

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212608Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 212608 Assessment #1

Drug Product Name	Ayvakit (avapritinib)
Dosage Form	Tablets
Strength	100 mg, 200 mg, and 300 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	06/14/2019	All
Quality Amendment 0003	07/17/2019	EA
Quality Amendment 0005	08/07/2019	Biopharm/DP
Quality Amendment 0012	09/18/2019	DS
Quality Amendment 0013	09/24/2019	Process/Biopharm/DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Raymond Frankewich	Suong Tran
Drug Product	Xing Wang	Anamitro Banerjee
Manufacturing	Diane Goll	Rakhi Shah
Microbiology	Diane Goll	Rakhi Shah
Biopharmaceutics	Parnali Chatterjee	Banu Zolnik
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Xing Wang	
Laboratory (OTR)	N/A	
Environmental	James Laurenson	N/A



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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted to NDA 212608 and found to be adequate upon completion of the review. Three PAIs (pre-approval inspection) were conducted and all drug substance and drug product facilities are found adequate.

OPQ recommends **APPROVAL** of NDA 212608 for AYVAKIT®(Avapritinib) Tablets 100 mg, 200 mg and 300 mg. OPQ grants an 18-month expiration period for the 100 mg and 200 mg avapritinib tablets and a 12-month expiration period for the 300 mg avapritinib tablets when stored at “20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. In addition, OPQ grants a (b) (4) month re-test period for the drug substance when stored at (b) (4).

The root cause of (b) (4) trend in the dissolution data for the 300 mg drug product during storage is under investigation.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants. Avapritinib drug substance is a white to off-white to yellow crystalline solid, one chiral center. The proposed manufacturing process generates (b) (4). Avapritinib drug product is an immediate release tablet for oral administration. It is a white film coated tablet, printed in blue ink with “BLU” on one side and the tablet strength on the other side. The tablets are available in 100 mg, 200 mg, and 300 mg strengths. Avapritinib tablets (30 counts) are packaged in 60 cc HDPE bottles (b) (4) caps with foil induction seal liner and 0.5 g (b) (4) desiccant canister. The recommended dosage is 300 mg orally once daily on an empty stomach, at least one hour before or two hours after a meal.

Proposed Indication(s) including Intended Patient Population	Avapritinib is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) - harboring a platelet-derived growth factor receptor alpha (PDGFRA) (b) (4) (b) (4) (b) (4)
Duration of Treatment	Until disease progression or unacceptable toxicity

Maximum Daily Dose	300 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Avapritinib drug substance is a white to off-white to yellow crystalline solid. The proposed manufacturing process generates (b) (4). Avapritinib has one chiral center. Avapritinib is manufactured using (b) (4) (b) (4)

(b) (4) Avapritinib drug substance is controlled using a specification that contains tests for Identity by IR spectrum, Assay and impurities using HPLC, undesired (b) (4) (b) (4) residual solvents, residual (b) (4), solid state form using XRPD, and particle size distribution (D10: NLT (b) (4) μm; D50: (b) (4) μm; D90: NMT (b) (4) μm). Avapritinib drug substance is packaged in (b) (4). The retest period for avapritinib drug substance is (b) (4) months, stored at (b) (4). The drug substance information in the NDA has been reviewed and found adequate.

Drug Product: Adequate

Avapritinib drug product is an immediate release tablet for oral administration. The tablets are available in 100 mg, 200 mg and 300 mg strengths. All tablet strengths are (b) (4) proportional in active and inactive ingredients. The proposed tablet has a high drug load (b) (4) % and contains common excipients for solid oral dosage form: microcrystalline cellulose ((b) (4)) copovidone ((b) (4)) croscarmellose sodium ((b) (4)) magnesium stearate ((b) (4)) and Opadry II (b) (4). The drug product specification includes appearance, identity, assay, content uniformity, degradation products, dissolution and (b) (4). There are no specified degradants. The applicant conducted a risk analysis for elemental impurities as per ICH Q3D and concluded the potential risk of elemental impurities in avapritinib tablets is low and no additional controls are required. Analytical methods are adequately validated. Avapritinib tablets (30 counts) are packaged in 60 cc HDPE bottles with (b) (4) caps with foil induction seal liner and 0.5 g (b) (4) desiccant canister. Based on provided 18 months stability data and Biopharm recommendation, an 18-month shelf-life is granted for the 100 mg and 200 mg strengths. A 12-month shelf-life is granted for the 300 mg strength. The NDA is recommended for APPROVAL from the drug product perspective.

Labeling: Adequate

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

Manufacturing: Adequate

Facilities underwent 3 PAIs and are all approvable.

The proposed commercial manufacturing process comprises (b) (4)

(b) (4)

(b) (4) The process description and process parameters match the values derived in process development. The applicant demonstrated that (b) (4) PSD does not have a significant impact on tablet dissolution. The proposed commercial batch size is the same as the exhibit batch size for all strength tablets. The commercial (b) (4) size can range between (b) (4) kg and (b) (4) kg and tablets are dose proportional. (b) (4)

(b) (4)

(b) (4)

The manufacturing information in the NDA is deemed adequate.

Biopharmaceutics: Adequate

Biopharm evaluated the totality of the dissolution profile data to support 1) the proposed dissolution method, 2) the proposed dissolution acceptance criterion, 3) the need for bridging different drug substance and drug product manufacturing sites and formulations throughout the product development stage, and 4) the biowaiver request for the 200 mg and 300 mg TBM drug product. The dissolution method is acceptable as a quality control method for batch release and stability testing of the 100 mg, 200 mg, and 300 mg proposed drug product. The Applicant agreed to implement the recommended acceptance criterion of “Q (b) (4) % in 45 minutes” for each strength of the proposed product. Some stability batches for the 300 mg drug product would be out-of-specification (and subjected to Stage 2 and Stage 3 testing) or fail the acceptance criterion of “Q (b) (4) % in 45 minutes” at 18-month thus the shelf-life for the 300 mg drug product would be set at 12 months. Bridging of batches due to changes of drug product, manufacturing site and process are acceptable. The biowaiver request for the 200 mg and 300 mg drug product is granted based on compositional proportionality, BE studies BLU-285-0105 and BLU-285-1101, and similarity in dissolution profiles. From the Biopharmaceutics perspective, NDA 212608 is recommended for APPROVAL.

Microbiology (if applicable): Adequate

Solid oral dosage form. Process is (b) (4)

(b) (4) No micro testing in DP release specs. Micro test results provided for all batch analyses. Adequate.

Environmental Assessment: Adequate

The applicant originally submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b). The CDER

EA Team reviewed the claim and responded that additional support for the claim would be needed because the active ingredient, a kinase inhibitor, appears to have a mechanism of action related to FDA guidance (USFDA, 2016, Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity). In response, the applicant submitted a weight-of-evidence assessment based on available toxicity and other data from the drug application and the literature, concluding that there is a sufficient margin of safety between the expected introduction concentration (EIC) and the derived no-effect level. After recalculating the EIC based on a substantially lower initial patient population than anticipated for this application, FDA determined that the data were indicative of no significant environmental impact from this application. Therefore, the claim for an exclusion from an EA is acceptable. Given the uncertainty involved with the environmental toxicity of this substance, however, additional support for any future exclusion claim will be needed.

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	Controlled via specs	L	
Physical Stability (solid state)	- Formulation - Raw materials - Process parameters - Scale/equipments - Site	M	(b) (4) of registration batches are consistent	L	
Content Uniformity	- Formulation - Raw materials - Process parameters - Scale/equipments - Site	L	High drug load (b) (4) %	L	
Microbial Limits	- Formulation - Container closure - Process parameters - Scale/equipments - Site	L	Registration batches confirmed low risk	L	
Dissolution – BCS Class II & IV	- Formulation - Container closure - Raw materials - Process parameters - Scale/equipments - Site	H	Dissolution method is discriminating. Shorter shelf life (12 months) is	M	Shorter shelf life is granted for the 300 mg tablets. Root cause of the (b) (4) dissolution trend during

			granted for the 300 mg strength.		storage is under investigation.
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Application Technical Lead Name and Date:

Xing Wang, Ph.D.

11-Nov-2019



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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	10/01/2019	DMF not reviewed since sufficient information is in the NDA and Per MAPP 5015.5 (Rev. 1).
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		
	III			Adequate		

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

Document	Application Number	Description
IND	125379	Drug development

2. CONSULTS N/A



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CHAPTER IV: LABELING

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	Pending	Remove (b) (4)
Established name(s)	avapritinib	Acceptable
Route(s) of administration	for oral use	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) tablets: 100 mg, 200 mg or 300 mg.	Remove (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not 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	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	(b) (4) tablets	Tablets
Strength(s) in metric system	100 mg, 200 mg and 300 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	No	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	100 mg, Round, white film-coated tablet, printed with blue ink "BLU" on one side and "100" on the other side. 200 mg, capsule shaped, white film-coated tablet, printed with blue ink "BLU" on one side and "200" on the other side. 300 mg, capsule shaped, white film-coated tablet, printed with blue ink "BLU" on one side and "300" on the other side.	Tablets: 100 mg, round, white, film-coated, printed with blue ink "BLU" on one side and "100" on the other side. 200 mg, capsule shaped, white, film-coated, printed with blue ink "BLU" on one side and "200" on the other side. 300 mg, capsule shaped, white, film-coated, printed with blue ink "BLU" on one side and "300" on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Pending	
Dosage form(s) and route(s) of administration	for oral use as printed, film-coated tablets	Acceptable.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not salt	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide. The blue printing ink contains esterified shellac, n-butyl alcohol, FD&C blue 1, isopropyl alcohol, titanium dioxide, black iron oxide, propylene glycol, and ammonium hydroxide.	Acceptable. Changed to alphabet order.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Minimal in printing ink (neglectable)	Acceptable
Pharmacological/therapeutic class	tyrosine kinase inhibitor	Acceptable
Chemical name, structural formula, molecular weight	Provided	Rearranged and edited
Other important chemical or physical properties (such as pKa or pH)	provided solubility of avapritinib	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	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	N/A

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)	Film-coated tablets	Acceptable
Strength(s) in metric system	100 mg, 200 mg, and 300 mg	Acceptable
Available units (e.g., bottles of 100 tablets)	bottles of 30 tablets (for all strengths)	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable. NDC numbers are not finalized yet.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
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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	N/A
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.”	None	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	USP controlled room temperature	Acceptable. Should be consistent with container/carton label.
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	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

NA

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, 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):
Acceptable. Minor edits.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



3.2 Carton Labeling

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Pending (avapritinib) tablets	
Dosage strength	Provided	Acceptable
Route of administration	For oral use	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Provided	Acceptable
"Rx only" displayed on the principal display	displayed	Acceptable
NDC number	Provided	Acceptable
Lot number and expiration date	Provided in Carton label	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Provided	Edited
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Provided	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Acceptable
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap over seal	N/A	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	N/A
And others, if space is available	(b) (4): see Prescribing Information. KEEP AWAY FROM CHILDREN	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate. All comments have been conveyed to OND during labeling review meeting. Please refer to the updated labels for detail.

Primary Labeling Assessor Name and Date:

Xing Wang, Ph.D. **Reviewer, ONDP/DNDPI/NDPBII**

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

Anamitro Banerjee, Ph.D. **Branch Chief, ONDP/DNDPI/NDPBII**



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QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics



BIOPHARMACEUTICS

Application No: NDA 212608; AYVAKIT[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg
Route of Administration: Oral
Applicant Name: Blueprint Medicines Corporation
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

Background:

The Applicant is seeking an approval of Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring the PDGFR α D842V mutation, (b) (4)

(b) (4) The recommended daily dose for Ayvakit[®] (avapritinib tablets) is 300 mg orally once daily.

Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg is an immediate-release, film-coated tablet product that received Orphan Drug Designation (ODD 15-5004, 01/06/2016), Breakthrough Therapy Designation (06/01/2017), and Fast Track Designation (10/04/2016) for the treatment of patients with GIST harboring the PDGFR α D842V mutation. A pivotal Phase I safety and efficacy study, BLU-285-1101 was conducted in which 3 $\times$ 100 mg and 4 $\times$ 100 mg Ayvakit[®] (avapritinib tablets) was dosed to the patients with GIST and other relapsed and refractory solid tumors. To establish a 'bridge' between the 4 $\times$ 100 mg drug product used in the pivotal Phase I clinical study, BLU-285-1101 and the 400 mg drug product, a comparative bioavailability/bioequivalence (BA/BE) study, BLU-285-0105 was conducted. The current submission also contains a 'biowaiver' request for the 200 mg and 300 mg drug product that will be discussed in latter sections.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated the totality of the dissolution profile data to support **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, **3)** the need for bridging different drug substance and drug product manufacturing sites and formulations throughout the product development stage, and **4)** the biowaiver request for the 200 mg and 300 mg TBM drug product.

➤ ***Proposed Dissolution Method:***

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method is **ACCEPTABLE** as a quality control method for batch release and stability testing of the 100 mg, 200 mg, and 300 mg proposed drug product.

Parameters	Dissolution Method ACCEPTABLE
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Media/Volume</i>	0.5% CTAB in 50 mM sodium acetate, pH 5.0/900 mL
<i>Bath temperature</i>	37.0 $\pm$ 0.5 C

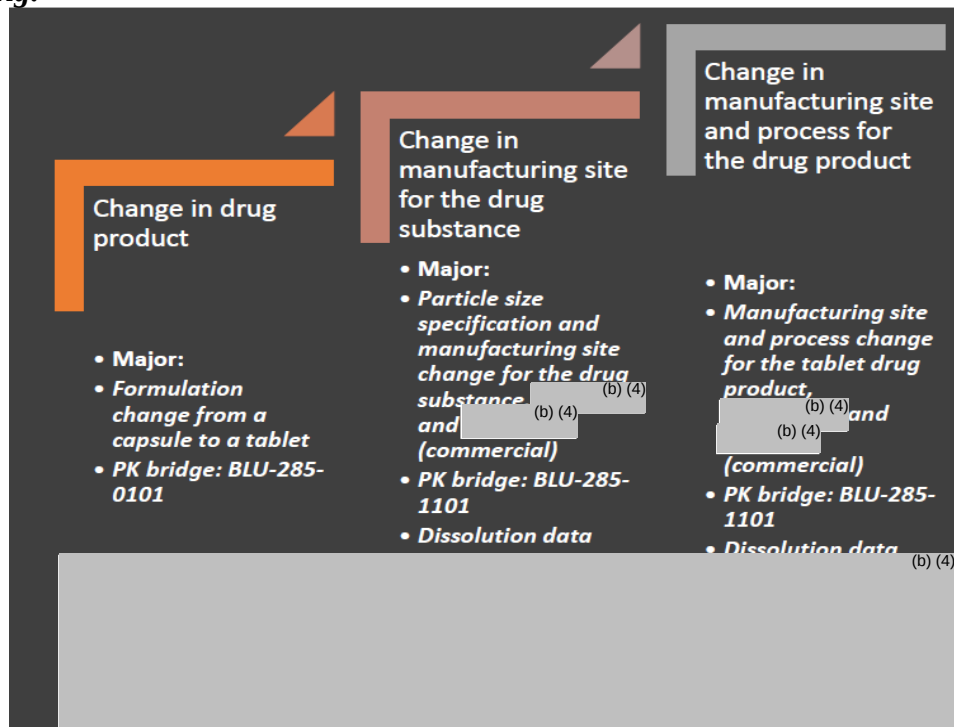
The proposed dissolution method exhibits limited discriminating ability with respect to the particle size distribution of the drug substance, presence and absence of (b) (4) in the tablet cores, (b) (4) for the 400 mg tablet cores, and on long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions.

➤ **Dissolution Acceptance Criterion:**

The proposed acceptance criterion of “Q (b) (4)% in 45 minutes” for batch release and stability testing of Ayvakit® (avapritinib tablets), 100 mg, 200 mg, and 300 mg drug product based on the clinical batch and registration batches was permissive and was not acceptable. An acceptance criterion of “Q (b) (4)% in 45 minutes” was recommended for the 100 mg, 200 mg, and 300 mg proposed product in an *Information Request* comment. The Applicant agreed to implement the recommended acceptance criterion of “Q (b) (4)% in 45 minutes” for each strength of the proposed product.

It should be noted that some stability batches for the 300 mg drug product would be out-of-specification (and subjected to Stage 2 and Stage 3 testing) or fail the acceptance criterion of “Q (b) (4)% in 45 minutes”. The Applicant requested (b) (4). Since, some stability batches for the 300 mg drug product would be out-of-specification or fail the acceptance criterion of “Q (b) (4)% in 45 minutes”, the shelf-life for the 300 mg drug product was set at 12 months by the Drug Product reviewer and the Applicant agreed.

➤ **Bridging:**



- *Bridging of Batches due to Change of the Drug Product :*

A relative bioavailability study BLU-285-0101 was conducted in 30 healthy adult male subjects to provide a 'bridge' for the 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product (Batches 16-0069 and 16-0083) manufactured at (b) (4) under fasted condition. The 90% confidence interval between the 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product (Batches 16-0069 and 16-0083) manufactured at (b) (4) under fasted condition dosed in the relative bioavailability study, BLU-285-0105 for C_{max} and AUC₀₋₇₂ are similar, indicating that the two products appears to exhibit similar bioavailability. However, the final determination of the adequacy of this data is made by the Office of Clinical Pharmacology (Please refer to OCP review for details).

- *Bridging of Batches due to Manufacturing Site Change for the Drug Substance:*

The commercial manufacturing site for the drug substance is (b) (4). However, a number of the 100 mg drug product batches used in the pivotal clinical trial, BLU-285-1101 were manufactured at (b) (4) using drug substance manufactured at (b) (4) and (b) (4). Since drug substance manufactured in both sites were used in the clinical trial, an additional bridging is not needed. However, it should be noted that the Applicant provided mean dissolution profile data for the drug product batches manufactured at (b) (4) using drug substance batches manufactured at (b) (4) and at (b) (4) that would be in compliance with the recommended dissolution acceptance criterion of '*Q* (b) (4) % in 45 minutes'.

- *Bridging of Batches due to Manufacturing Site and Manufacturing Process Change for the Drug Product :*

The Applicant identified (b) (4) as the commercial manufacturing site for the TBM 100 mg, 200 mg, and 300 mg drug product. A drug-in-capsule product was initially manufactured at (b) (4) and dosed in the pivotal safety and efficacy clinical trial BLU-285-1101. Later, the 100 mg and 200 mg tablet product that was manufactured at (b) (4) was introduced in the pivotal clinical trial BLU-285-1101.

The manufacturing process for the 100 mg tablet product was later transferred from (b) (4) to the commercial manufacturing site, (b) (4). The 200 mg, 300 mg, and 400 mg tablet drug product were also manufactured at the commercial manufacturing site, (b) (4). The 100 mg tablet product manufactured at (b) (4) was dosed in the pivotal clinical trial BLU-285-1101 to provide a bridge to the 100 mg drug product manufactured at (b) (4). The Applicant also provided mean in vitro dissolution profile data for the 100 mg drug product using the proposed dissolution method for batches manufactured at (b) (4) and (b) (4) using drug substance batches manufactured at (b) (4) that would be in compliance with the recommended dissolution acceptance criterion of '*Q* (b) (4) % in 45 minutes'.

➤ **Biowaiver Request:**

The biowaiver request for the 200 mg and 300 mg drug product is granted based on 1) the compositional proportionality between the 100 mg, 200 mg, 300 mg, and 400 mg strength drug product with respect to avapritinib, the active pharmaceutical ingredient (API) and excipients; 2) bioequivalence between the 4×100 mg and 400 mg drug products in the bioequivalence (BE) study, BLU-285-0105; 3) linear pharmacokinetics of the avapritinib drug product between the dose ranges of 100 mg-400 mg under fasted condition based on the bioavailability study BLU-285-1101; and 4) similarity in the dissolution profile data for the 100 mg, 200 mg, 300 mg, and 400 mg drug product.

➤ **Biopharmaceutics Risk Assessment:**

Avapritinib is a low solubility drug substance that exhibits several polymorphic forms. (b) (4) (b) (4) the most stable form. However, the (b) (4) can convert to (b) (4); and a (b) (4) can convert to (b) (4). Additionally, the drug product contains (b) (4). Avapritinib is a (b) (4) drug substance that has the potential to interact with (b) (4) on stability. From a Biopharmaceutics perspective, the potential of (b) (4) to convert to (b) (4) and/or interact with (b) (4) on stability may be the reason for the observed dissolution trend.

Several batches of the 300 mg and 400 mg drug product demonstrated a (b) (4) trend in the dissolution profile data on long-term and accelerated stability conditions that either required Stage 2 or Stage 3 testing or to be out-of-specification with the recommended dissolution acceptance criterion of ' $Q_{(b) (4)} \% \text{ in } 45 \text{ minutes}$ '. The Applicant was requested to address the (b) (4) trend in the dissolution data for the 300 mg drug product and provide mitigating solutions to avert dissolution failures. The Applicant requested (b) (4) (b) (4). As the 300 mg drug product exhibits (b) (4) trend in the dissolution profile data on stability, a 12-month shelf-life was granted for 300 mg drug product to avert quality risk to the drug product.

➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 212608 for AYVAKIT® (avapritinib tablets) containing 100 mg, 200 mg, and 300 mg avapritinib is recommended for **APPROVAL**.



QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics



BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
IND 125379 Meeting Minutes	Dated 07/18/2017 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2017-07-18-ind-125379-type-b-prelim-comments-ltr.pdf)
	Dated 07/27/2017 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2017-07-27-ind-125379-mtg-mins-ltr-registration-batch-size.pdf)
	Dated 10/10/2017 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2017-10-10-ind-125379-eop2-cmc-mtg-mins-ltr.pdf)
	Dated 09/24/2018 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2018-09-24-ind-125379-cmc-wro-ltr.pdf)
	Dated 02/15/2019 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2019-02-15-ind-125379-cmc-pre-nda-mtg-prelim-comments-ltr.pdf)
	Dated 03/28/2019 (\\cdsesub1\evsprod\nda212608\0001\m1\us\2019-03-28-ind-125379-cmc-pre-nda-mtg-mins.pdf)
Dissolution Method Advice Letter	Dated 05/07/2019 (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804f26d0)
Original NDA Submission 212608	Dated 06/14/2019, SDN 1 (\\cdsesub1\evsprod\nda212608\0001\m2\27-clin-sum\summary-biopharm.pdf)
Response to Information Request Comment #1	Dated 08/07/2019, SDN 5 (\\cdsesub1\evsprod\nda212608\0005\m1\us\quality-info-amend-ir-12july2019-dissolution-data.pdf)
Response to Information Request Comment #2	Dated 09/25/2019, SDN 15 (\\cdsesub1\evsprod\nda212608\0013\m1\us\quality-info-amend-ir-06sep2019-in-process-testing.pdf)

➤ **DRUG SUBSTANCE**

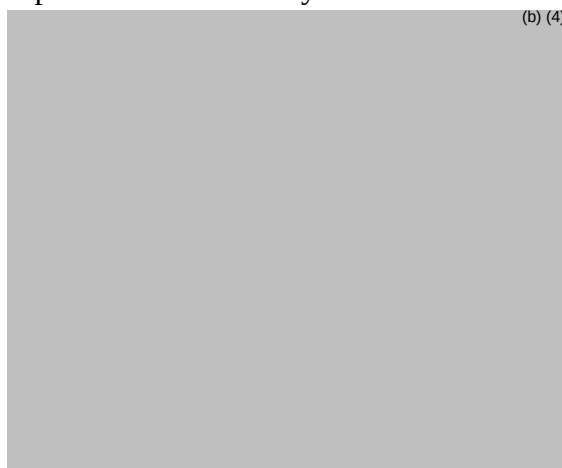
Avapritinib (molecular weight 498.57 grams/mole, free base) is the active ingredient in the proposed drug product with four (4) pKa's: 1.51 (pKa 4), 3.50 (pKa 3), 4.57 (pKa 2), and 6.97 (pKa1).

The drug substance exhibits one (1) chiral center with 'S' configuration and several (16) polymorphic forms including, (b) (4). The polymorphic forms can interconvert (b) (4), however, only one polymorph, (b) (4) It should be noted that the (b) (4) (b) (4); however, (b) (4) The (b) (4) is controlled during manufacturing process, at batch release, and on stability through analytical testing. The drug substance exhibits aggregate/agglomerate-like morphology.

Figure 1a. Different polymorphic forms of avapritinib



Figure 1b. Effect of temperature and humidity on the interconversion of avapritinib polymorphic



- **Solubility:**

The equilibrium solubility of avapritinib was conducted in fasted simulated gastric fluid (FaSSGF), and fasted and fed simulated intestinal fluids (FaSSIF and FeSSIF) at 37 C for 24 hours and 120

hours (see **Table 1a**) and in buffer solutions across the physiological pH range 1.0-8.01 at room temperature for 24 hours and 120 hours (see **Table 1b**).

Table 1a. Equilibrium solubility of avapritinib in simulated gastric (FaSSGF) and intestinal fluids (FaSSIF and FeSSIF) at 37 C for 24 hours and 120 hours

Solvent System	Final pH	Solubility (mg/mL) (after 1 hour)	USP Definition
Fasted state simulated gastric fluid (FaSSGF) ¹	5.61	17.22	Sparingly Soluble
Fasted state simulated intestinal fluid (FaSSIF)	6.51	0.03	Practically Insoluble
Fed state simulated intestinal fluid (FeSSIF)	5.21	1.16	Slightly Soluble

¹ Solubility was measured after one hour due to compound precipitation as HCl salt
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

Table 1b. Equilibrium solubility of avapritinib in buffer solutions across the physiological pH range 1.0-8.01 for 24 hours and 120 hours at room temperature

Target pH	Final pH (120 h)	Solubility mg/mL (USP Definition) (24 h)	Solubility mg/mL (USP Definition) (120 h)
pH 1.00 (0.1N HCl)	3.58	4.38 (Slightly Soluble)	3.64 (Slightly Soluble)
pH 2.53 (Potassium hydrogen phthalate and hydrochloric acid buffer solution)	4.23	0.17 (Very Slightly Soluble)	0.14 (Very Slightly Soluble)
pH 4.01 Potassium hydrogen phthalate and hydrochloric acid buffer solution	5.23	0.05 (Very Slightly Soluble)	0.07 (Very Slightly Soluble)
pH 6.03 Monobasic potassium phosphate and sodium hydroxide buffer solution	6.06	<0.002 (Practically Insoluble)	<0.007 (Practically Insoluble)
pH 7.02 Monobasic potassium phosphate and sodium hydroxide buffer solution	6.93	<0.001 (Practically Insoluble)	<0.001 (Practically Insoluble)
pH 8.01 Boric acid, potassium chloride, and sodium hydroxide buffer solution	7.99	<0.001 (Practically Insoluble)	<0.001 (Practically Insoluble)
Water	--	<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

Reviewer's Assessment of Drug Substance Solubility:

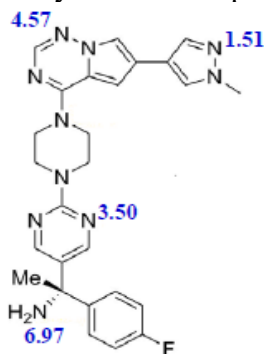
The free base exhibits pH-dependent low solubility (3.64 mg/mL) in pH 1.0 following 120 hours equilibration and very low solubility (<0.2 mg/mL) in phosphate buffer, pH 2.53-8.01 at room temperature at the end of 120 hours equilibration (see **Table 1b**). However, following 1 hour equilibration the drug substance exhibits comparatively high solubility (17.22 mg/mL) in FaSSGF. Consequently, the highest dose of the drug substance, i.e., 300 mg is not soluble in 250 mL buffer solutions across the physiological pH range 1.0-8.01 (**Table 1a** and **Table 1b**). Therefore, avapritinib is classified as a low soluble drug substance per Biopharmaceutics Classification System (BCS).

It should be noted that avapritinib demonstrates buffering capacity, shifting the pH of the acidic buffers from pH 1.0-4.01 to weakly acidic buffers, pH 3.58-5.23.

- **Permeability/Absorption:**

Avapritinib has four (4) pKa's: pKa (1)=6.97, pKa (2)=4.57, pKa (3)=3.50, and pKa (4)=1.51 (see **Figure 2**). The LogP and LogD of avapritinib will approximately be similar at pH 7.4 (due to the pKa (1)) and was experimentally determined to be 3.20 and 3.34 (at pH 7.4).

Figure 2. Experimentally determined pKa's in avapritinib



The apparent permeability (P_{app}) of avapritinib (10 μ M) was determined to be 7.9×10^{-6} cm/s in human intestinal epithelial monolayers (Caco-2 cells) that was comparable to compounds that exhibit moderate-high permeability in humans. The efflux ratio was determined to <2.0, suggesting that avapritinib is not a P-glycoprotein substrate.

Additionally, following a single oral dose of 310 mg (100 μ Ci) [¹⁴C]-avapritinib, in healthy volunteers (Study BLU-285-0103), approximately 70.3% of the total radioactive dose was recovered in feces and 17.9% was recovered in urine. The mean recovery of the total administered radioactive dose was approximately 88.2%. Unchanged avapritinib accounted for 11% of >90% recovered radioactive dose in feces, whereas the remaining 59.6% of the recovered radioactivity in feces represented different metabolites. In urine, unchanged avapritinib accounted for only 0.23% of the >90% recovered radioactive dose; whereas metabolites accounted for 14.4% of the recovered dose.

On the other hand, median time to reach maximum concentration (T_{max}) following a single 200 mg (2 $\times$ 100 mg) oral dose of avapritinib tablets in N=30 healthy adult male subjects in the open-label,

randomized, 2-way cross-over food effect study BLU-285-1012 is approximately 4.375 (2.00-24.16) hours under fasted condition and approximately 5.502 (2.00-10.00) hours under fed condition. The maximum concentration, $C_{\max}$ =195 (42.9) ng/mL and exposure ($AUC_{0-\infty}$)=10840 (36.9) hours×ng/mL under fasted state, and 311.3 (19.6) ng/mL and 14030 (32.2) hours×ng/mL, respectively under fed state, demonstrating that high calorie food has an impact on the $C_{\max}$ and overall exposure of the drug. In the same study, the terminal half-life ($t_{1/2}$) was determined to be long, 49.532 hours and the clearance (CL/F) was determined to be slow (18.44 L/hours).

Reviewer's Assessment of Permeability/Absorption:

Based on the in vitro permeability and in vivo bioavailability studies, avapritinib can be categorized as a 'moderate' permeability drug substance. From totality of the solubility and permeability data, avapritinib may be classified as a low soluble and moderate permeability BCS Class II/IV drug substance, per Biopharmaceutics Classification System (BCS).

MANUFACTURING SITES FOR THE PROPOSED DRUG SUBSTANCE:

The commercial manufacturing site for the drug substance is (b) (4).

However, some batches of the 100 mg drug product used in the pivotal clinical trial, BLU-285-1101 were manufactured using drug substance manufactured at (b) (4) and (b) (4). Additionally, the (b) (4) site was also used for manufacturing some drug substance batches that were used in the manufacture of the 100 mg drug product (18K23G) used in clinical trials. The drug substance batches manufactured at different manufacturing sites is provided in **Table 2a**, **Table 2b**, and **Table 2c**.

Table 2a. Drug substance batches manufactured at (b) (4) manufacturing site, using Process (b) (4)

Batch	Date of Manufacture	Batch Size	Use	Drug Product Lots (Manufacture)	Tablet Strength
0285P/01	Nov 2017	(b) (4)	Clinical	18C13G, 18G05G	100
0285P/02	Jun 2018		Clinical	19B02G	100 mg
				19B04G	100 mg
				18L10G	200 mg
				18L14G	300 mg

Table 2b. Drug substance batches manufactured at commercial manufacturing site, (b) (4) using Process (b) (4)

Batch	Date of Manufacture	Batch Size (kg)	Use	Drug Product Lots (Manufacture)	Tablet Strength (mg)
BG0635	Mar 2016	(b) (4)	Clinical, Stability	16-0067 16-0069 16-0083 16-0156	10 100 100 200
BG0677	Nov 2016		Clinical	16-0198 16-0199 17-0001 17-0026 17-0052 17-0063	100 100 100 100 100 100
BH0709	Apr 2017		Clinical	17-0061	100
BH0710	Apr 2017		Clinical	17-0061	100
BH0725	Jun 2017		Clinical, Registration Stability	17G03C 17L10G 17M04G	100 100 100
BH0732	Aug 2017		Clinical, Registration Stability	17H15G 17L06G 17L10G 17M04G	100 100 100 100
BH0734	Aug 2017		Clinical, Registration Stability	17L03G 17L10G 17M04G 17K20G 17K21G 17M05G	100 100 100 200 300 400
BH0741	Sep 2017		Clinical	17M01G	100
BH0774	Dec 2017		Clinical	18B03G 18B14G	100
BJ0864	Nov 2018		PPQ		
BJ0869	Dec 2018		PPQ		
BJ0870	Dec 2018		PPQ		

¹ Lot BH0670 recovered from (b) (4) obtained from lot BG0677 manufacturing) and is not representative of the Process (b) (4) A (b) (4) was employed on this and all subsequent lots

Table 2c. Drug substance batches manufactured at (b) (4) manufacturing site, using Process (b) (4)

Batch	Date of Manufacture	Batch Size	Use	Drug Product Lots (Manufacture)	Tablet Strength
17600T001	Dec 2017	(b) (4)	Clinical	18K23G	100 mg
17600T002	Dec 2017		Clinical		
17600T003	Dec 2017		Clinical		

➤ **DRUG PRODUCT:**

The to-be-marketed (TBM) drug product is an immediate-release, film-coated, 100 mg (round shape), 200 mg (caplet shape), or 300 mg (caplet shape) avapritinib tablet product (see **Table 3** for composition of the 100 mg, 200 mg, and 300 mg drug product). The TBM drug product is manufactured using (b) (4) method.

Table 3. Composition of Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg

Description	Component	Percent (w/w)	Target Quantity (mg/tablet)		
			100 mg	200 mg	300 mg
Core Tablet	Avapritinib	(b) (4)	100.0	200.0	300.0
	Microcrystalline cellulose	(b) (4)	(b) (4)		
	(b) (4)				
	Copovidone				
	Croscarmellose Sodium				
	Magnesium Stearate				
	(b) (4)				
Total Core Weight (mg)					
Film Coat	(b) (4)		(b) (4)		
Printing Ink					
Total Tablet Weight (mg)			257.5	515.0	772.5

a

(b) (4)

➤ **MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:**

(b) (4) is identified as the commercial manufacturing site for the to-be-marketed (TBM) Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg drug product.

Initially, 5-100 mg drug-in-capsule product manufactured at (b) (4) was dosed in the pivotal safety and efficacy clinical trial BLU-285-1101. However, the drug-in-capsule product was replaced by the 100 mg and 200 mg tablet drug product that was manufactured at (b) (4) (see **Table 4a**). The 100 mg tablet product was dosed in the pivotal clinical trial BLU-285-1101.

The manufacturing process for the 100 mg tablet product was later transferred from (b) (4) to the commercial manufacturing site, (b) (4). The 200 mg, 300 mg, and 400 mg tablet drug product were also manufactured at the commercial manufacturing site, (b) (4) to support some clinical trials (see **Table 4b**). The 100 mg tablet product manufactured at (b) (4) was dosed in the pivotal clinical trial BLU-285-1101 to provide a bridge to the 100 mg drug product manufactured at (b) (4).

In addition, the Applicant provided in vitro dissolution profile data for the 100 mg drug product using the proposed dissolution method for batches manufactured at (b) (4) and (b) (4) and will be discussed under “**Bridging of Batches**”.

Table 4a. Early clinical batches of avapritinib drug product manufactured at (b) (4) and used in Phase 1 and 2 clinical trials

Strength	Lot No.	Date of Manuf.	Lot Size (units)	Drug Substance		Clinical			Stability
				Batch No.	Process	1101	0101	2101	
Drug in Capsules									
5 mg	15-0060	May-15	(b) (4)	BE0581	(b) (4)	X	--	X	X
10 mg	15-0013	Jan-15		BG0635		X	--	X	X
	16-0067	Apr-16				X	--	X	X
30 mg	15-0014	Jan-15		BE0581		X	--	X	X
	15-0117	Oct-15				X	--	X	--
100 mg	15-0015	Feb-15		BE0581		X	--	X	X
	15-0118	Oct-15				X	--	X	--
	16-0069	Apr-16		BG0635		X	X	X	X
	16-0083	May-16				X	X	X	--
	16-0198	Nov-16				X	--	X	--
	16-0199	Dec-16		BG0677		X	--	X	--
	17-0001	Jan-17				X	--	X	--
	17-0063	Apr-17				X	--	X	--
Tablet Formulation									
100 mg	17-0026 ¹	Feb-17	(b) (4)	BG0677	(b) (4)	X	--	X	X
	17-0052	Mar-17		BG0677		X	--	X	--
	17-0061	Apr-17		BH0709, BH0710		X	--	X	X
200 mg	16-0156	Aug-16		BG0635		--	X	--	--

¹ lot also used in 0102 and 0103 studies

Table 4b. Clinical batches of avapritinib drug product manufactured at commercial manufacturing site, (b) (4) and used in Phase 1 and 2 clinical trials

Manufacturing Site,				and used in Phase 1 and 2 clinical trials								
Strength	(b) (4)	Lot No. ¹	Date of Manuf.	Lot Size (units) ²	Drug Substance		Clinical					Stability Lot no.
	Lot No.				Batch No.	Process	1101	1303	0102	0105	2101	
100 mg	17G01C	17G03C	Jul-17	(b) (4)	(b) (4)	(b) (4)	X	--	--	--	X	17K17G (P)
	17H07G	17H15G ³	Aug-17	(b) (4)	(b) (4)	(b) (4)	X	--	--	X	X	17K18G (P)
		17L06G	Aug-17				X	--	--	--	X	NA
	17J02G	17L03G	Sep-17	(b) (4)	(b) (4)	(b) (4)	X	--	--	--	X	17K19G (P)
	17G01C	17L10G	Jul-17				X	X	--	--	X	NA
	17L21G	17M04G	Dec-17	(b) (4)	(b) (4)	(b) (4)	X	X	--	--	X	NA
	17L15G	17M01G	Nov-17				X	--	--	--	X	NA
	18A07G	18B03G	Jan-18	(b) (4)	(b) (4)	(b) (4)	X	X	--	--	X	NA
	18A12G	18B14G	Feb-18				X	X	--	--	X	NA
	18B18G	18C13G	Mar-18	(b) (4)	(b) (4)	(b) (4)	X	X	--	--	X	NA
	18G03G	18G14G	Jul-18	(b) (4)	(b) (4)	(b) (4)	X	X	--	--	X	NA
	18G18G	18H07G	Jul-18	(b) (4)	(b) (4)	(b) (4)	X	X	--	--	X	NA
	18H19G	18K23G	Aug-18	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA
200 mg	18K24G	19B02G	Oct-18	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA
	19B04G	Oct-18	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA	
	17J02G	17K20G	Sep-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	17K20G (S)
300 mg	17L15G	17L18G	Nov-17	(b) (4)	(b) (4)	(b) (4)						NA
	18K24G	18L10G	Mar-19	(b) (4)	(b) (4)	(b) (4)						NA
	17J02G	17K21G ³	Sep-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	17K21G (S)
	17L15G	17L20G	Nov-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA
400 mg	18A07G	18D11G	Jan-18	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA
	18K24G	18L14G	Mar-19	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	NA
	17G01C	17K22G	Jul-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	17K22G (P)
400 mg	17H07G	17K23G	Aug-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	--	--	17K23G (P)
	17J02G	17M05G	Sep-17	(b) (4)	(b) (4)	(b) (4)	--	--	--	X	--	17K24G (P)

(P) – primary registration stability; (S) – supportive stability

- 1 Lot number are from packaging records for all 100 mg and from (b) (4) record for all 200 mg, 300 mg and 400 mg (except for 400 mg lot 17M05G which is from packaging record)
- 2 Lot size shown here are approximate packaged units for 100 mg and (b) (4) lots for 200mg, 300 mg and 400 mg
- 3 (b) (4) batch record for this lot was inadvertently lost. Refer to 3.2.P.2.2 Drug Product – (b) (4) for more information

Particle Size Distribution (PSD) for the Drug Substance and (b) (4)

Avapritinib is a low aqueous soluble drug substance. The drug substance exhibits (b) (4) stable polymorph with aggregate/agglomerate-like morphology. The TBM drug product uses (b) (4) manufacturing method. The PSD of the drug substance and (b) (4) (see **Table 5a**) was evaluated throughout the product development using the proposed dissolution method to determine if particle size of the drug substance and/or (b) (4) altered the dissolution of the drug product.

Table 5a. Effect of particle size distribution (PSD) of the drug substance and (b) (4) on the dissolution of the 100 mg drug product (at 45 minutes) during product development

Drug Product Batch Number	Drug Substance				(b) (4)			Dissolution (% Release at 45 Minutes)	
	Manufacturer and Batch Number	D10, μm	D50, μm	D90, μm	D10, μm	D50, μm	D90, μm		
17K17G	(b) (4) BH0725	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	96.1	
17K18G								BH0732	97.7
17K19G								BH0734	92.1
17L10G ^a								BH0725	91.6
17M01G								BH0741	92.1
17M04G ^b								BH0732 (91%), BH0734 (9%)	98.2
18B03G								BH0774	91.7
18B14G									91.6
18C13G	(b) (4) 0285P/01	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	89.4	
18G14G									93.1
18H07G									94.3
18K23G ^b								17600T0001 (33%) 17600T0002 (67%)	86.8
19B02G ^c								0285/02	81.3
19B04G ^c									83.0
19C25G ^b								18600T0001 (22%) 18600T5004 (40%) 18600T9005 (38%)	87.4
19E27G								17600T0003 (62%) 18600T9005 (38%)	91.1
19F23G	0285/03	91.0							
Correlation (r ²) to % Dissolved at 45 minutes (number of batches)		0.003 (n=12)	0.590 (n=12)	0.843 (n=12)	0.000 (n=14)	0.149 (n=14)	0.157 (n=14)	N/A	

^a Batch data was omitted from regression analyses due to unknown impact of (b) (4)

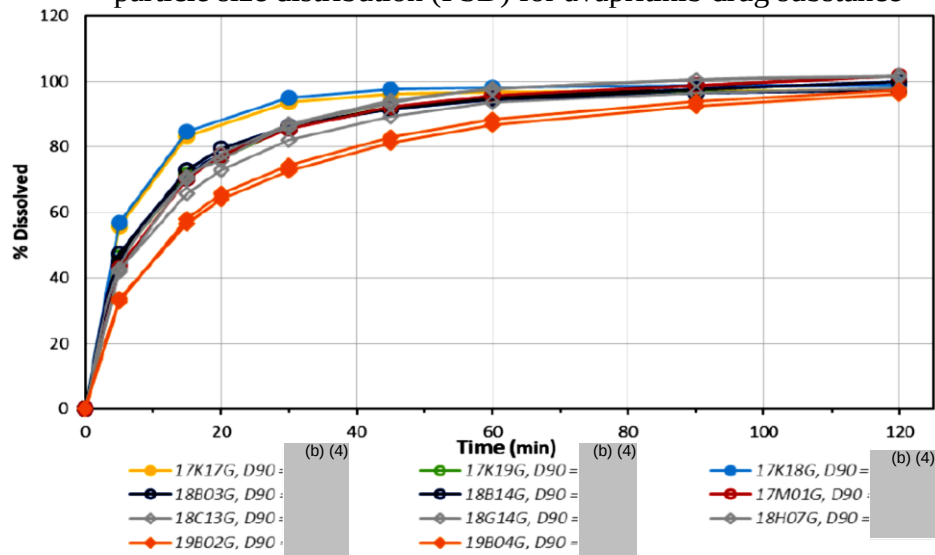
^b Batch data was omitted from DS regression analyses due to multiple DS batches being combined; DS particle size calculated via weighted average (b) (4)

^c Batch was split (b) (4) into two tablet batches

Drug product batches listed in **Table 5a** were manufactured with drug substance manufactured at either (b) (4) facility. However, drug product batches manufactured with (b) (4) drug substance were either dosed in the Phase 1 clinical trial and/or are stability batches.

Mean dissolution profile data for 100 mg drug product (see **Figure 3a**) manufactured with smaller particle size: $D_{90} = (b) (4) \mu\text{m}$ of avapritinib drug substance demonstrates >85% release of avapritinib at 45 minutes. However, the release of avapritinib is significantly slower for drug product manufactured with larger particle size: $D_{90} = (b) (4) \mu\text{m}$ of avapritinib drug substance.

Figure 3a. Mean dissolution profile data for 100 mg drug product to support the proposed particle size distribution (PSD) for avapritinib drug substance



Reviewer's Assessment of the proposed PSD for the drug substance:

Based on the totality of the dissolution data for registration, clinical, and PPQ drug product batches manufactured with drug substance from (b) (4) and three (3) sigma (σ) calculations (see **Table 5a** and **Table 5b**), the Applicant proposed the three-tier PSD: $D_{10} = \text{NLT } (b) (4) \mu\text{m}$, $D_{50} = (b) (4) \mu\text{m}$, and $D_{90} = \text{NMT } (b) (4) \mu\text{m}$ for the drug substance. The adequacy of the proposed drug substance particle size is determined by the DS reviewer, refer to DS review section.

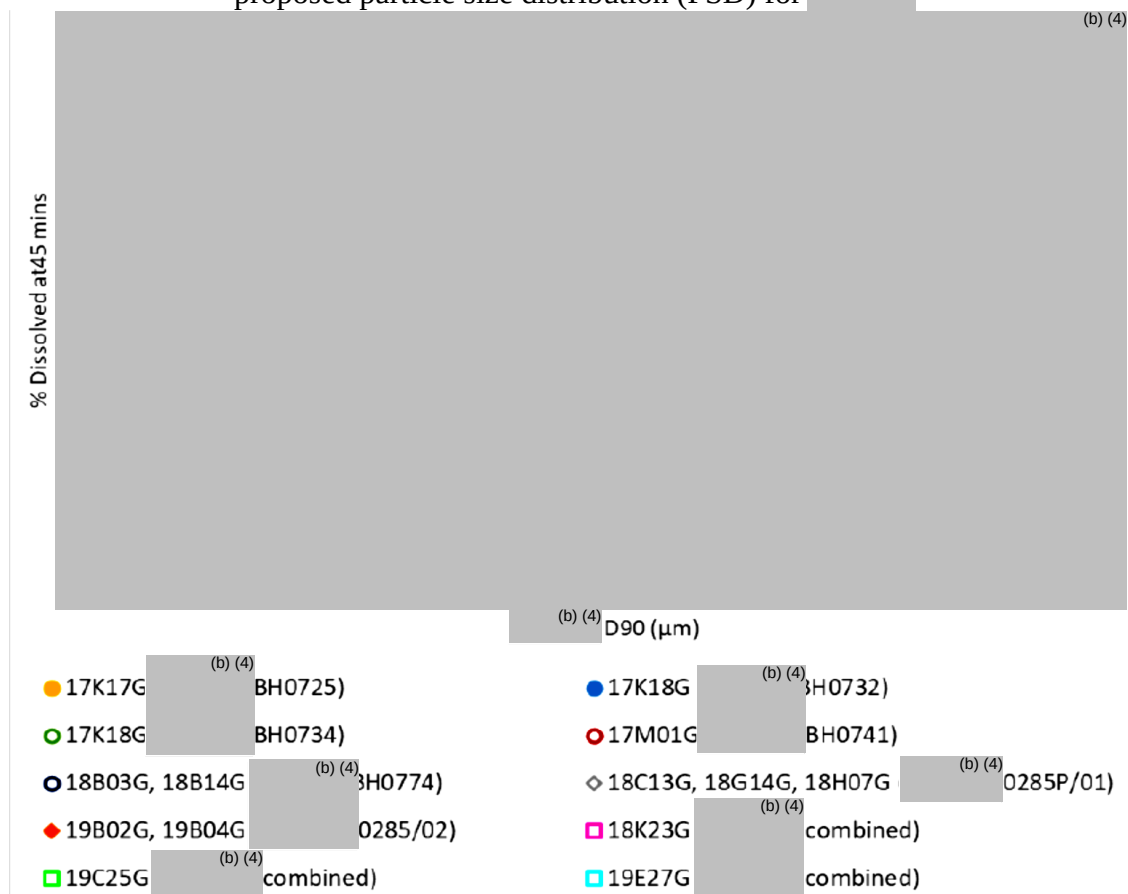
Table 5b. PSD of the drug substance manufactured at (b) (4) used to manufacture registration, clinical and PPQ drug product batches

Clinical and PPQ drug product batches		d10	d50	d90
Batch #	Use	(b) (4)		
BH0725	Registration, Clinical			
BH0732	Registration, Clinical			
BH0734	Registration, Clinical			
BH0741	Clinical			
BH0774	Clinical			
BJ0864	PPQ			
BJ0869	PPQ			
BJ0870	PPQ			
St Dev				
Min				
Max				
Mean				
-3σ				
+3σ				

Reviewer's Assessment of the PSD for (b) (4):

Because PSD of the drug substance and (b) (4) can have an impact on the dissolution of the final drug product, the Applicant was recommended to propose a three-tier PSD for the (b) (4) in an *Information Request*. The Applicant provided a correlation between D₉₀ of the (b) (4) and dissolution data at 45 minutes to demonstrate that PSD of the (b) (4) did not have an impact on the dissolution of the final drug product (see **Figure 3b**). However, for most (b) (4) batches, (b) (4) D₉₀ < (b) (4) μm demonstrated >85% release of avapritinib in 45 minutes. The adequacy of the (b) (4) particle size is determined by the Process and Facilities reviewer, refer to Process and Facilities review section.

Figure 3b. Mean dissolution profile data at 45 minutes for 100 mg drug product to support the proposed particle size distribution (PSD) for (b) (4)



➤ **DISSOLUTION INFORMATION:**

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and was utilized as a quality control tool throughout the product development process, for release of batches used in the pivotal clinical PK studies, and for batches on long-term and accelerated stability conditions. The dissolution method was also utilized to bridge the drug substance and drug product batches manufactured at various manufacturing sites, and for the

‘waiver’ of in vivo bioequivalence studies for the 200 mg and 300 mg strength commercial drug product.

➤ **DISSOLUTION METHOD:**

The dissolution method proposed for routine quality control testing of the proposed drug product is provided in **Table 6a**. The dissolution method development was performed with the 100 mg drug product.

Table 6a. Proposed dissolution method for quality control testing of Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, 300 mg, and 400 mg drug product

Parameters	Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Media/Volume</i>	0.5% CTAB in 50 mM sodium acetate buffer, pH 5.0/900 mL
<i>Bath temperature</i>	37.0±0.5 C

Selection of Dissolution Medium and Volume:

(b) (4)

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Discriminating Ability of the Proposed Dissolution Method:

The Applicant identified the following critical material attributes (CMA) and critical process parameters (CPP) to support the discriminating ability of the proposed dissolution method:

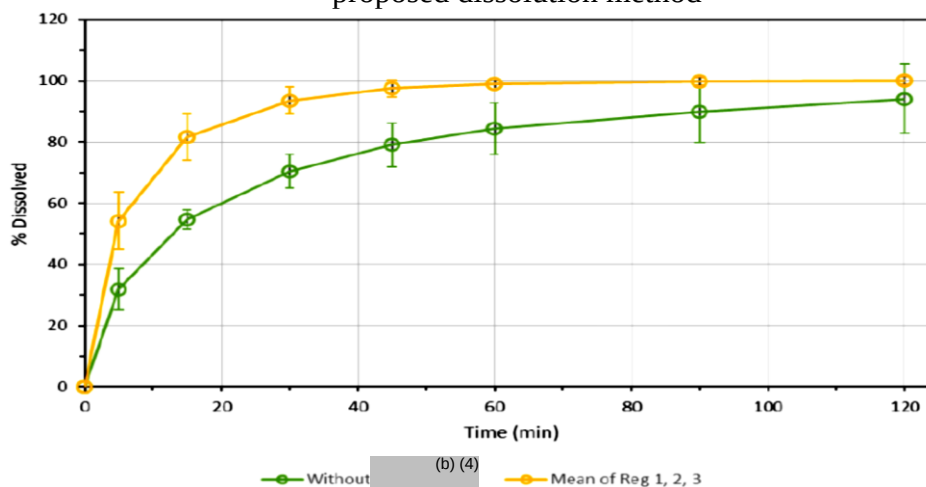
Table 7. Critical Quality Attributes (CQA) evaluated to support the discriminating ability of the proposed dissolution method

CPP	Impact on dissolution
(b) (4)	Increased hardness of tablet cores results in decreased dissolution rate.
CMA	Impact on dissolution
Physical characteristics of the API	Increased particle size (D90) of the API results in decreased dissolution rate.
Additional Factors Investigated	Impact on dissolution
Formulation changes	Removal of (b) (4) from the formulation results in decreased dissolution rate.
Amount of film coating	No impact on dissolution rate.
Stability of avapritinib tablets	Exposure of tablets to accelerated stability results in decreased dissolution rate.

Effect of (b) (4) on the Dissolution of the Tablet Cores:

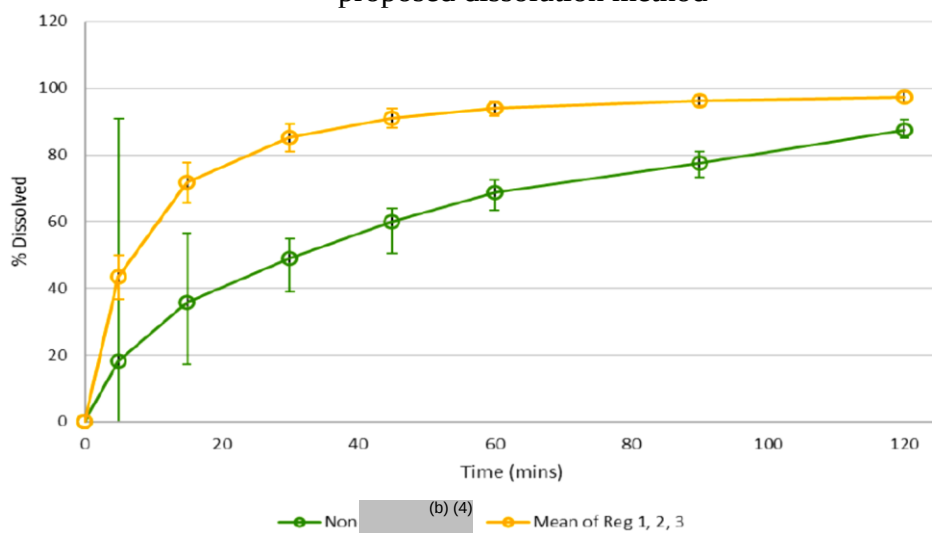
The effect of presence and absence of (b) (4) in the proposed product) on the dissolution of the tablet cores was evaluated to support the discriminating ability of the proposed dissolution method.

Figure 8a. Effect of (b) (4) on the dissolution of the 100 mg tablet cores using the proposed dissolution method



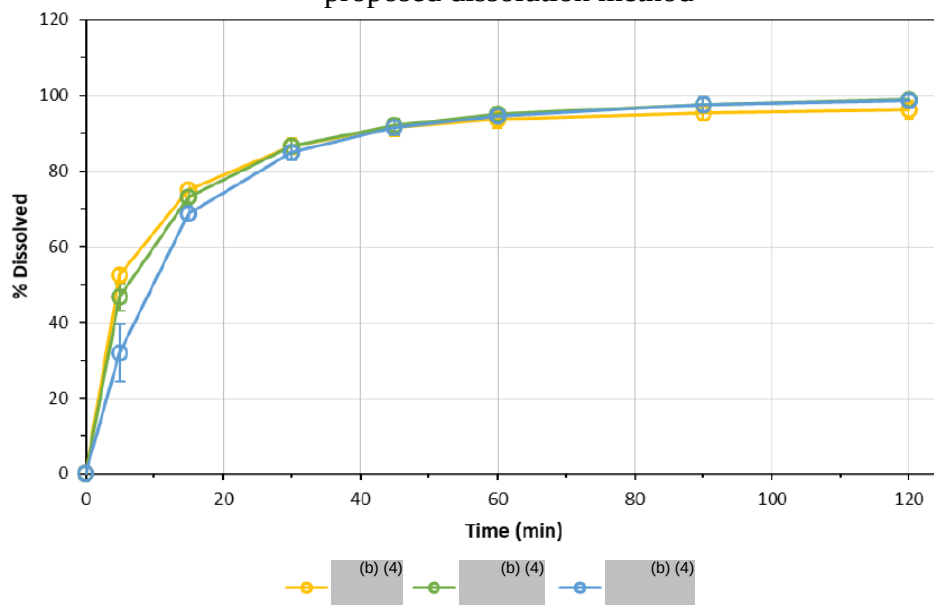
The dissolution of the 100 mg tablet cores was significantly slowed in the absence of (b) (4) using the proposed dissolution method. Similar results were obtained with 400 mg tablet cores in the absence of (b) (4) and would fail the dissolution acceptance criterion of $Q_{(b) (4)}\%$ at 45 minutes (see **Figure 8a** and **Figure 8b**).

Figure 8b. Effect of (b) (4) on the dissolution of the 400 mg tablet cores using the proposed dissolution method



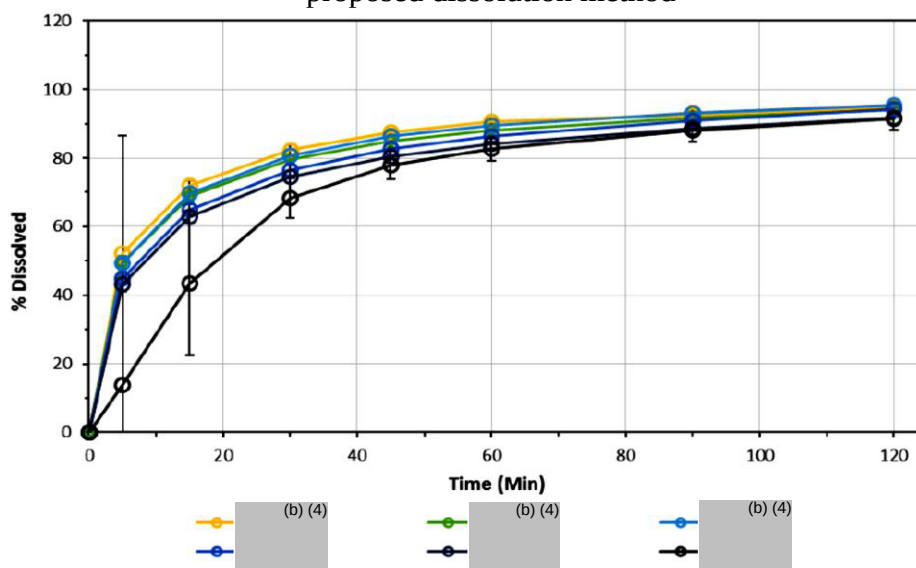
Effect of (b) (4) on Dissolution of Tablet Cores:

Figure 9a. Effect of (b) (4) on the dissolution of the 100 mg tablet cores using proposed dissolution method



Dissolution of the 100 mg tablet cores was similar, with >85% release of avapritinib in 45 minutes using the proposed dissolution method when (b) (4). Similar results were obtained with 400 mg tablet cores at (b) (4). However, dissolution of the 400 mg tablet cores slowed and would fail the dissolution acceptance criterion of Q (b) (4)% at 45 minutes when (b) (4) (see **Figure 9a** and **Figure 9b**).

Figure 9b. Effect of (b) (4) on the dissolution of the 400 mg tablet cores using proposed dissolution method



Effect of Long-Term and Accelerated Stability Conditions:

Figure 10a. Effect of long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions on the dissolution of the 100 mg TBM product, Batch 17K19G using proposed dissolution method

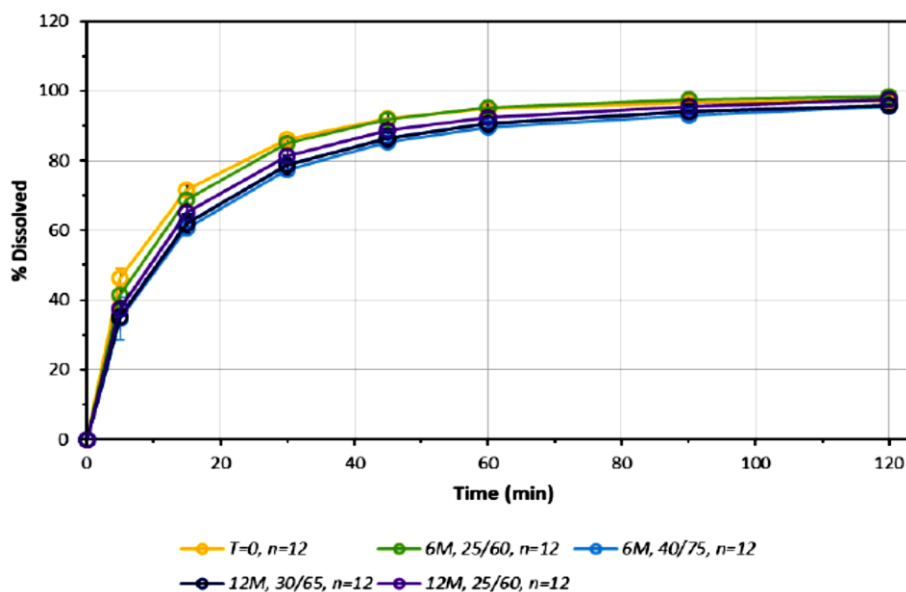
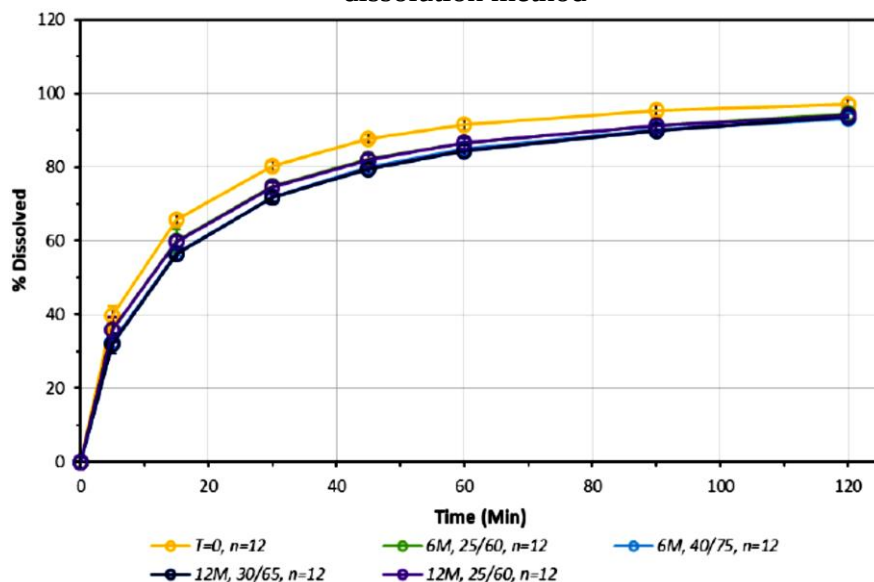


Figure 10b. Effect of long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions on the dissolution of the 400 mg TBM product, Batch 17K24G using proposed dissolution method



A (b) (4) trend in the mean dissolution data of the 100 mg (Batch 17K19G) and 400 mg (Batch 17K24G) TBM drug product is observed on long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions for up to 12 months, with <85% release of avapritinib in 45 minutes using the proposed dissolution method. The 400 mg (Batch 17K24G) TBM drug product would fail the dissolution acceptance criterion of ‘Q (b) (4) % at 45 minutes’ on long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions at 6 months and 12 months (see **Figure 10a** and **Figure 10 b**).

Taken together, based on the totality of the mean dissolution profile data, the proposed dissolution method exhibits limited discriminating ability with respect to the particle size distribution of the drug substance, presence and absence of (b) (4) in the tablet cores, higher (b) (4) for the 400 mg tablet cores, and on long-term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions.

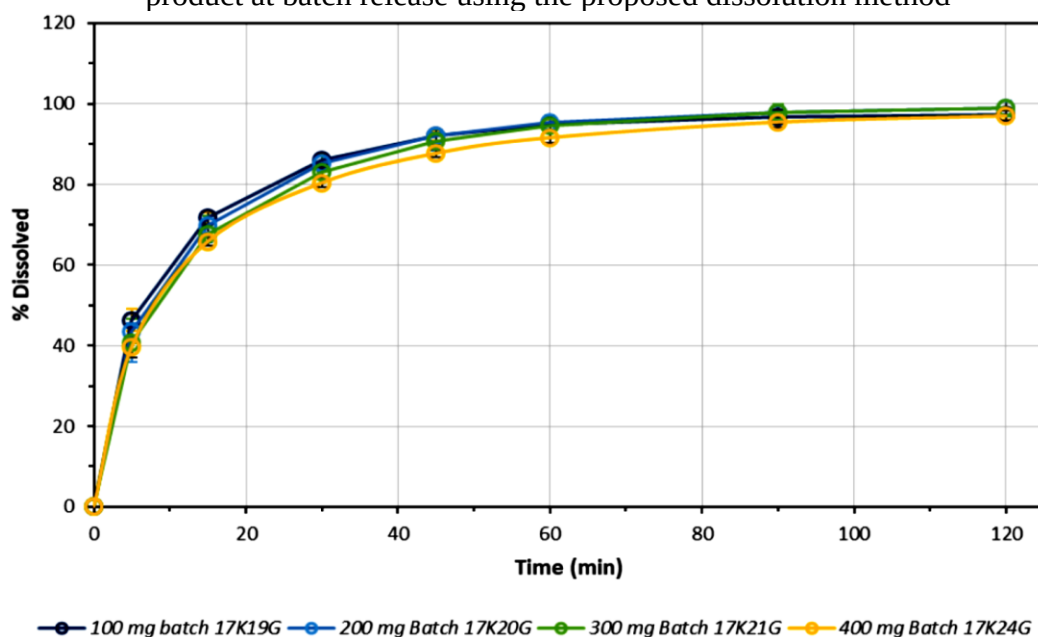
➤ **PROPOSED DISSOLUTION ACCEPTANCE CRITERION:**

The Applicant proposed “Q (b) (4) % in 45 minutes” as the dissolution acceptance criterion for batch release and stability testing of Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, 300 mg, and 400 mg drug product, which is permissive and not acceptable.

Dissolution Data at Batch Release:

The mean dissolution profile data for the 100 mg, 200 mg, 300 mg, and 400 mg drug product at batch release using the proposed dissolution method is provided in **Figure 11**.

Figure 11. Mean dissolution profile data for the 100 mg, 200 mg, 300 mg, and 400 mg drug product at batch release using the proposed dissolution method



Greater than 85% of avapritinib is released in 45 minutes from the 100 mg, 200 mg, 300 mg, and 400 mg drug product. The similarity factor ' f_2 ' value between the 100 mg, 200 mg, and 300 mg drug product, and 400 mg drug product is >50 using the Automation Tool that is indicative of similarity in the dissolution profiles. It should be noted that only 100 mg, 200 mg, and 300 mg drug product will be commercialized.

Based on the overall mean dissolution profile data for the 100 mg, 200 mg, 300 mg, and 400 mg drug product at batch release, " $Q^{(b)}(4)\%$ in 45 minutes" was recommended as the acceptance criterion for each strength of the drug product in an *Information Request* comment on 09/06/2019. In response to the *Information Request* the Applicant accepted the recommended acceptance criterion for the 100 mg, 200 mg, and 300 mg drug product.

Dissolution Data at Long-Term Stability Testing:

The mean dissolution profile data for the 100 mg and 200 mg drug product on long-term (25 C/65%RH) stability conditions for up to 12 months indicate $>85\%$ release of avapritinib in 45 minutes (see **Figure 12a** and **Figure 12b**).

Figure 12a. Mean dissolution profile data for 100 mg (bio-batch 17K17G) drug product on long-term stability for up to 12 months using the proposed dissolution method

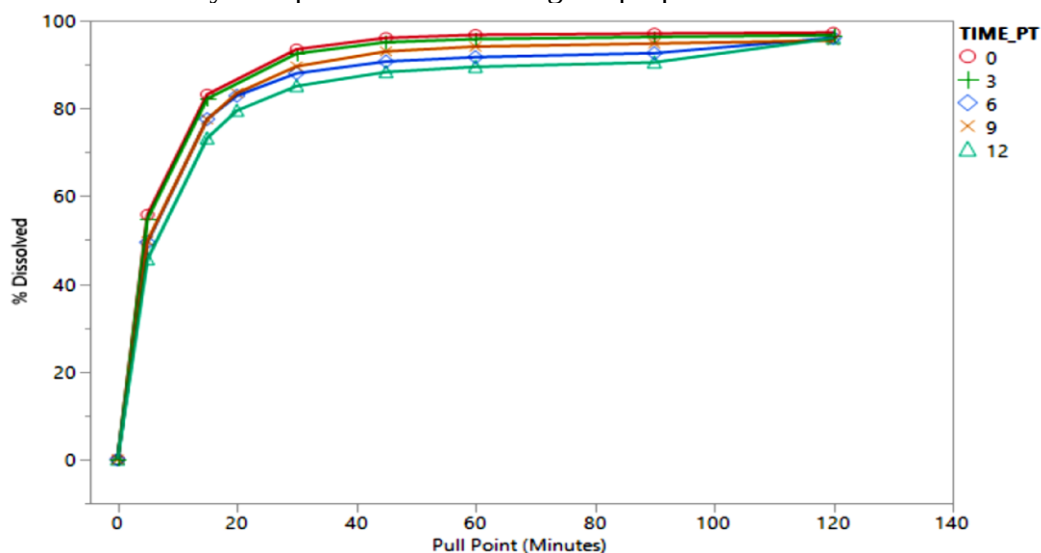
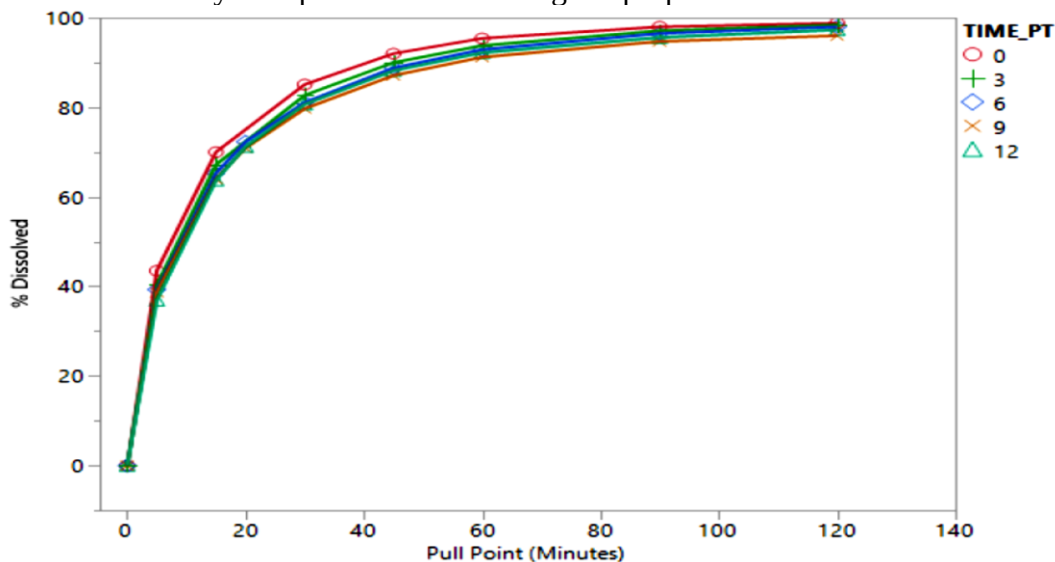


Figure 12b. Mean dissolution profile data for 200 mg (batch 17K20G) drug product on long-term stability for up to 12 months using the proposed dissolution method



However, a (b) (4) trend in the mean dissolution profile data is observed for the 300 mg (batch 17K21G) drug product on long-term stability for up to 12 months using the proposed dissolution method, with (b) (4)% release of avapritinib in 45 minutes (see **Figure 12c**) and would fail the recommended acceptance criterion of " $Q^{(b) (4)}$ % in 45 minutes".

Similar trend is not observed for the mean dissolution profile data for the 400 mg (batch 17K22G) drug product on long-term stability for up to 12 months; however other registration batches of the

400 mg drug product exhibit a (b) (4) trend in the mean dissolution profile data on long-term stability for up to 12 months (see Figure 12d).

Figure 12c. Mean dissolution profile data for 300 mg (batch 17K21G) drug product on long-term stability for up to 12 months using the proposed dissolution method

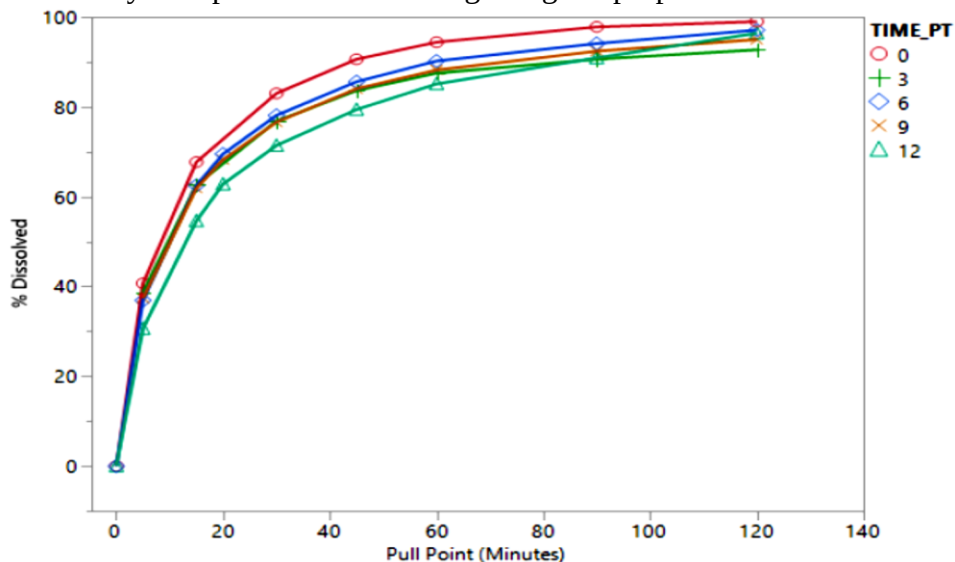
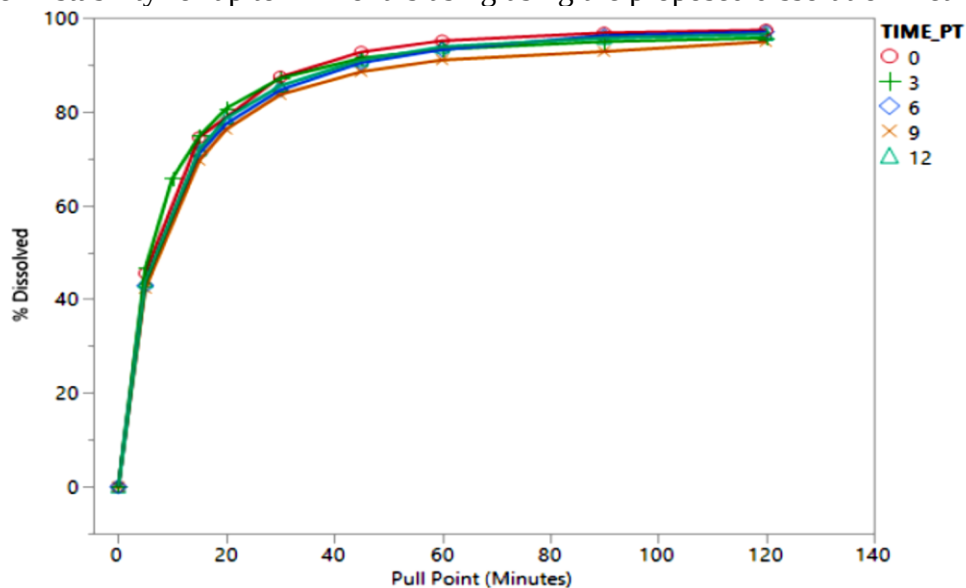


Figure 12d. Mean dissolution profile data for 400 mg (batch 17K22G) drug product on long-term stability for up to 12 months using the proposed dissolution method



Reviewer's Assessment of the Proposed Dissolution Acceptance Criterion:

Based on the totality of the dissolution data at batch release and on stability, " $Q^{(b)}(4)\%$ in 45 minutes" is recommended for each strength of the drug product. The Applicant agreed to implement the recommended dissolution acceptance criterion for 100 mg, 200 mg, and 300 mg

drug product in response to the *Information Request* that was conveyed to the Applicant on 09/06/2019.

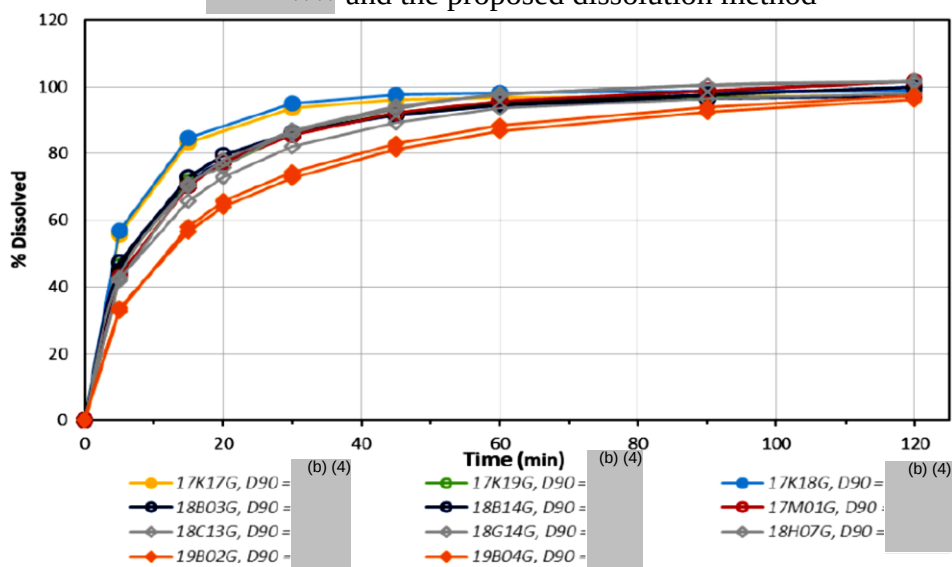
Additionally, the Applicant requested (b) (4). However, based on the overall dissolution data, the Applicant was granted a 18-month shelf-life for the 100 mg and 200 mg drug product and 12-month shelf-life for the 300 mg drug product.

➤ **Bridging of Batches due to Drug Substance Manufacturing Site Change:**

The Applicant identified (b) (4) as the commercial manufacturing site for the drug substance. Some 100 mg drug product batches used in the pivotal clinical trial, BLU-285-1101 were manufactured using drug substance manufactured at (b) (4) and (b) (4). The drug substance batches manufactured at (b) (4) and (b) (4) manufacturing sites is provided in **Table 2a** and **Table 2b**.

The drug substance batches manufactured at (b) (4) and (b) (4) were used in the manufacture of the drug product batches dosed in pivotal Phase 1 clinical trial BLU-285-1101 and manufactured at (b) (4). The Applicant provided in vitro dissolution profile data for the 100 mg drug product for batches manufactured at (b) (4) using drug substance batches manufactured at (b) (4) and (b) (4) and the proposed dissolution method (see **Figure 13a**).

Figure 13a . Mean dissolution profile data for the 100 mg drug product batches manufactured at (b) (4) using drug substance batches manufactured at (b) (4) and and (b) (4) and the proposed dissolution method



The mean dissolution profile data for the drug product batches 17K17G, 17K19G, 17K18G, 18B03G, 18B14G manufactured at (b) (4) using drug substance batches manufactured at (b) (4) is similar to the drug product batches 18C13G, 18G14G, 18H07G and

manufactured at (b) (4) using drug substance batches manufactured at (b) (4) and would be in compliance with the recommended dissolution acceptance criterion of ' Q (b) (4) % in 45 minutes' (see **Figure 13a**).

Mean dissolution profile data for (b) (4) batches 19B02G and 19B04G manufactured using drug substance batches from (b) (4) have larger particle size: D_{90} = (b) (4) μm of avapritinib drug substance and would not be in compliance with the recommended dissolution acceptance criterion of ' Q (b) (4) % in 45 minutes'.

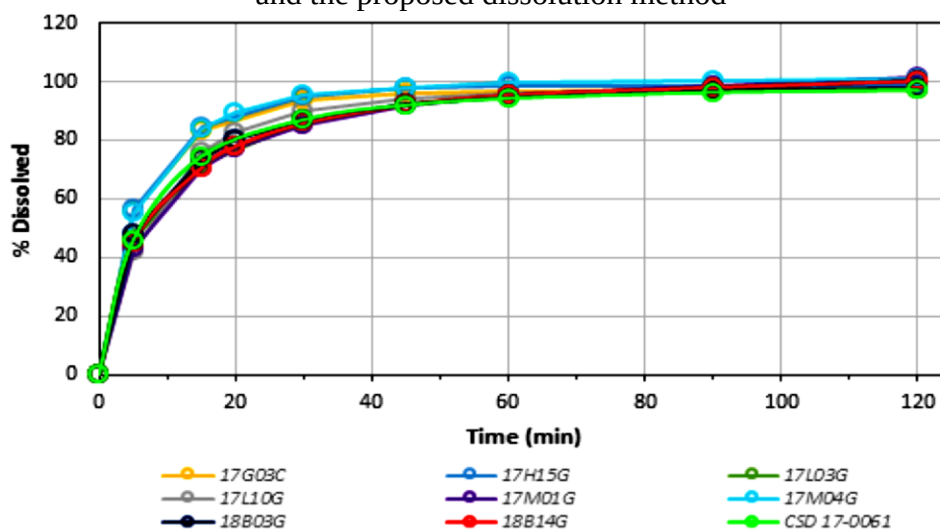
➤ **Bridging of Batches due to Drug Product Manufacturing Site and Process Change:**

The Applicant identified (b) (4) as the commercial manufacturing site for the to-be-marketed (TBM) Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg drug product.

Initially, a drug-in-capsule product was manufactured at (b) (4) and dosed in the pivotal safety and efficacy clinical trial BLU-285-1101. Later, the 100 mg and 200 mg tablet product that was manufactured at (b) (4) was introduced in the pivotal clinical trial BLU-285-1101 (see **Table 4a**).

The manufacturing process for the 100 mg tablet product was later transferred from (b) (4) to the commercial manufacturing site, (b) (4). The 200 mg, 300 mg, and 400 mg tablet drug product were also manufactured at the commercial manufacturing site, (b) (4) (see **Table 4b**). The 100 mg tablet product manufactured at (b) (4) was dosed in the pivotal clinical trial BLU-285-1101 to provide a bridge to the 100 mg drug product manufactured at (b) (4). The Applicant also provided in vitro dissolution profile data for the 100 mg drug product using the proposed dissolution method for batches manufactured at (b) (4) and (b) (4) using drug substance batches manufactured at (b) (4) (see **Figure 13 b**).

Figure 13b . Mean dissolution profile data for the 100 mg drug product batches manufactured at (b) (4) and (b) (4) using drug substance batches manufactured at (b) (4) and the proposed dissolution method

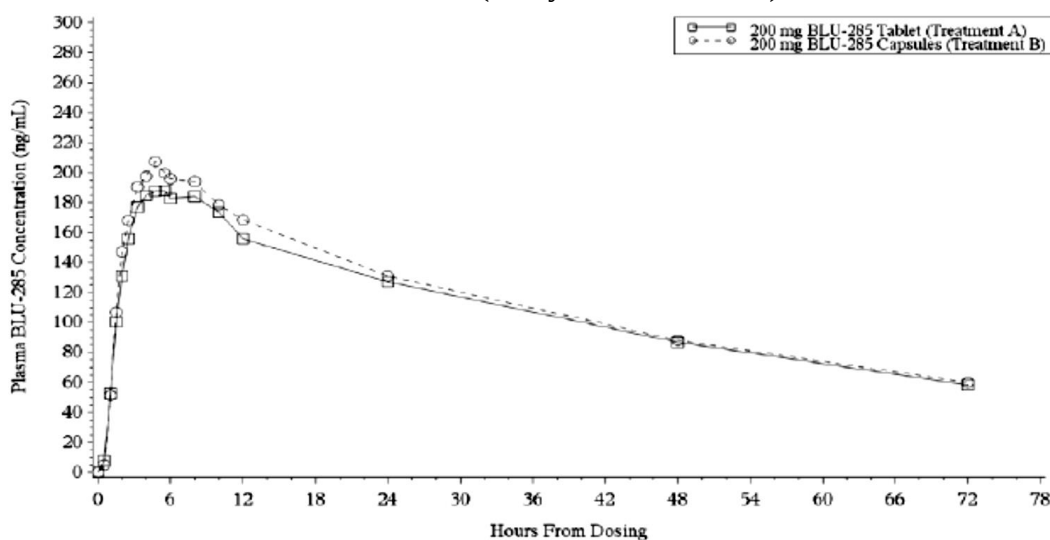


The mean dissolution profile data for the drug product batches 17G03C, 17H15G, 17L03G, 17L10G, 17M01G, 17M04G, 18B03G, 18B14G manufactured at (b) (4) using drug substance batches manufactured at (b) (4) is similar ($f_2 > 50$) to the drug product batch 17-0061 and manufactured at (b) (4). Services using drug substance batches manufactured at (b) (4) and would be in compliance with the recommended dissolution acceptance criterion of ' Q (b) (4) % in 45 minutes'.

➤ **Bridging of Batches due to Drug Product Changes:**

An open-label, randomized, 2-way cross-over relative bioavailability study BLU-285-0101 was conducted in 30 healthy adult male subjects to provide a 'bridge' for the 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product (Batches 16-0069 and 16-0083) manufactured at (b) (4) under fasted condition. The mean plasma concentration-time profile of avapritinib is provided in **Figure 13c**.

Figure 13c. Mean plasma concentration-time profile of avapritinib following administration of 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product (Batches 16-0069 and 16-0083) manufactured at (b) (4) under fasted condition (Study BLU-285-0101)



The 90% confidence interval (see **Table 8**) between the 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product (Batches 16-0069 and 16-0083) manufactured at (b) (4) under fasted condition dosed in the relative bioavailability study, BLU-285-0105 for C_{max} = 179.8 (66 ng/mL) and 200.2 (52 ng/mL), respectively, and AUC_{0-72} =7070 (53.7 h.ng/mL) and 7520 (46.6 h.ng/mL) respectively, indicating that the two products appears to exhibit similar bioavailability. It should be noted that the adequacy of this data is assessed by the OCP reviewer (refer to OCP review).

Table 8. Statistical analysis of comparative pharmacokinetic parameters of avapritinib following administration of 1×200 mg tablet drug product (Batch 16-0156) manufactured at (b) (4) and 2×100 mg drug-in-capsule product manufactured at (b) (4) under fasted condition (Study BLU-285-0101)

Parameter	Geo.Mean (Geo.Mean %CV) ^a		Geometric Mean Ratio (%)	90% Confidence Interval (Lower-Upper)
	1 × 200 mg Avapritinib Tablet (Test)	2 × 100 mg Avapritinib Capsules (Reference)		
N	30	30	-	-
C _{max} (ng/mL)	179.8 (66.0)	200.2 (52.0)	89.81	78.54-102.69
T _{max} (h)	5.502 (1.50-24.13)	4.797 (2.00-24.06)	-	-
AUC ₀₋₂₄ (h•ng/mL)	3119 (63.6)	3460 (48.6)	90.16	80.76-100.65
AUC ₀₋₇₂ (h•ng/mL)	7070 (53.7)	7520 (46.6)	94.02	86.56-102.11
t _{1/2} (h)	41.372 (11.9891)	42.318 (13.7057)	-	-

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours postdose; AUC₀₋₇₂ = area under the plasma concentration-time curve from time 0 to 72 hours postdose; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; N = number of subjects in pharmacokinetic population; t_{1/2} = apparent terminal elimination half-life; T_{max} = time of maximal plasma concentration.

^a Median (minimum-maximum) for T_{max} and arithmetic mean (standard deviation) for t_{1/2}.

Source: CSR BLU-285-0101, Table 11-2 and Table 11-3.

➤ **Biowaiver for the 200 mg and 300 mg Drug Product:**

The Applicant is seeking approval of Ayvakit[®] (avapritinib tablets), 100 mg, 200 mg, and 300 mg drug product. The biowaiver request for the 200 mg and 300 mg drug product is granted based on the following observations:

1. The 100 mg, 200 mg, and 300 mg strength drug product are compositionally proportional with respect to avapritinib, the active pharmaceutical ingredient (API) and excipients (see **Table 3**) to the 400 mg drug product.
2. The 100 mg, 200 mg, and 300 mg strength drug product demonstrate similar mean dissolution profile data (with >85% release of avapritinib in 45 minutes) to the 400 mg drug product at batch release ($f_2 > 50$ using the Automation Tool) using the acceptable dissolution method (see **Figure 11**).
3. The 400 mg drug product and 4×100 mg drug product was dosed in the bioequivalence (BE) study BLU-285-0105 (see **Table 9**).

Table 9. Statistical analysis of comparative pharmacokinetic parameters of avapritinib following administration of 4×100 mg and 1×400 mg tablets in healthy subjects under fasted conditions (BLU-285-0105)

Parameter	GeoMean (GeoMean %CV) ^a		Geometric Mean Ratio (%)	90% Confidence Interval (Lower, Upper)
	1 × 400 mg Avapritinib Tablet (Test)	4 × 100 mg Avapritinib Tablets (Reference)		
N	62	62	-	-
C _{max} (ng/mL)	418.8 (58.7)	397.5 (46.7)	105.34	93.25, 119.00
T _{max} (h) ^b	4.001 (1.00-36.03)	3.650 (1.50-36.04)	-	-
AUC ₀₋₂₄ (h•ng/mL)	6531 (50.2)	6563 (40.0)	-	-
AUC _{0-t} (h•ng/mL)	22970 (44.6)	23680 (37.8)	97.00	90.01, 104.53
AUC _{0-∞} (h•ng/mL)	23910 (45.8)	24710 (39.0)	96.86	89.77, 104.52
t _{1/2} (h)	54.661 (14.9298)	53.914 (14.6959)	-	-

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours postdose; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration above the lower limit of quantitation; AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; N = number of subjects in the pharmacokinetic population; t_{1/2} = apparent terminal elimination half-life; T_{max} = time of the maximum observed plasma concentration.

^a Median (minimum-maximum) for T_{max} and arithmetic mean (standard deviation) for t_{1/2}.

^b Treatment difference: 0.507 h; p = 0.067 (Wilcoxon signed-rank test).

Source: CSR BLU-285-0105, Table 11-2 and Table 11-3.

The 90% confidence interval (see **Table 9**) between the 400 mg and 4×100 mg drug products dosed in the BE study, BLU-285-0105 for C_{max}= 418.8 (58.7 ng/mL) and 397.5 (46.7 ng/mL), respectively, and AUC_{0-∞}=23910 (45.8 h.ng/mL) and 24710 (39.0 h.ng/mL) respectively, indicating that the two products are bioequivalent.

- The drug product exhibits linear pharmacokinetics with respect to C_{max} and AUC_{0-∞} between the dose ranges of 30 mg-400 mg following single-dose administration of 30 mg-100 mg drug-in-capsule product on Cycle 1, Day 1 in subjects with GIST based on the relative bioavailability study BLU-285-1101 (see **Table 10**).

Table 10. Summary of pharmacokinetic parameters of avapritinib following single-dose administration of 30 mg-100 mg drug-in-capsule product on Cycle 1, Day 1 in subjects with GIST (BLU-285-1101)

Parameter	Statistic	30 mg	60 mg	90 mg	135 mg	200 mg	300 mg	400 mg
C_{max} (ng/mL)	N	6	5	6	6	6	113	50
	GeoMean (%CV)	23.4 (82.2)	53.2 (68.7)	79.4 (50.3)	121 (53.8)	213 (45.6)	264 (62.1)	288 (72.9)
T_{max} (h)	N	6	5	6	6	6	113	50
	Median (Min- Max)	4.06 (3.85- 8.00)	4.00 (2.00- 8.05)	2.02 (2.0- 23.8)	3.97 (1.97- 7.98)	2.98 (1.98- 8.02)	4.00 (0.98- 23.5)	4.02 (1.97- 24.0)
C_{24} (ng/mL)	N	6	5	6	6	6	36	19
	GeoMean (%CV)	12.6 (53.5)	32.8 (37.6)	43.6 (17.1)	68.1 (29.2)	97.3 (19.8)	124 (44.6)	166 (55.1)
AUC_{0-24} (h•ng/mL)	N	6	5	6	6	6	36	19
	GeoMean (%CV)	348 (64.8)	883 (57.6)	1240 (40.1)	1900 (34.1)	3060 (31.8)	4140 (47.4)	4840 (50.3)
CL/F (L/h)	N	3	4	5	6	6	23	8
	GeoMean (%CV)	17.2 (52.3)	18.5 (32.7)	18.4 (44.0)	22.2 (29.6)	22.0 (38.6)	28.6 (46.4)	24.6 (77.6)
V_z/F (L)	N	3	4	5	6	6	23	8
	GeoMean (%CV)	1200 (44.3)	1150 (64.9)	1270 (34.1)	1350 (31.1)	1290 (22.3)	1200 (43.3)	1240 (42.1)
$t_{1/2}$ (h)	N	3	4	5	6	6	23	8
	Mean (%CV)	51.0 (41.0)	47.8 (59.6)	56.7 (67.7)	43.8 (29.9)	43.6 (38.6)	32.1 (48.4)	43.5 (65.3)

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; C_{24} = plasma concentration at 24 hours postdose; CL/F = apparent oral clearance, unadjusted for bioavailability; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; GIST = gastrointestinal stromal tumor; Max = maximum; Min = minimum; N = number of observations; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time of maximal plasma concentration; V_z/F = apparent volume of distribution during the terminal phase after oral administration.

Note: The difference in the N (number of observations), if any, across the pharmacokinetic parameters in a given cohort is due to insufficient data to estimate the particular parameter.

Source: (b) (4) PK Report BLUE201803, Table 3.

Based on the totality of the in vitro dissolution data and in vivo bioavailability study, an adequate data is provided to bridge the 200 mg and 300 mg drug product to the 400 mg drug product. Therefore, biowaiver is granted for the 200 mg and 300 mg drug product.

➤ BIOPHARMACEUTICS RISK ASSESSMENT:

Avapritinib is a low solubility drug substance that exhibits several polymorphic forms. (b) (4). However, the (b) (4) can convert to (b) (4); and a (b) (4) can convert to (b) (4). Additionally, the drug product contains



QUALITY ASSESSMENT

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(b) (4). Avapritinib is a (b) (4) drug substance that has the potential to interact with (b) (4) on stability. From a Biopharmaceutics perspective, the potential of (b) (4) to convert to (b) (4) and/or interact with (b) (4) on stability may be the reason for the observed dissolution trend.

Several batches of the 300 mg and 400 mg drug product demonstrated a (b) (4) trend in the dissolution profile data on long-term and accelerated stability conditions that either required Stage 2 or Stage 3 testing or to be out-of-specification with the recommended dissolution acceptance criterion of ' $Q_{(b) (4)} \% \text{ in } 45 \text{ minutes}$ '. The Applicant was requested to address the (b) (4) trend in the dissolution data for the 300 mg drug product and provide mitigating solutions to avert dissolution failures. The Applicant requested (b) (4). As the 300 mg drug product exhibits (b) (4) trend in the dissolution profile data on stability, a 12-month shelf-life was granted for 300 mg drug product to avert quality risk to the drug product.

Additionally, the Applicant made a commitment to provide mitigating solutions to avert dissolution failures for the 300 mg strength drug product in a post-approval supplement (PAS).

➤ **POST-APPROVAL COMMITMENTS: None**

➤ **LIST OF DEFICIENCIES: None**

➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 212608 for Ayvakit® containing 100 mg, 200 mg, and 300 mg of avapritinib is recommended for **APPROVAL**.



Parnali
Chatterjee

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Zolnik

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XING WANG
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