CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213756Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213756
Assessment 1

Drug Product Name	Koselugo (Selumetinib)
Dosage Form	Capsule
Strength	10 mg, 25 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	AstraZeneca Pharmaceuticals LP
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	08/30/2019	All CMC
Quality Amendment 0013	10/24/2019	DS, DP, Biopharm, and OPMA
Quality Amendment 0015	11/15/2019	EA
Quality Amendment 0027	01/22/2020	DP, OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Suong Tran
Drug Product	Olen Stephens	Anamitro Banerjee
Manufacturing	Byeongtaek Oh	Bogdan Kurtyka
Microbiology	Byeongtaek Oh	Bogdan Kurtyka
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Xing Wang	
Laboratory (OTR)	N/A	N/A
Environmental	James Laurenson	N/A

Xing Wang

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted in NDA 213756 and found to be adequate. PAI conducted at Patheon Pharmaceuticals had four 483 observations. Patheon's response was received on 2-Jan-2020. The manufacturing facility is considered Recommend Approval. Post approval inspection of the Patheon facility is recommended.

OPQ recommends APPROVAL of NDA 213756 for selumetinib capsules, 10 mg and 25 mg. OPQ grants a 36-month expiration period for selumetinib capsules, 10 mg and 25 mg, when stored at "25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]." In addition, OPQ grants a (b) (4) re-test period for selumetinib hyd-sulfate drug substance when stored (b) (4) (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Selumetinib is an uncompetitive inhibitor of mitogen-activated protein kinase (MEK). Selumetinib free base is a BCS class 4 compound and poorly soluble across the physiological pH range. The hyd-sulfate salt was identified as exhibiting a kinetic solubility advantage which translated to a bioavailability advantage *in vivo*. An age-appropriate IR capsule formulation intended for the treatment of neurofibromatosis 1 (NF1) related plexiform neurofibromas (PN) in pediatrics has been developed. This consists of (b) (4) selumetinib hyd-sulfate (b) (4) (b) (4) (b) (4) capsules shell presented as 10 mg and 25 mg strengths. The 10 mg capsule is presented as a white capsule marked with 'SEL 10' printed in black ink. The 25 mg capsule is presented as a blue capsule marked with 'SEL 25' printed in black ink. The two strengths of selumetinib capsules (b) (4) The commercial primary pack for the selumetinib capsules is a 75 mL white, HDPE bottle with a (b) (4) screw closure. The bottle includes (b) (4) desiccant and an induction seal membrane. The drug product should be stored at 25°C, with excursions permitted to 15°C to 30°C (59°F to 86°F). The recommended dose is 25 mg/m^2, taken orally twice daily.

Proposed Indication(s) including Intended Patient Population	Selumetinib is indicated for the treatment of pediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN).
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	50 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

(b) (4)

The drug substance is a white to yellow crystalline powder. Critical process parameters and drug substance specifications ensure manufacture of the (b) (4) drug substance, (b) (4) The four specified impurities in selumetinib drug substance were qualified at the proposed limits, and unspecified impurities are controlled at (b) (4) each. Control strategies for potential mutagenic impurities were based on a combination of process understanding, calculated purge factors, and analytical data, according to ICH M7 Option 3 and Option 4 approaches. The drug substance is manufactured (b) (4) Starting material designation was agreed upon in response to previous Agency feedback. The retest period for selumetinib hyd-sulfate drug substance is (b) (4) when stored (b) (4)

Drug Product: Adequate

Selumetinib capsules are formulated using the selumetinib hyd-sulfate salt form, which exhibits improved solubility relative to the free base. (b) (4) The melting point of TPGS is 37-41^{O}C. The TPGS excipient and manufacturing process (b) (4) The drug product specification includes description, identification, assay, degradation products, dissolution and uniformity of dosage units. The specification for specific impurity (b) (4) is justified by qualification studies. The specification limit for individual unspecified impurities complies with the ICH Q3B limit. The applicant conducted a risk analysis for elemental impurities as per ICH Q3D and concluded there are no high-risk sources of elemental impurities in the

drug product manufacturing process thus release testing for elemental impurities is not necessary. Analytical methods are adequately validated. The commercial primary pack for the selumetinib capsules is a 75 mL white, HDPE bottle with a (b) (4) screw closure. The bottle includes (b) (4) desiccant and an induction seal membrane. The drug product should be stored at 25°C, with excursions permitted to 15°C to 30°C (59°F to 86°F). A shelf-life of 36-month is granted based on stability data provided.

The applicant requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (b). The waiver request is granted.

Labeling: Adequate

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

Manufacturing: Adequate

The manufacturing process (b) (4) l. PAI conducted at Patheon Pharmaceuticals had four 483 observations mainly related to (b) (4). Patheon's response was received on 2-Jan-2020. The manufacturing facility is considered Recommend Approval. Post approval inspection of the Patheon facility is recommended.

Biopharmaceutics: Adequate

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, (ii) the in vitro formulation bridging between the clinical phase II formulation and the to-be-marketed formulation.
The proposed dissolution method showed an acceptable discriminating ability with regards (b) (4) and TPGS quality, therefore, the proposed dissolution method is acceptable as a quality control (QC) test for the propose drug product for batch release and stability testing.
The clinical Phase II and commercial formulations that were produced from (b) (4) and Patheon manufacturing sites showed comparable in vitro dissolution profiles, and the proposed 10 mg and 25 mg selumetinib capsules showed comparable dissolution profiles, therefore, the in vitro formulation bridging of both selumetinib 10 mg and 25 mg capsules have

been established, so that no additional in vitro bridging studies are needed.
The in vivo clinical pharmacokinetics (PK) studies (e.g., D1532C00005, Study 5; D1532C00066, Study 66) and the cross-study comparison of PK parameters to support the in vivo formulation bridging are under purview by the Office of Clinical Pharmacology (OCP).

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**	(b) (4)	**L**	
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	**L**		**L**	
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	**M**		**L**	
Microbial Limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	**L**		**L**	
Dissolution – BCS Class II & IV	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	**H**		**M**	**The free base is BCS class 4 compound. TPGS melting point 37^{O}C to 41^{O}C. TPGS can also be hydrolyzed.**

D. List of Deficiencies for Complete Response N/A

Application Technical Lead Name and Date:
Xing Wang, Ph.D.
06-Feb-2020

Xing Wang

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U.S. FOOD & DRUG ADMINISTRATION

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)	Adequate	11/21/2019	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		
	III			Adequate		
	III			Adequate		

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

Document	Application Number	Description
IND	(b) (4)	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: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Koselugo	Koselugo
Established name(s)	Selumetinib	Adequate; complies with USAN
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 10 mg and 25 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No scoring	NA
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.	NA	NA

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)	Swallow capsules whole with water. Do not chew, dissolve or open capsule	Adequate; integrity of the capsule maintains the selumetinib hyd-sulfate salt form, which is critical to the function of the capsule.

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)	Capsules	Adequate
Strength(s) in metric system	10 mg and 25 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Complies with Salt Policy; salt equivalence statement is not included here and is not required.	Adequate; addressed in section 11 and product label
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Ink markings and color coding is delineated	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Koselugo Selumetinib	Adequate; Complies with USAN
Dosage form(s) and route(s) of administration	Capsules for oral use	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Sulfate salt	Adequate; equivalence statements included
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	USP/NF names used	Adequate
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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	Not sterile	NA
Pharmacological/ therapeutic class	Kinase Inhibitor	Adequate
Chemical name, structural formula, molecular weight	Provided and accurate	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Drug substance description, solubility, pKa values added to initial label	Adequate

Section 11 (DESCRIPTION) Continued

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

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)	Capsules	Adequate
Strength(s) in metric system	10 mg and 25 mg	Adequate
Available units (e.g., bottles of 100 tablets)	60-Count	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Capsule color and ink markings described	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

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.)	Dispense in original bottle. Do not remove desiccant. Protect from moisture.	Adequate
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."	Sufficiently different size and shape	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		
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."	NA	NA
		(b) (4)

1.2.5 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	Distributed by: AstraZeneca Pharmaceuticals LP Wilmington, DE 19850	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate; sufficient description of the product and usage is included.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

None

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Koselugo (selumetinib sulfate) capsules	Inadequate; inconsistent with USAN; information request pending response
Dosage strength	10 mg and 25 mg	Adequate
Route of administration	For Oral Use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Salt equivalence stated	Adequate
Net contents (e.g. tablet count)	60 capsules	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space reserved	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage conditions uses the abbreviated "Store at 25^{O}C" with excursions due to lack of space	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	The labels above represent the sales and samples for the 10 mg and 25 mg capsules, respectively	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	AstraZeneca AB, Sodertalje, Sweden SE-15185	Adequate
Medication Guide (if applicable)	Provided	Adequate
No text on Ferrule and Cap overseal	NA	NA
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.	NA	NA
And others, if space is available	"Keep out of the reach of children"	Adequate

Assessment of Carton and Container Labeling: Adequate pending response from the applicant

ITEMS FOR ADDITIONAL ASSESSMENT

1. **None**

Overall Assessment and Recommendation:

Adequate pending response from the applicant;
The product labels are pending addition of the recently approved proprietary name. Also, the product labels express the nonproprietary name as (b) (4) which is inconsistent with the USAN name of the active ingredient and current salt nomenclature guidance. The proprietary name is correct in the rest of the label and a pending information request to make the change to 'selumetinib' has not been received at the time of this review. DMEPA is aware of these pending changes and concurs. Labeling review will proceed with the clinical division and the final label captured in the action package.

Primary Labeling Assessor Name and Date: Olen Stephens 1/23/2020

Secondary Assessor Name and Date: Anamitro Banerjee 1/23/2020

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 213756 [505(b)(1)]
Drug Product Name/Strength: Koselugo™ (selumetinib) Capsules, 10 mg and 25 mg
Route of Administration: Oral
Proposed Indication: NF-1 related plexiform neurofibroma
Applicant Name: AstraZeneca Pharmaceuticals LP
Submission Date: 09/13/2019
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY

Selumetinib is a potent, selective, uncompetitive inhibitor of mitogen-activated protein kinase (MEK). (b) (4)

The proposed drug product (DP), Selumetinib capsule, 10 mg (white capsule) and 25 mg (blue capsule), are opaque two-piece hard hypromellose capsules (b) (4) band, which are the immediate release capsules for oral administration. The recommended dose is 25 mg/m^2 of body surface area (BSA) taken orally with the dose range of 10 mg to 50 mg twice daily.

In the current NDA 213756 submission, 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, (ii) the in vitro formulation bridging between the clinical phase II formulation and the to-be-marketed/commercial formulation.

Since the pharmacokinetic (PK) characteristics of both the proposed 10 mg and 25 mg strengths drug product have been studied in clinical studies (e.g., D1532C00082 and D1532C00086), the biowaiver request for the 10 mg capsule is not needed.

In Vitro Dissolution Testing of the Finished Product:
The dissolution parameters have been evaluated. The proposed dissolution method showed an acceptable discriminating ability with regards to the (b) (4) and TPGS quality, therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for the propose drug product for batch release and stability testing.

The final approved in vitro dissolution method and acceptance criterion for the finished drug product are presented below:

USP Apparatus	II (Paddle) with a sinker suitable for (b) (4) capsule
Rotation Speed	75 rpm
Dissolution Medium	1000 mL of sodium phosphate buffer, pH 6.5, with 0.5% w/v polysorbate 80
Temperature	37°C±0.5°C
Acceptance Criterion	Q= (b) (4)% in 45 minutes

The In Vitro Formulation Bridging:
The in vivo clinical pharmacokinetics (PK) studies (e.g., D1532C00005, Study 5; D1532C00066, Study 66) and the cross-study comparison of PK parameters to support the in vivo formulation bridging are under purview by the Office of Clinical Pharmacology (OCP).

The clinical Phase II and commercial formulations that were produced from (b) (4) and Pathon manufacturing sites showed comparable in vitro dissolution profiles, and the proposed 10 mg and 25 mg selumetinib capsules showed comparable dissolution profiles, therefore, the in vitro formulation bridging of both selumetinib 10 mg and 25 mg capsules have been established.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213756 for the proposed Koselugo™ (selumetinib) Capsules, 10 mg and 25 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 proposed dissolution method and acceptance criterion are listed as below, while the dissolution method development report is submitted in M.3.2.P.2.2.

USP Apparatus	II (Paddle) with a sinker suitable for (b) (4) capsule
Rotation Speed	75 rpm
Dissolution Medium	1000 mL of sodium phosphate buffer, pH 6.5, with 0.5% w/v polysorbate 80
Temperature	37°C±0.5°C
Acceptance Criterion	Q= (b) (4)% in 45 minutes

(b) (4)

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(b) (4)

(4) Discriminating ability:

(i) (b) (4)

(b) (4)

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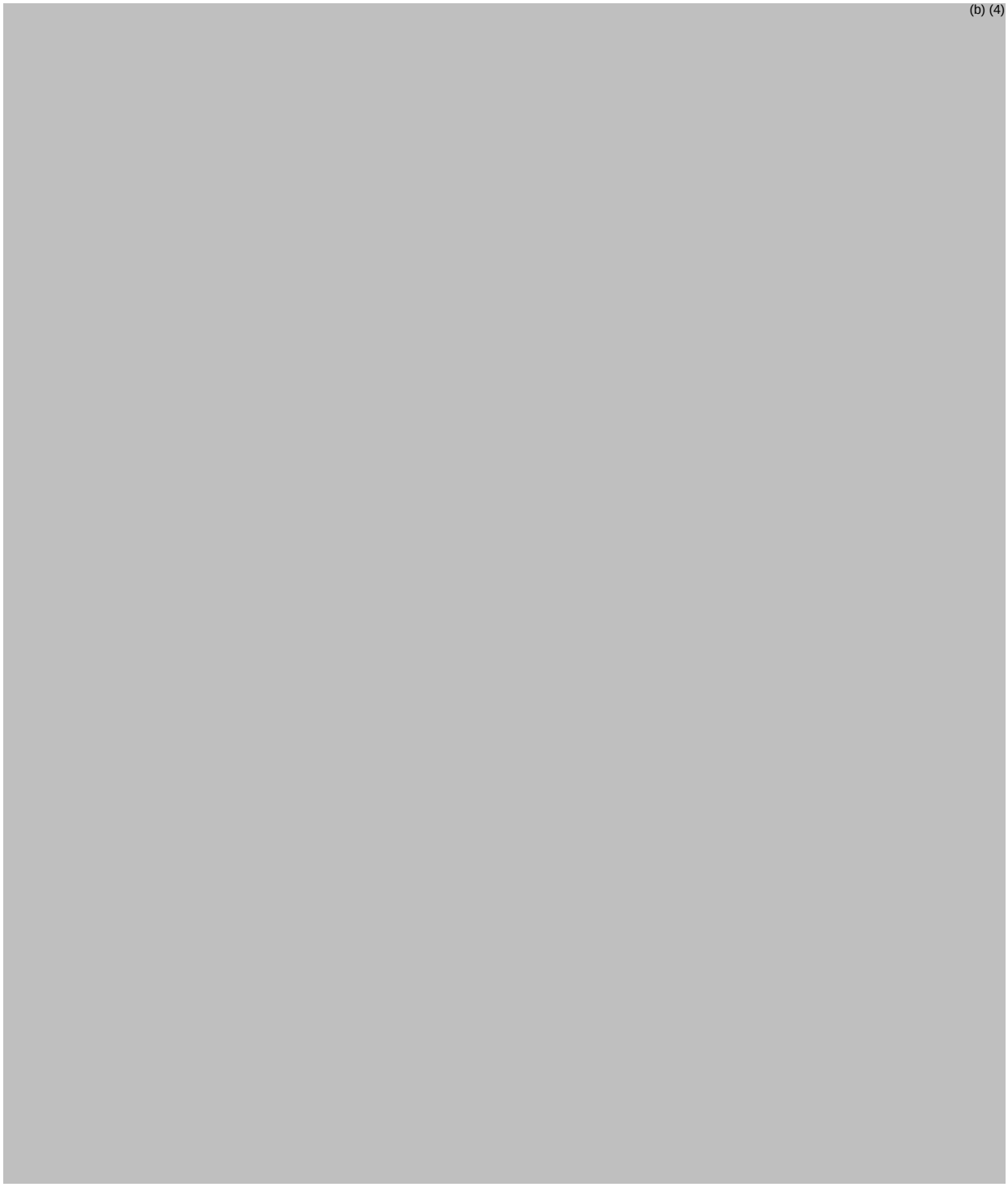
(b) (4)

(ii) TPGS quality will impact dissolution. Per the Applicant, TPGS is a synthetic water soluble-derivative of vitamin E produced by esterification of d-α-tocopherol acid succinate with polyethylene glycol (PEG) 1000. The nominal component in TPGS is mono-esterified polyethylene glycol (monoester) but also contains a number of concomitant components namely di-esterified polyethylene glycol (diester), free PEG and free d-α-tocopherol. The USP monograph does not specify ranges for the levels of the individual components but does contain a compositional clause for d-α-tocopherol content of ≥25.0%.

(b) (4)



The Applicant conducted an in vivo bioavailability/bioequivalence (BA/BE) study (D1532C00078, study 78) to evaluate the impact of formulation variants (clinical formulation, free base variant, and TPGS variant) on in vivo performance and in vitro dissolution. The formulation variants include:

- A clinical batch as reference (Treatment A in Study 78).
- Free base [redacted] form the "free base variant", batch 3447H14 (Treatment B in Study 78). [redacted]
- TPGS [redacted] the "TPGS variant", batch 3342G14 (Treatment C in Study 78).

As the data presented in the following Table 2 and Figure 16, Treatment B and C showed four-fold reduction in AUC and ten-fold reduction in C_{max} compared to Treatment A.

Table 2: Statistical comparison of pharmacokinetic parameters measured for variants of selumetinib capsules 25 mg relative to a clinical reference in BA/BE Study 78

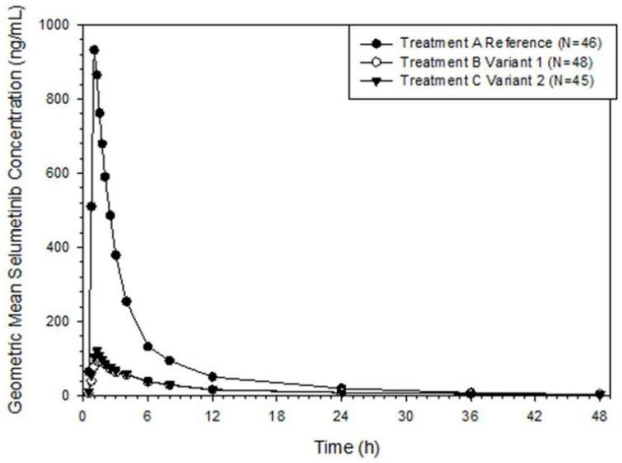
Parameter (units)	Trt [a]	n	Geometric LS mean	Geometric LS mean 95% CI	Pairwise comparison		
					Pair	Ratio (%)	90% CI
AUC (ng.h/mL)	A	45	3758	(3450, 4094)			
	B	41	911.9	(835.3, 995.5)	B/A	24.26	(22.62, 26.03)
	C	40	984.8	(901.1, 1076)	C/A	26.20	(24.44, 28.09)
C_{max} (ng/mL)	A	46	1330	(1169, 1512)			
	B	48	124.0	(109.3, 140.6)	B/A	9.32	(8.25, 10.53)
	C	44	172.0	(150.9, 196.0)	C/A	12.93	(11.42, 14.65)

[a] Treatment A: selumetinib capsule 25 mg reference (3 x 25 mg);
Treatment B: selumetinib capsule 25 mg free base variant (3 x 25 mg);
Treatment C: selumetinib capsule 25 mg TPGS variant (3 x 25 mg).

LS Least squares.

CI Confidence interval.

Figure 16: Plasma concentration-time profile of a 75 mg (3×25 mg) dose of selumetinib capsules in Study 78



The dissolution profiles showed that Treatment B and C had much slower dissolution than Treatment A (presented in Figures 17, 18 and 19 below). From the results, the proposed dissolution method (pH 6.5 medium with 0.5% w/v polysorbate 80 medium)

has adequate discriminating ability to discriminate the non-BE batches (Treatment B and C, as presented in Figure 10).

Figure 17: Mean dissolution profiles of selumetinib capsule 25 mg with formulation variants in study 78, in (b) (4) medium

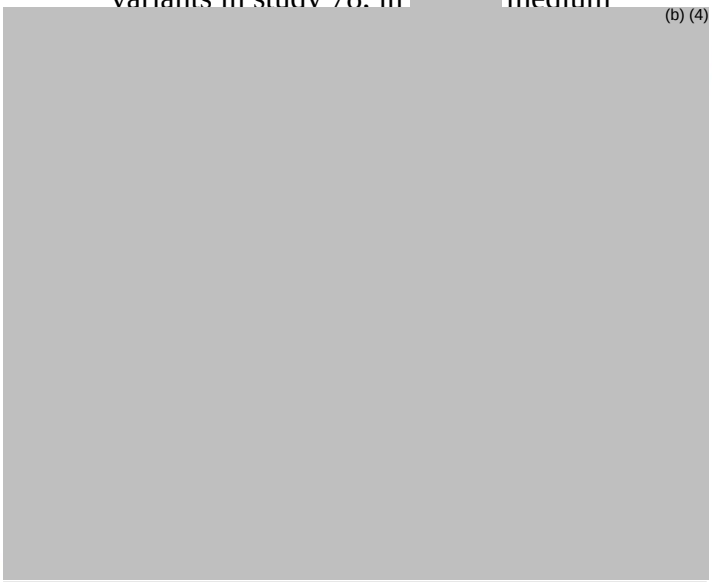


Figure 18: Mean dissolution profiles of selumetinib capsule 25 mg with formulation variants in study 78, in pH 6.5 medium

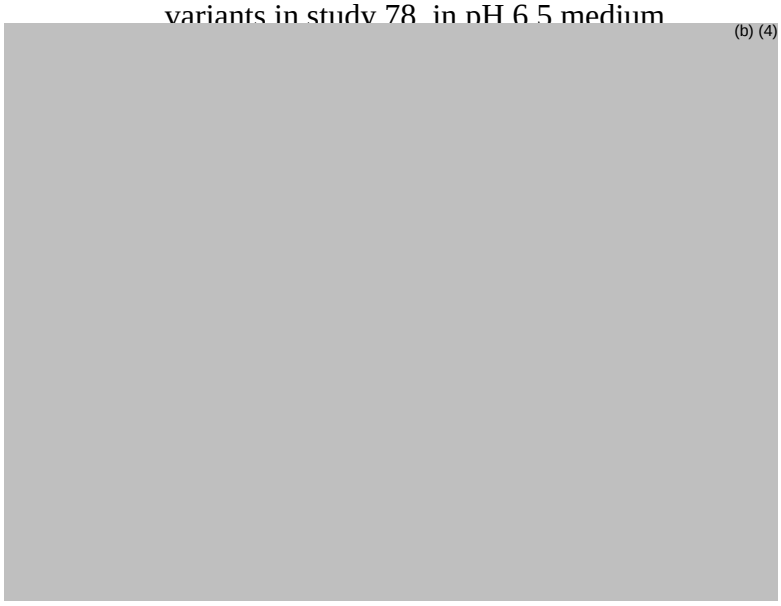


Figure 19: Mean dissolution profiles of selumetinib capsule 25 mg with formulation variants in study 78, in pH 6.5 medium with 0.5% w/v polysorbate 80

(iii) Particle size distribution (PSD) of drug substance (DS) selumetinib hyd-sulfate salt. Per the Applicant, DS PSD is controlled by (b) (4) . The proposed DS PSD specification is d(v,0.9) NMT (b) (4) µm, while the clinical batches have DS PSD range of (b) (4) to (b) (4) µm, therefore, the drug substance that has (b) (4) µm is not accessible. In addition, a larger DS PSD batch (> (b) (4) µm) from (b) (4) selumetinib hyd-sulfate was used in human ADME clinical study (D1532C00077) but showed no adverse effect on in vivo exposure. Therefore, DS PSD is expected to have no significant impact on drug product dissolution.

Per the Applicant, although the selumetinib is a BCS IV compound [e.g., highest solubility of selumetinib free base is 146.3 µg/mL; apparent permeability coefficient ($P_{app\ AtoB}$) of selumetinib free base at 10 µM is 23.6 $\times 10^{-6}$ cm/s, while high permeability marker propranolol P_{app} is 27.5 $\times 10^{-6}$ cm/s], the exposure from selumetinib capsules are not dissolution nor permeability limited, because the absolute bioavailability of selumetinib capsules for a 75 mg oral dose was determined as 62.1% (90% CI; 60.1, 64.1) for which a conservative estimate of the fraction absorbed can be made and is at least 72%.

Overall, this Reviewer considers the proposed dissolution method (USP Apparatus II Paddle, 75 rpm, with sinker, 1000 mL of pH 6.5 sodium phosphate buffer with 0.5% w/v polysorbate 80) showed adequate discriminating ability, which is acceptable as a QC test for the proposed drug product.

2. Dissolution Data and Acceptance Criterion

Per the Applicant, 20 batches of selumetinib capsules 10 mg and 34 batches of selumetinib capsules 25 mg were manufactured from (b) (4) which are the clinical batches that were used in Phase II clinical studies. 1 batch of selumetinib

capsules 10 mg and 22 batches of selumetinib capsules 25 mg were manufactured from Patheon Pharmaceuticals Inc, Cincinnati, USA, which are commercial batches.

The dissolution data profiles of clinical batches (produced from (b) (4)) are presented in Table 3 and Figures 20 and 21 below. Per the Applicant, (i) the variability in dissolution decreased once the complete release occurs at 45 minutes, so that the variability is not influenced by the dissolution method but is caused by the erosion behavior of selumetinib capsule during dissolution; (ii) high variability in individual dissolution data was observed in (b) (4) minutes but the consistent complete release was achieved in 45 minutes. Therefore, the Applicant proposed a dissolution acceptance criterion as "Q= (b) (4) % in 45 minutes" for both the proposed selumetinib capsules 10 mg and 25 mg.

Table 3: Summarized dissolution data of clinical batches

	Time (minutes)	10 mg % release [a]	25 mg % release [b]
Range of individual dosage unit % release	15	5-57	4-70
	30	59-102	58-108
	45	91-103	90-111
	60	32-105	91-111
Range of mean (batch) % release	15	13-38	11-38
	30	83-98	75-97
	45	96-101	95-103
	60	97-102	95-103
Range of Std Dev (batch) % release	15	4.4-16.3	6.4-28.8
	30	2.6-15.9	1.9-17.2
	45	0.5-4.4	0.4-4.5
	60	0.5-2.5	0.5-4.2

[a] n= 114 for individual dosage units and n= 16 for mean batch results. Some batches were tested on repeat to support development, no Stage 2 testing requirements occurred.

[b] n= 222 for individual dosage units and n= 30 for mean batch results. Some batches were tested on repeat to support development, no Stage 2 testing requirements occurred.

Figure 20: Mean dissolution profiles of clinical batches of selumetinib capsules 10 mg and 25 mg

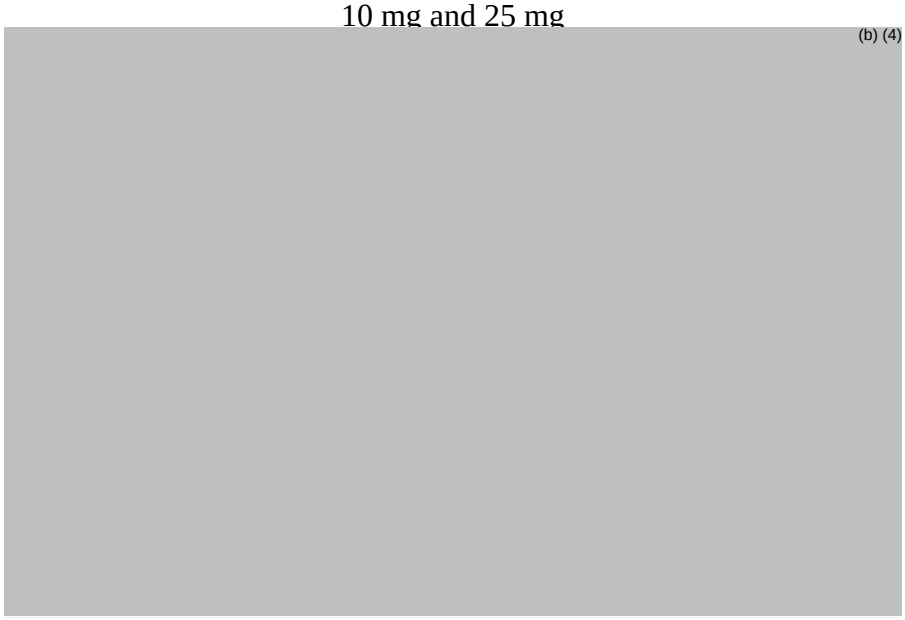
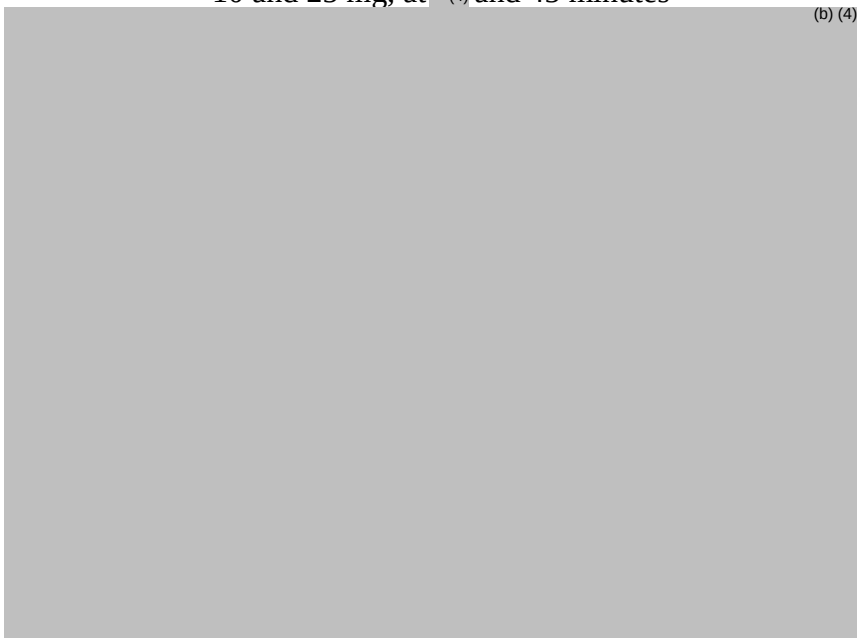


Figure 21: Individual dissolution data of clinical batches of selumetinib capsules 10 and 25 mg, at (b) (4) and 45 minutes



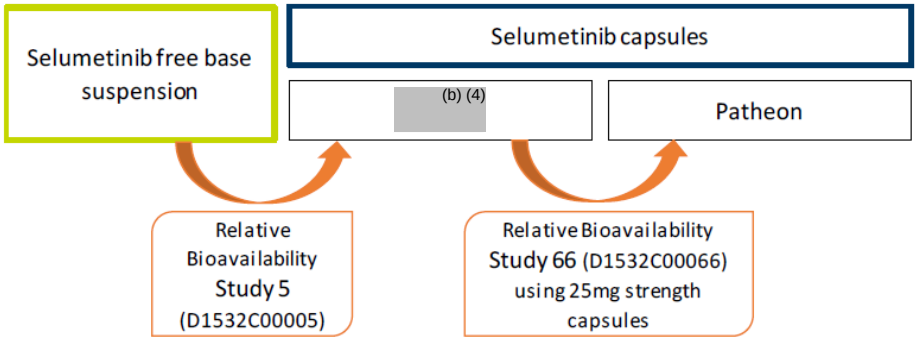
The dissolution data of registration batches (10 mg, batch # 3402E14, 3403E14, batch 3421F14; 25 mg, batch # 3110658R, 3110675R, 3110678R; produced from Patheon) have mean dissolution >96% and individual dissolution (b) (4)% at 45 minutes under long-term stability condition (25°C/60% RH, in HDPE bottles) for up to 36 months with no trend observed.

Overall, this Reviewer considers the proposed dissolution acceptance criterion of "Q=(b)(4)% in 45 minutes" is acceptable.

3. In Vitro Formulation Bridging Studies

Per the Applicant, the early development formulation was selumetinib free base suspension 100 mg, which however exhibited insufficient exposure in Phase I and II clinical studies due to the low solubility of selumentinib free base. (b) (4) Selumetinib hyd-sulfate capsules were then developed as the final commercial formulation. The Applicant summarized the in vivo bridging studies from early to commercial formulations, which are presented in the following Figure 22.

Figure 22: Summary of selumetinib in vivo formulations and bridging studies



(b) (4) and is the development manufacturing site of selumetinib capsules. 'Patheon' refers to Patheon Pharmaceuticals Inc, Cincinnati, USA and is the commercial manufacturing site of selumetinib capsules.

The differences between clinical Phase II formulation and commercial formulations are:

a. Capsule color change from white (clinical Phase II formulation) to blue (commercial formulation) for 25 mg capsule, while 10 mg capsule has same white color.

b. The (b) (4) manufacturing process change, which was considered a level 1 process change per FDA SUPAC-IR guidance from the CMC drug product reviewer's (Dr. Olen Stephens) perspective during 10/24/2019 OPQ kick off meeting.

c. Manufacturing site change from (b) (4) (development site) to Pathon (commercial site).

The Applicant conducted the cross-study comparison to demonstrate the similar clinical PK among formulations (presented in Tables 4 and 5 below). All the in vivo clinical

pharmacokinetics (PK) studies (e.g., D1532C00005, Study 5; D1532C00066, Study 66) to support in vivo formulation bridging are under purview by the Office of Clinical Pharmacology (OCP).

Table 4: Statistical comparison of key PK parameters measured for selumetinib capsules 25 mg in healthy volunteers (Study 66)

Parameter (units)	Trt	n	Geometric LS mean	Geometric LS mean 95% CI	Pairwise comparison		
					Pair	Ratio (%)	90% CI
AUC (ng.h/mL)	A[a]	27	4097	(3645, 4605)	B/A	90.01	(81.74, 99.11)
	B[b]	26	3687	(3275, 4151)			
C_{max} (ng/mL)	A[a]	27	1401	(1195, 1642)	B/A	81.97	(69.01, 97.36)
	B[b]	26	1148	(976.3, 1350)			

[a] Treatment A: selumetinib white capsule 25 mg (3×25 mg).

[b] Treatment B: selumetinib blue capsule 25 mg (3×25 mg).

AUC area under the plasma concentration-time curve; CI confidence interval; C_{max} maximum plasma concentration; LS least squares; n number; Trt treatment.

Note that Treatment A is clinical Phase II formulation. Treatment B is commercial formulation.

Table 5: Cross-study comparison of PK parameters for a single dose of 75 mg selumetinib capsules (3×25 mg)

Study (N)/Parameter (unit)	Formulation	AUC (ng·h/mL)[a]	C_{max} (ng/mL)[a]	t_{max} (h)[b]
Study 5 N=27 Part B	75 mg white capsule	4736 (37.3)	1307 (76.3)	1.5 (0.48-2.28)
Study 20 N=28		5635 (28.0)	1365 (67.7)	1.22 (0.37-4.0)
Study 66 N=27		4060 (23.9)	1390 (40.4)	1 (1-2)
Study 66 N=26	75 mg blue capsule	3680 (32.5)	1150 (47.8)	1 (1-4)
Study 69 fasted N=34		4160 (25.3)	1430 (36.1)	1 (1-3)
Study 71 N=50		4070 (24.6)	1240 (33.1)	1 (0.5-2.5)
Study 78 N=46		3750 (24.1)	1330 (36.6)	1 (0.75-4)
Study 80 N=12		4100 (24.1)	1390 (35.4)	1 (1-4)
Study 85 control N=22		4480 (19.9)	1440 (36.5)	1.27 (1-2.5)

[a] Geometric mean, GCV% geometric coefficient of variation.

[b] Median (range).

AUC area under the plasma concentration-time curve; Cmax maximum plasma concentration; N number; PK pharmacokinetics; tmax time to maximum plasma concentration

The in vitro comparative dissolution data profiles of selumetinib 10 mg and 25 mg capsules produced from (b) (4) and Pathon are provided, as presented in Figures 23 and 24 below. From the results, the 10 mg and 25 mg capsules produced from two manufacturing sites showed comparable dissolution profiles.

Figure 23: Dissolution of selumetinib capsules 25 mg manufactured at (b) (4) and Patheon in pH 6.5 with 0.5% w/v polysorbate 80 media (Mean±95% CI; n=12)

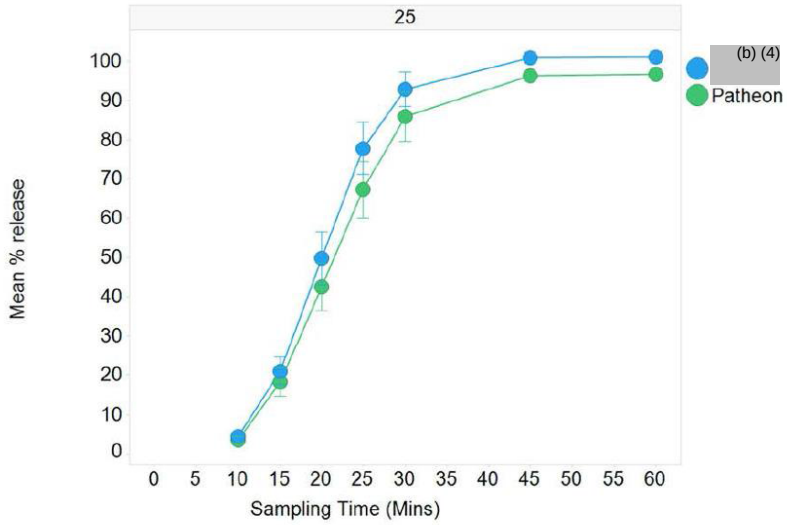
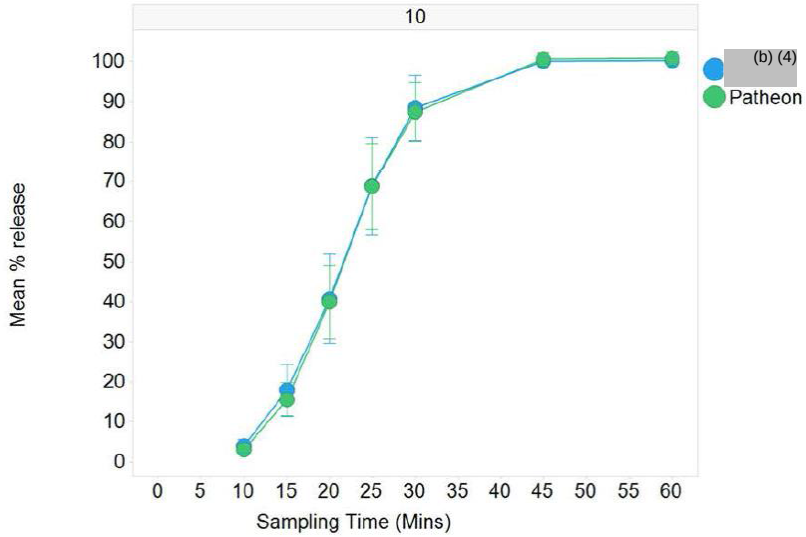


Figure 24: Dissolution of selumetinib capsules 10 mg manufactured at (b) (4) and Patheon in pH 6.5 with 0.5% w/v polysorbate 80 media (Mean±95% CI; n=12)



Overall, this Reviewer considers the in vitro formulation bridging for both 10 mg and 25 mg selumetinib capsules have been established, therefore, no additional in vitro bridging studies are needed.

Mei Ou

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Banu Zolnik

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XING WANG
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