mean	0	24	51	67	84	93	96	99
	%RSD	0	44	21	14	8	3	2	1
Lot 3722146_60 count_9M	mean	0	24	54	71	84	92	94	99
	%RSD	0	42	12	7	4	3	3	1
Lot 3722146_120 count_9M	mean	0	28	56	72	85	91	94	98
	%RSD	0	34	14	8	4	4	3	2

Figure 13: Mean dissolution profiles of 100 mg capsule registration batches (lot 3722135, lot 3722141, and lot 3722146) under long-term stability condition for up to 9 months



As the data profiles presented above, three registration batches showed comparable dissolution profiles with similarity factors (f_2) are more than 50 by comparing to each other.

Per the Applicant, the lowest individual dissolution ($(b) (4) \%$) at 45 minutes was observed for a supportive lot 18E07G, as summarized in the following Table 7. All pralsetinib capsules have showed stable dissolution throughout the development and stability studies with no trends observed. Therefore, the proposed the dissolution acceptance criterion is " $Q = (b) (4) \%$ in 45 minutes". This Reviewer considers the overall data support the proposed dissolution acceptance criterion.

Table 7: Dissolution results for 100 mg lots (45 minutes)
(from Table 1 in M.3.2.P.5.6)

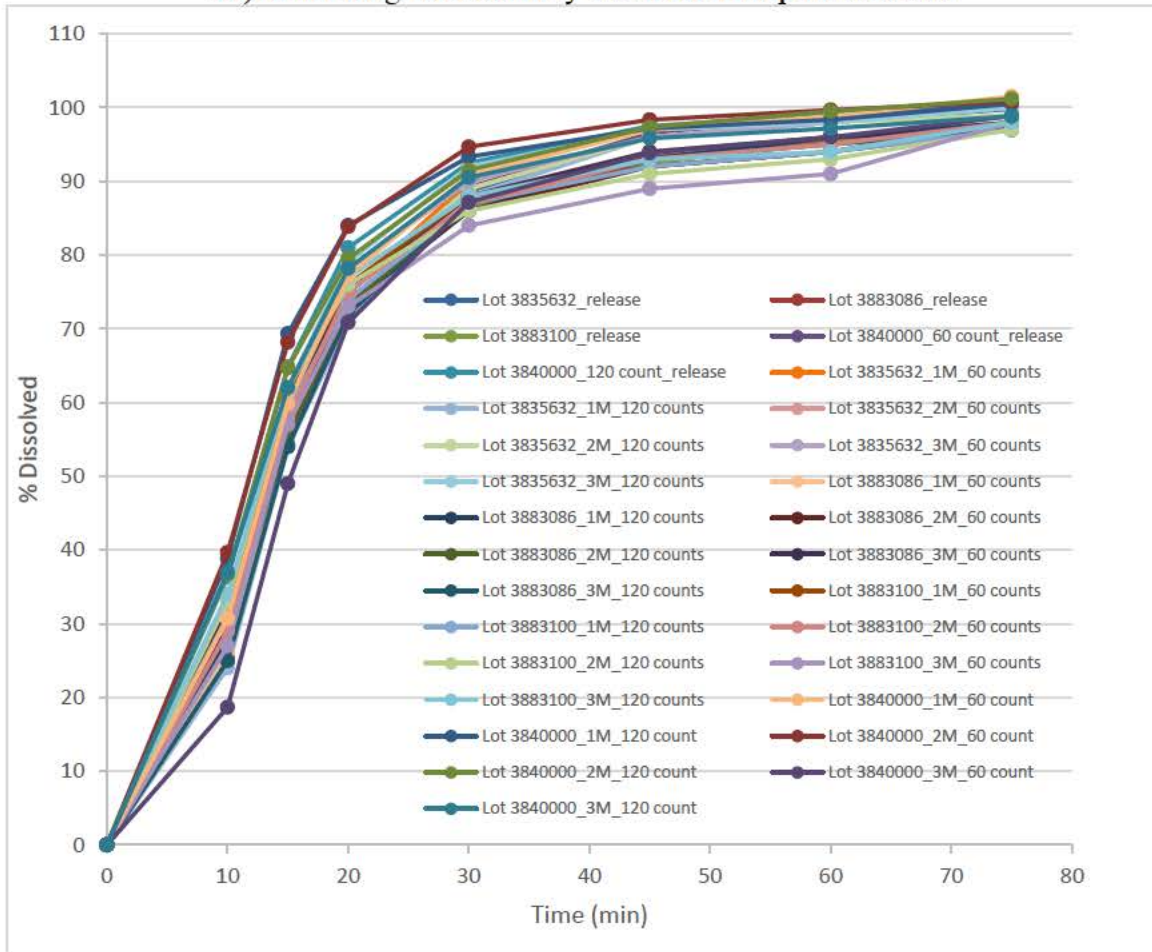
Batch No.	Results		
	Min %	Max %	Mean %
3722135		(b) (4)	96.1
3722141			96.7
3722146			97.0
3635632			92.3
3883086			93.3
3883100			92.5
18E07G			85.9
19D11G			92.4

Table 8: Mean dissolution data of 100 mg capsules from supportive process III batches (lot 3835632, lot 3883086, and lot 3883100) and printed capsules (lot 3840000, process III) under long-term stability condition for release (from 03/23/2020 submission) and 1, 2, and 3 months (from 04/22/2020 submissions)

		Time (min)							
		0	10	15	20	30	45	60	75
Lot 3835632_release	mean	0	25	54	75	89	96	98	100
	%RSD	0	62	21	11	5	3	2	2
Lot 3883086_release	mean	0	26	56	72	87	93	95	97
	%RSD	0	48	13	7	3	1	1	1
Lot 3883100_release	mean	0	28	58	73	86	93	95	97
	%RSD	0	51	16	9	4	2	1	1
Lot 3840000_60 count_release	mean	0	28	58	75	89	97	99	101
	%RSD	0	15	10	10	5	2	1	1
Lot 3840000_120 count_release	mean	0	36	65	81	93	98	99	101
	%RSD	0	28	10	4	1	1	1	0
Lot 3835632_1M_60 counts	mean	0	28	56	75	90	96	98	100
	%RSD	0	32	15	9	4	2	1	1
Lot 3835632_1M_120 counts	mean	0	24	54	71	88	96	98	100
	%RSD	0	57	18	12	5	2	1	1
Lot 3835632_2M_60 counts	mean	0	27	58	75	89	96	98	100
	%RSD	0	39	11	7	4	2	2	1
Lot 3835632_2M_120 counts	mean	0	27	58	75	89	96	98	99
	%RSD	0	44	11	8	5	3	2	2
Lot 3835632_3M_60 counts	mean	0	32	61	78	90	96	98	100
	%RSD	0	37	16	8	3	1	1	1
Lot 3835632_3M_120 counts	mean	0	31	62	79	92	97	98	100
	%RSD	0	50	15	7	3	1	1	1
Lot 3883086_1M_60 counts	mean	0	26	56	73	88	94	96	98
	%RSD	0	44	14	7	4	2	2	1
Lot 3883086_1M_120 counts	mean	0	28	56	73	86	93	96	98

	%RSD	0	43	18	12	7	3	2	1
Lot 3883086_2M_60 counts	mean	0	32	58	74	86	92	94	97
	%RSD	0	20	8	5	3	3	2	1
Lot 3883086_2M_120 counts	mean	0	29	56	73	87	92	94	98
	%RSD	0	46	23	14	7	5	4	1
Lot 3883086_3M_60 counts	mean	0	30	60	75	88	94	96	97
	%RSD	0	35	11	6	2	2	1	1
Lot 3883086_3M_120 counts	mean	0	25	54	72	87	93	95	97
	%RSD	0	53	17	9	4	2	1	1
Lot 3883100_1M_60 counts	mean	0	31	61	76	88	92	94	98
	%RSD	0	37	13	7	4	3	2	1
Lot 3883100_1M_120 counts	mean	0	31	59	74	87	92	94	97
	%RSD	0	23	9	6	3	2	2	1
Lot 3883100_2M_60 counts	mean	0	29	58	75	87	93	95	98
	%RSD	0	48	23	10	4	3	2	1
Lot 3883100_2M_120 counts	mean	0	33	62	76	86	91	93	97
	%RSD	0	36	13	7	4	3	2	1
Lot 3883100_3M_60 counts	mean	0	27	57	73	84	89	91	98
	%RSD	0	61	19	11	6	4	3	1
Lot 3883100_3M_120 counts	mean	0	34	62	77	88	93	94	98
	%RSD	0	28	10	6	3	2	2	1
Lot 3840000_1M_60 count	mean	0	31	60	77	91	97	99	102
	%RSD	0	26	13	8	3	1	1	1
Lot 3840000_1M_120 count	mean	0	39	69	84	93	97	98	101
	%RSD	0	33	11	6	4	2	1	1
Lot 3840000_2M_60 count	mean	0	40	68	84	95	98	100	101
	%RSD	0	17	8	5	2	2	1	1
Lot 3840000_2M_120 count	mean	0	37	65	80	92	97	100	101
	%RSD	0	52	18	9	3	1	1	1
Lot 3840000_3M_60 count	mean	0	19	49	71	87	94	96	99
	%RSD	0	101	30	9	4	3	3	3
Lot 3840000_3M_120 count	mean	0	37	62	78	91	96	97	99
	%RSD	0	36	16	9	4	3	3	2

Figure 14: Mean dissolution profiles of 100 mg capsule supportive process III batches (lot 3835632, lot 3883086, and lot 3883100) and printed capsules (lot 3840000, process III) under long-term stability condition for up to 3 months



3. Formulation bridging

While the drug product composition and formulation remained unchanged during the pharmaceutical development, the drug product manufacturing process underwent optimization and resulted in 3 manufacturing processes (I, II, and III) of the pralsetinib 100 mg capsule formulation.

Process I capsules were initially used in most of the dose-escalation phase, and the early part of the expansion (registration-enabling) phase, of Study BLU-667-1101.

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

Process II capsules were used in most of the expansion phase of Study BLU-667-1101 and in Studies BLU-667-0101 and BLU-667-0102 in healthy subjects. As the clinical development of pralsetinib progressed into the expansion (registration-enabling) phase of Study BLU-667-1101, the manufacturing process for pralsetinib capsules had to be improved

(b) (4)

(b) (4)

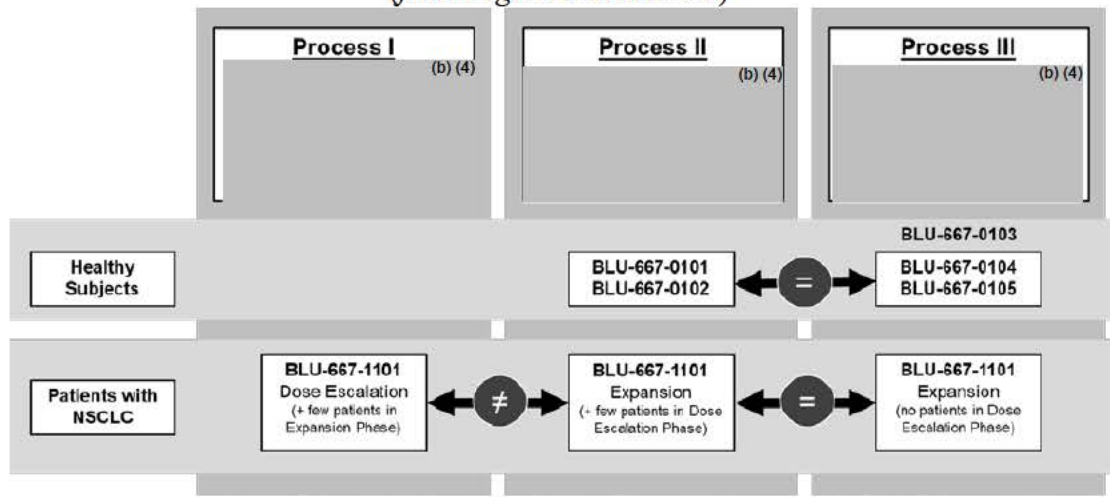
Process III capsules (capsules made with the proposed commercial manufacturing process) were deployed from May 2019 for the ongoing expansion (registration-enabling) phase of Study BLU-667-1101
667-0105 in healthy subjects.

(b) (4)

(b) (4)

The Applicant summarized the three manufacturing processes and related clinical studies that these three processes capsules being used, in Figure 15 below. The Applicant conducted PK studies for each of pralsetinib drug product manufactured with Process I, II, or III.

Figure 15: Overview of changes to Pralsetinib capsule manufacturing process, and manufacturing process used for capsules administered in clinical studies
(from Figure 5 in M.2.7.1)



Abbreviations: NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s).

Note: Clinical studies in white boxes indicate studies that provided PK data for comparisons between capsule processes. Arrows indicate similarity or lack of similarity of pralsetinib PK when administered as Process I versus Process II capsules (population PK analysis) or as Process II versus Process III capsules (noncompartmental and population PK analysis).

Source: Information available in [Module 3.2.P.2.2](#); [Module 2.7.2](#), [Section 2.4.2.1](#); [Section 3.2.1.3](#).

The PK information of process I, II and III capsules is under purview of the Office of Clinical Pharmacology (OCP).

1) Process I and Process II capsules bridging:

The dissolution data showed that process I capsules had slower dissolution than process II capsules, which is aligned with the in vivo results that process I capsules had lower exposure than process II capsules. Per our communication with the OCP reviewers, Dr. Amal Ayyoub and Dr. Hong Zhao, OCP assessment will address the impact of lower exposure observed with Process 1 capsules. From Biopharmaceutics perspective, bridging is established as the Applicant conducted the PK studies with Process I and Process II capsules.

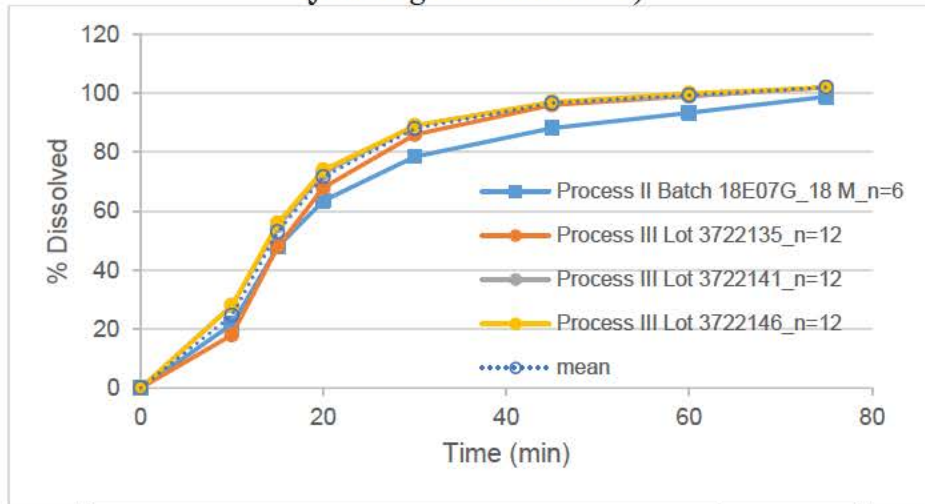
2) Process II and Process III capsules bridging:

The dissolution data showed process II and III capsules had comparable dissolution profiles. It appears that process II and III capsules have similar in vivo performances, however, the final assessment will be determined by the OCP reviewers, Dr. Amal Ayyoub and Dr. Hong Zhao. From Biopharmaceutics perspective, bridging is established as the Applicant conducted the PK studies with Process II and Process III capsules.

The dissolution profiles of process II and III capsules are comparable (Figure 16). Note that the Applicant only plotted the average dissolution (*mean*) from three registration lots in the submission, however, the use of average data (*mean*) of three registration lots for calculating similarity factor (f_2) between process II and III batches is not acceptable. Therefore, this Reviewer plotted the following dissolution profiles by using individual

registration batches data. The f_2 calculation ($f_2 > 50$) indicated that the change in capsule manufacturing process from Process II to Process III had no impact on the in vitro dissolution of pralsetinib. The proposed commercial dissolution method was developed as a quality control method to be discriminating with respect to meaningful variations in the material attributes and manufacturing process parameters but is not intended to imply an in vivo/in vitro correlation.

Figure 16: Dissolution profile for process II batch 18E07G vs. process III three registration batches with the proposed commercial Dissolution Method-3 (from Figure 2 in M.2.7.1)



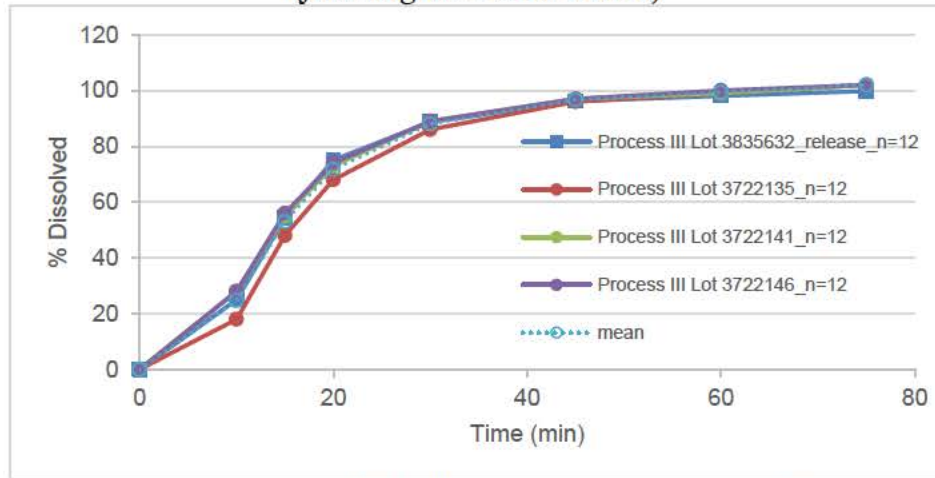
	Batch #	f_2
Process II Batch 18E07G_18 M_n=6	Process III Lot 3722135 n=12	66
	Process III Lot 3722141 n=12	53
	Process III Lot 3722146 n=12	52

3) Bridging Pralsetinib (b) (4) manufacturing sites: clinical site (b) (4) vs. commercial site (b) (4) :

Two registration batches (lot 3722135 and 3722141) were manufactured using drug substance produced from Pralsetinib (b) (4) clinical manufacturing site (b) (4) (b) (4)). Two registration batch (lot 3722146 and 3835632) were manufactured using drug substance produced from Pralsetinib (b) (4) commercial manufacturing site (b) (4) (b) (4)). Note that all drug product registration batches are manufactured using Process III, which is the commercial manufacturing process.

The comparative dissolution profiles of all above four Process III capsules are presented in Figure 17 below. Note that the Applicant only plotted the mean dissolution data of three registration lots in the submitted profiles. This Reviewer plotted the dissolution profiles from individual registration batches. The f_2 calculation ($f_2 > 50$) indicated that the change in Pralsetinib (b) (4) manufacturing sites for Process III capsules had no impact on the in vitro dissolution of pralsetinib.

Figure 17: Dissolution profile for process III batch 3835632 vs. process III three registration batches with the proposed Dissolution Method-3
(from Figure 4 in M.3.2.P.2)



	Batch #	f2
Process III Lot 3835632_release_n=12	Process III Lot 3722135 n=12	61
	Process III Lot 3722141 n=12	84
	Process III Lot 3722146 n=12	84

The dissolution profiles of capsules produced from same commercial manufacturing process III but using Pralsetinib (b) (4) from different manufacturing sites (clinical site (b) (4) vs. commercial site (b) (4)) are comparable, indicating the change in Pralsetinib (b) (4) manufacturing sites had no impact on the in vitro dissolution of final drug product. Therefore, in vitro bridging has been established, and no additional in vivo and in vitro bridging studies are needed.

APPENDIX 1
BIOPHARMACEUTICS INFORMATION REQUEST AND
APPLICANT'S RESPONSE

Biopharmaceutics IRs (conveyed on 04/30/2020):

1.

2.

(b) (4)

Applicant's Responses (submitted on 05/14/2020):

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/s/

XING WANG
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