CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216387
Applicant Name	AstraZeneca UK Ltd.
Drug Product Name	Acalabrutinib Maleate
Dosage Form.	Tablet
Proposed Strength(s)	100
Route of Administration	Oral
Maximum Daily Dose	200 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
Drug Product Description	Acalabrutinib is an orally bioavailable, Bruton tyrosine kinase (BTK) inhibitor. Acalabrutinib was approved under NDA 210259 in 2017 in a capsule formulation of the free base. The current label for this product restricts its administration with acid reducing agents (ARAs), including the recommendation that patients avoid co-administration with proton-pump inhibitors (PPIs). (b) (4) This restriction is of particular concern for cancer patients who are likely to take an average of five concomitant medications, of which ARAs are commonly administered. The current NDA presents a new salt tablet. (b) (4) The drug product is presented as an immediate release, film-coated tablet containing 129 mg acalabrutinib maleate (equivalent to 100 mg acalabrutinib). The QTPP for the drug product was defined to frame the pharmaceutical

	development program for the new oral tablet while ensuring the establishment of a robust formulation and manufacturing process which delivers a product consistently meeting the established critical quality attributes. The Applicant studied physical compatibility with the NG tube, etc. The compatibility studies support the dispersion of Acalabrutinib maleate film-coated tablets in 15 mL water and administered *via* nasogastric tube to patients.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20 °C - 25 °C USP CRT		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ray Frankewich	Hari Sarker
	Drug Product/ Labeling	Yang Nan	Sherita McLamore
	Manufacturing	Huiquan Wu	Zhaoyang Meng
	Biopharmaceutics	Min Kang	Qi Zhang
	Microbiology	Huiquan Wu	Zhaoyang Meng
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore	
Consults	OLDP		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed product has a **24-month expiry** when stored under USP controlled room temperature.

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 21637 for commercialization of Acalabrutinib Maleate 100 mg Tablets. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): Yes

Comments:

The Comparability Protocol includes the addition of alternative (unspecified) drug substance and drug product manufacturing and testing facilities. The comparability protocol proposed for the changes to be submitted to the agency by way of CBE-30 supplement. OLDP was informally consulted and it was concluded by all disciplines that the proposed post-approval changes included the Comparability Protocol are acceptable.

Additional Lifecycle Comments: N/A

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CHAPTER III: ENVIRONMENTAL

R. REGIONAL INFORMATION

Environmental
Assessment: *Adequate*

CHCHAPTER IV: LABELING

ASSESSMENT OF LABELING

Assessment of Product Quality-Related Information in the PI:
Adequate

HIGHLIGHTS OF PRESCRIBING INFORMATION

Information provided in the submission

Refer to the original prescribing information (PI).

Assessment: Acceptable from product quality perspective.

FULL PRESCRIBING INFORMATION

SECTION 2 DOSAGE AND ADMINISTRATION

Assessment: Acceptable from product quality perspective.

SECTION 3 DOSAGE FORMS AND STRENGTHS

Assessment: Identification characteristics of the tablets are not included. Recommend revision as follows:

> *Tablets: 100 mg acalabrutinib, orange, oval, film-coated, biconvex, debossed with 'ACA 100' on one side and plain on the other.*

The Applicant accepted the recommendation.

SECTION 11 DESCRIPTION

Assessment: In the last paragraph, there is no salt equivalency statement. Also, the excipients are not organized alphabetically. Recommended revision for this paragraph as follows:

CALQUENCE tablets are for oral administration. Each tablet contains 100 mg of acalabrutinib (equivalent to 129 mg of acalabrutinib maleate). Inactive ingredients in the tablet core are low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide.

The Applicant accepted the recommendation.

SECTION 16 HOW SUPPLIED/STORAGE AND HANDLING

Assessment: Acceptable.

OTHER SECTIONS OF THE PI

END OF THE PI (AFTER SECTION 17)

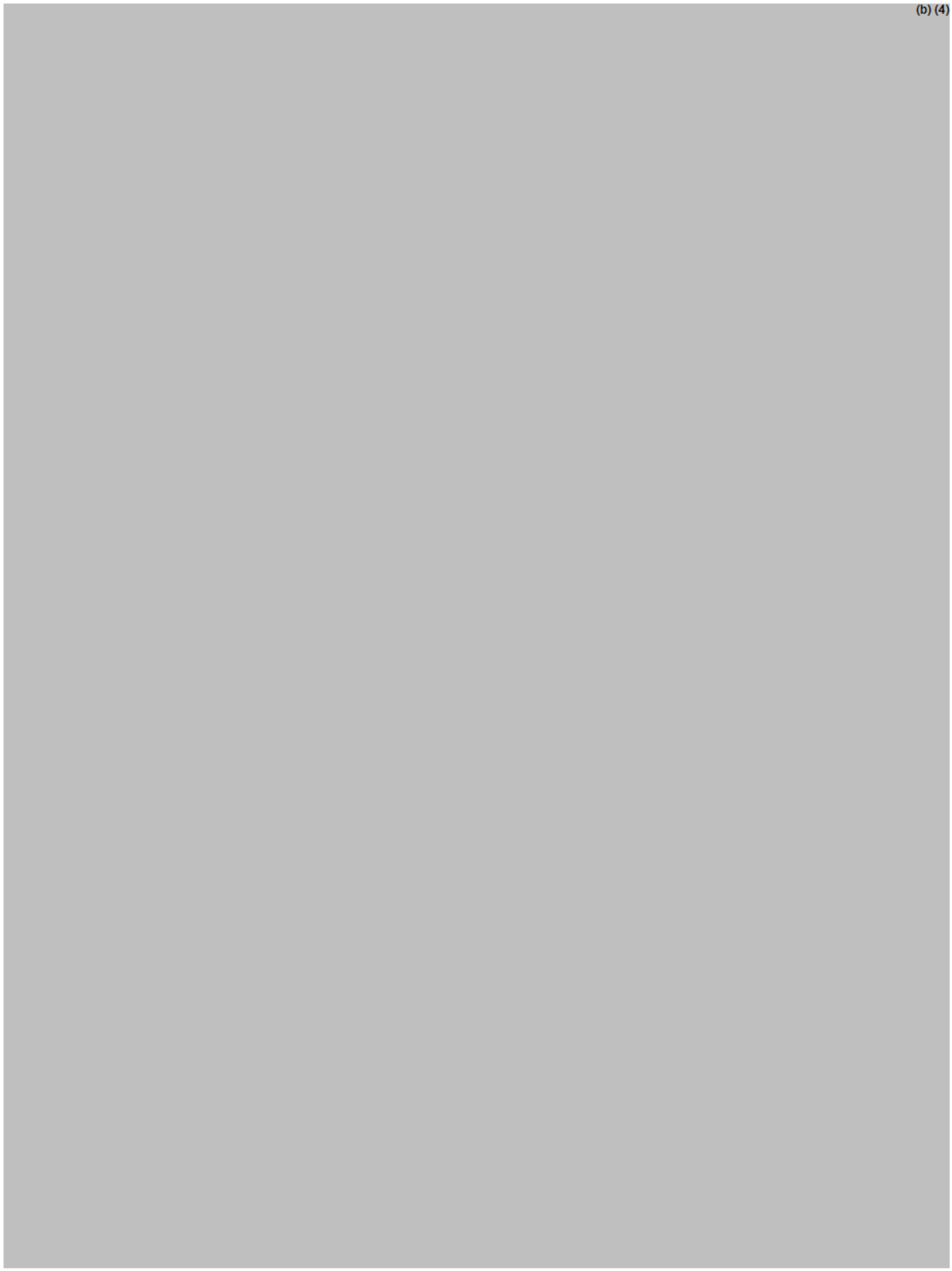
Assessment: No street name is included for the manufacturer or distributor. Recommended to include street address of the manufacturer or distributor. In a response by an email dated June 20, 2022, AstraZeneca stated that based on 21CFR201.1(i), "The street address may be omitted if it is shown in a current city directory or telephone directory." In addition, based on precedence AstraZeneca has not listed the actual address on other approved products.

The Applicant justification for omission of the street address is acceptable.

Assessment of Product Quality-Related Information in the Container Labels and Carton Labeling

Container Labels

For sales



ITEMS FOR ADDITIONAL ASSESSMENT

None

APPEARS THIS WAY ON ORIGINAL

Yang Nan

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Sherita McLamore

Digitally signed by Sherita McLamore
Date: 6/22/2022 04:58:50PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	Calquence® (Acalabrutinib) Capsules, 100 mg; NDA 210259 by AstraZeneca, Approved on 10/31/2017
Assessment Cycle Number	1
Drug Product Name/ Strength	Calquence® (Acalabrutinib Maleate) Tablets, 100 mg
Route of Administration	Oral
Applicant Name	AstraZeneca
Therapeutic Classification/ OND Division	DHM2
RLD/RS Number	Calquence® (Acalabrutinib) Capsules, 100 mg; NDA 210259 by AstraZeneca, Approved on 10/31/2017
Proposed Indication	CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy. • This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma
Primary Reviewer	Min Kang, PharmD, MS
Secondary Reviewer	Qi Zhang, PhD
PBBM Advisor	Gerlie Gieser, PhD
Assessment Recommendation	**Adequate**

***Background*:**

The Applicant submitted this 505(b)(1) NDA seeking approval for Calquence® (Acalabrutinib Maleate) Film-coated Tablets, 100 mg. Acalabrutinib is a potent, highly selective, irreversible Bruton tyrosine kinase (BTK) inhibitor currently approved for the treatment of adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL) who have received at least one prior therapy. The proposed Acalabrutinib maleate immediate-release film-coated oral tablets, 100 mg are manufactured using (b) (4) . The recommended dose is 100 mg orally, approximately every 12 hours, and swallow whole tablet with water and with or without food.

The current labeling for the listed drug, Calquence® (Acalabrutinib) Capsules, includes recommendations that patients should avoid co-administration with proton-pump

inhibitors (PPIs) and that dosing should be staggered with H2 receptor antagonists and antiacid due to the fact that its co-administration would result in significant AUC and Cmax reductions. Thus, the Applicant has developed the same drug product with new formulation (Acalabrutinib Maleate Film-coated Tablets, 100 mg, also referred to as AMT hereafter), (b) (4) , with the purpose of supporting the same indications without the existing PPI-restriction in the current labeling. This application is primarily supported by the clinical program consisting of the Pivotal Bioequivalence Study D8223C00013 and Bioavailability Study D8220C00018 (ACE-HV-115).

***Assessment Summary*:**

This Biopharmaceutics Review focuses on evaluation of (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for AMT, (2) the Physiologically-Based Biopharmaceutics Model (PBBM) developed and validated to support the proposed dissolution acceptance criterion for AMT, and (3) the bridging between the clinical and commercial AMT.

- **In Vitro Dissolution Method and Acceptance Criterion:**

The proposed in vitro dissolution method and the revised dissolution acceptance criterion shown in the table below are approved for the Quality Control (QC) testing of AMT, for batch release and stability testing:

Approved Dissolution Method and Acceptance Criterion for Calquence® (Acalabrutinib Maleate) Tablets, 100 mg				
Apparatus	**Speed**	**Volume/ Temp**	**Medium**	**Acceptance Criterion**
USP II (Paddle)	75 rpm	900 mL/ 37 °C	5 mM Phosphate Buffer (pH 6.8)	Q = (b) (4) % at 20 min

CQAs	**Initial Risk Ranking**	**Comments**	**Updated Risk Ranking after Assessment**	**Comments**
Dissolution	Medium	Lowly soluble drug substance with pH-dependent solubility	Low	(1) The proposed dissolution method exhibits discriminating ability against different API particle sizes, (2) The dissolution acceptance criterion has been tightened from "Q= (b) (4) % in (b) (4) min" to "Q= (b) (4) % in 20 min"

- **Physiologically-Based Biopharmaceutics Modeling (PBBM):**

The Applicant utilized PBBM (b) (4) approach to support a widened dissolution acceptance criterion of "Q = (b) (4)% in (b) (4) min". However, based on the FDA's assessment of the proposed PBBM, the results of the submitted modeling are inadequate to support an extended dissolution safe space, because the virtual batch VBB representing (b) (4)% dissolution at (b) (4) min is not expected to be bioequivalent to reference batch TAAB (administered without PPI); FDA recommended that the dissolution acceptance criterion be tightened to "Q = (b) (4)% in 20 min" based on the in vitro dissolution profile data of the clinical batches (TAAB/TAAC/L013537) that were demonstrated to be bioequivalent to the approved acalabrutinib capsules. It is also noted that any further application of this model for other purposes will be assessed separately with its supporting data. Refer to Section B.3. of this review for details regarding the PBBM assessment.

- **Product Bridging:**

The formulation of the clinical drug product (Batches TAAB/TAAC/L013700 AstraZeneca AB, Sweden) is the same as the formulation of the proposed to-be marketed drug product. There were no changes to the manufacturing process, nor manufacturing site that required bridging between the clinical and the to-be-marketed drug products. Also refer to Section R of this review for the Applicant's Comparability Protocol proposal for an addition of a future drug product manufacturing site.

List of Submissions Being Assessed:

eCTD sequence #	Date of response or meeting	Document
0001	10/04/2021	Original NDA submission
0002	11/16/2021	Quality/Response[1] to Quality/Biopharmaceutics IR #1 dated 11/12/21; CMC-Application Orientation Meeting held on 11/15/21
0012	04/08/2022	Quality/Response[2] to Quality/Biopharmaceutics IR #2 dated 03/25/22

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*:
None.

Overall Recommendation:
From the Biopharmaceutics perspective, NDA 216387-ORIG-1 for the proposed Calquence® (Acalabrutinib Maleate) Film-coated Tablets, 100 mg, is **Adequate** and recommended for Approval.

[1] \\CDSESUB1\evsprod\nda216387\0002\m1\us\responses-quality.pdf
[2] \\CDSESUB1\evsprod\nda216387\0012\m1\us\responses-quality.pdf

B.1 BCS DESIGNATION

Assessment: A BCS designation is not requested nor required

Solubility: Acalabrutinib maleate is manufactured as a (b) (4) and is demonstrated be a (b) (4) form under ambient conditions. Acalabrutinib maleate (b) (4) is considered as a lowly soluble drug substance based on the BCS criteria (b) (4)

(b) (4)

Permeability: The apparent permeability (Papp) was measured in bidirectional Transwell™ assay using MDCK-MDR1 cells cultured in 96 well plates. The Papp was scaled to human effective jejunal permeability values (Peff). Using the correlation to human Peff, the Peff for acalabrutinib was estimated to be 5.4×10^{-4} cm/sec.

Reviewer's comments:

A BCS designation is not requested by the Applicant, nor required by the FDA. Based on the submitted solubility and permeability data, this Reviewer considers acalabrutinib maleate as lowly soluble and highly permeable drug substance.

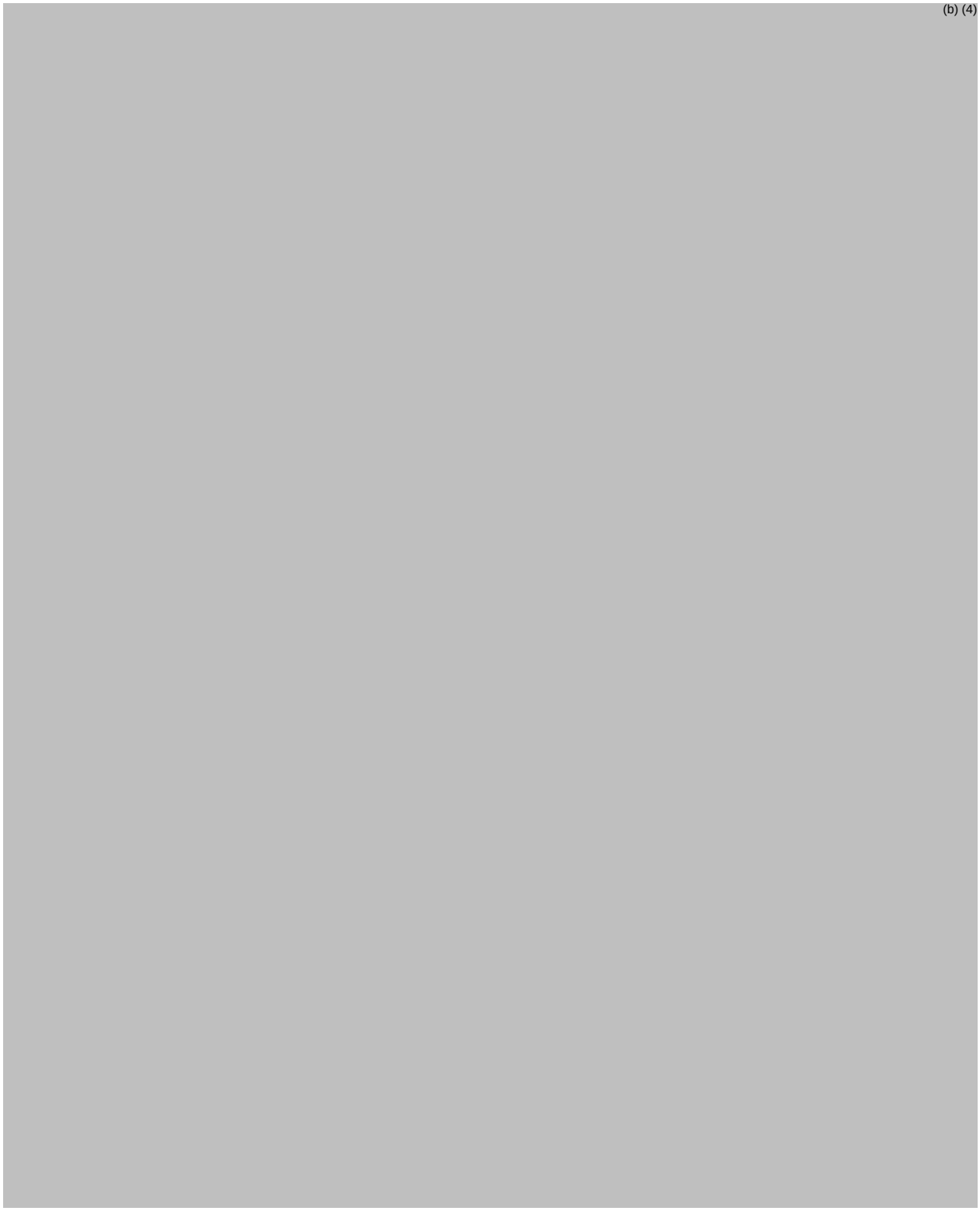
B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

Table 3: Applicant Proposed dissolution parameters for AMT[3]

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP II (Paddle)	75 rpm	900 mL/ 37 °C	5 mM Phosphate Buffer (pH 6.8)	*Originally Proposed*: Q= (b) (4)% at (b) (4) min *Revised*: Q= (b) (4)% at 20 min

(b) (4)



B.2.3. Discriminating ability: The Applicant investigated the dissolution method's discriminating ability against the following Critical Bioavailability Attributes [CBAs]: (i) Critical Material Attributes [CMAs] such as varying particle sizes of the drug substance; see **Figure 4**, **Tables 4** and **5**, (ii) Critical Formulation Attributes [CFAs]

such as varying amounts of the [redacted]; **Figure 5**, (iii) Critical Processing Parameters [CPPs] such as varying amounts of [redacted]; **Figure 6**, (iv) Combination of formulation and manufacturing process variants; **Figure 7** and **Table 6**, (v) Varying storage conditions; **Figure 8**.

Table 4: Composition of variant products

Batch references	EB18-431421 EB19-033107 EB19-033109	EB19-033106 EB19-033108 EB19-033110
Component	**Formulation (%w/w)**	
Acalabrutinib maleate	[redacted]	
Microcrystalline cellulose (MCC)		
Mannitol		
Hydroxypropyl cellulose, low-substituted (L-HPC)		
Sodium stearyl fumarate (SSF)		

Table 5: Proposed commercial quantitative formulation

Material	[redacted]
Acalabrutinib maleate	
Mannitol	
MCC	
L-HPC	
SSF	

Figure 4: Impact of API particle size on dissolution profiles of AMT (e.g., d_{90}: ≥ [redacted]; *target particle size (PSD) is* d_{90}: [redacted])

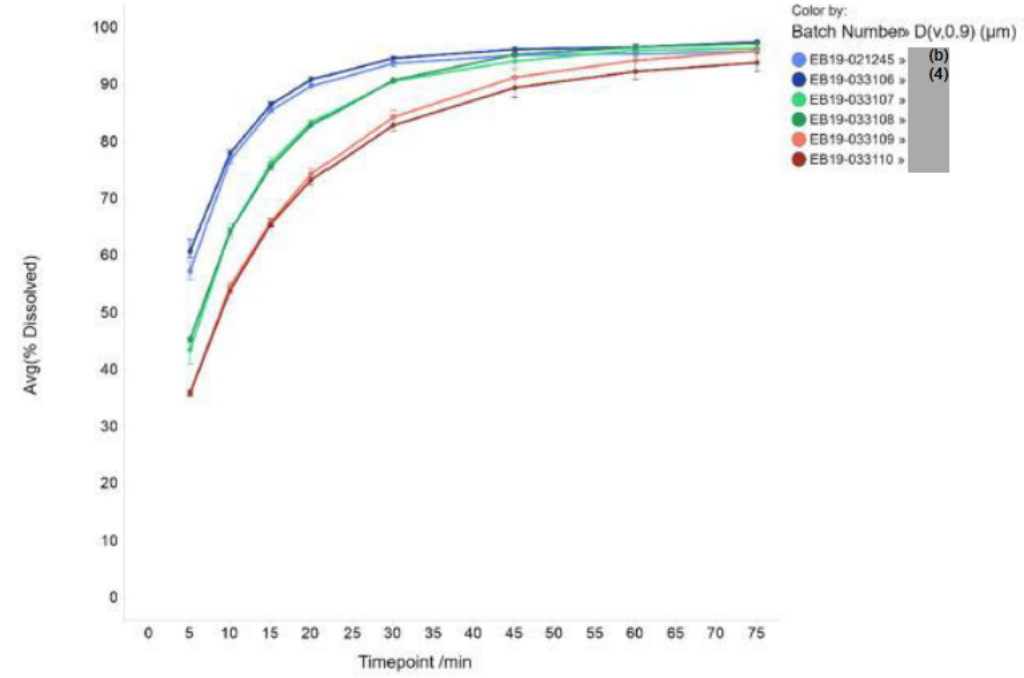


Figure 5: Dissolution profiles of a [redacted] variant (EB19-272802; [redacted]) vs. a control (EB20-189217; [redacted])

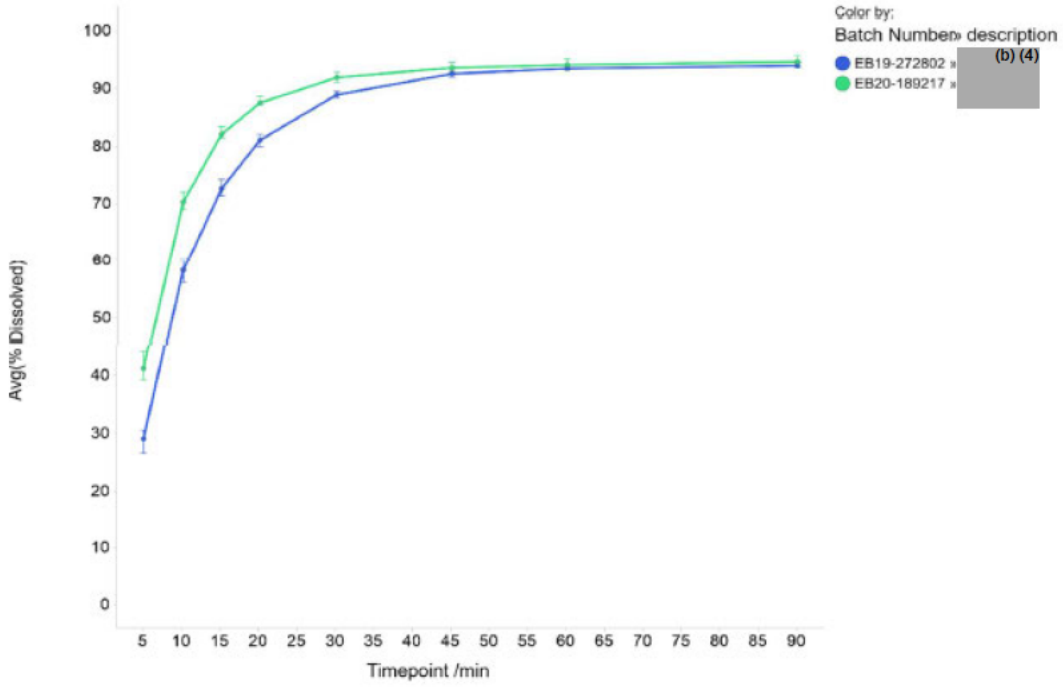


Figure 6: Dissolution profiles of [redacted] variant (EB19-079701; [redacted]) vs. a control (EB19-144101; [redacted])

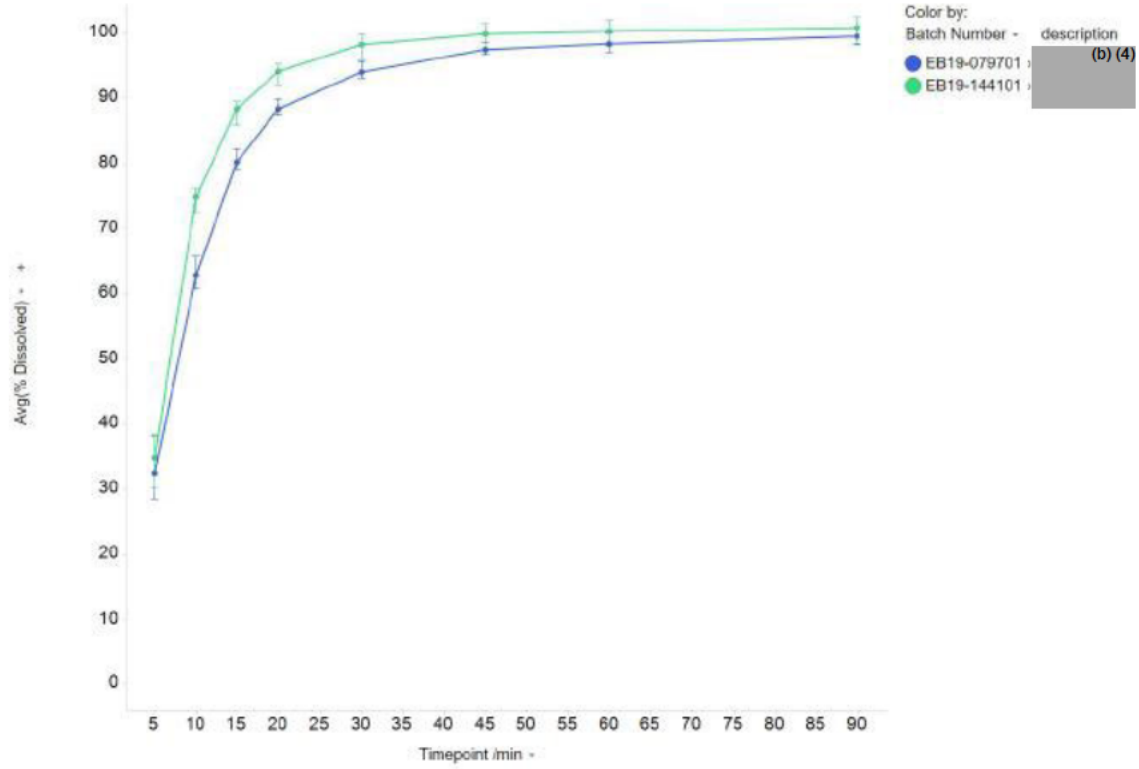


Figure 7: Dissolution profiles of formulation and manufacturing process variants

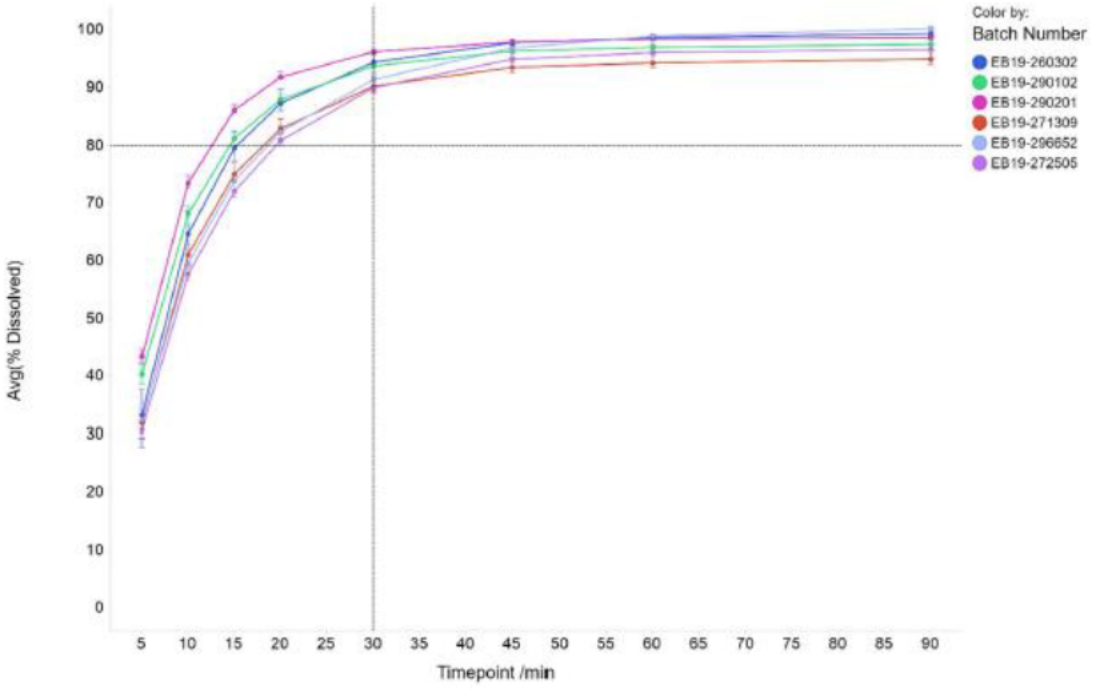
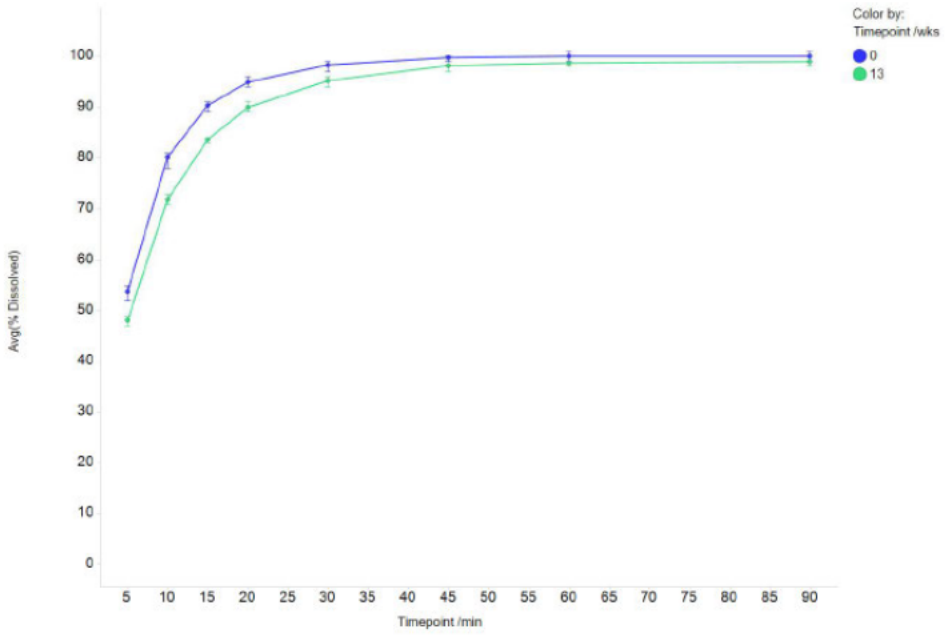


Table 6: Combination of formulation and manufacturing process variants

Factor	EB19-260302	EB19-290102	EB19-290201	EB19-271309	EB19-296652	EB19-272505
Acalabrutinib maleate particle size $D_{(v,0.9)}$	(b) (4)					(b) (4)

Figure 8: Dissolution profiles of Initial storage condition vs. Accelerated storage variant (e.g., Batch TAAB stored unprotected (b) (4))



***Reviewer's comments*:**

The Applicant proposed an in-house dissolution method [Apparatus II (Paddle), 900 mL in 5 mM Phosphate Buffer (pH 6.8) at 75 rpm] and justified the use of each dissolution method parameters as described above: (b) (4)

. Note that the Applicant has included a one tier particle size control (b) (4) in the drug substance specification.

For drug substances classified as lowly soluble, like Acalabrutinib maleate, it is important to select a dissolution method that is discriminating (i.e., can reject unacceptable quality drug product batches) to mitigate the product risk for dissolution. Since the Applicant showed that the proposed dissolution method exhibited discriminating ability against the different API particle size, one of the most critical material attributes for tablet dosage forms containing low solubility drug substances, the proposed dissolution method with the revised dissolution acceptance criterion of Q= (b) (4) % at 20 min is suitable for the routine QC testing of AMT.

B.2.4. Dissolution Data and Acceptance Criterion:

Figure 9: Dissolution Profile of registration batches (n=6, error bars = max/min)

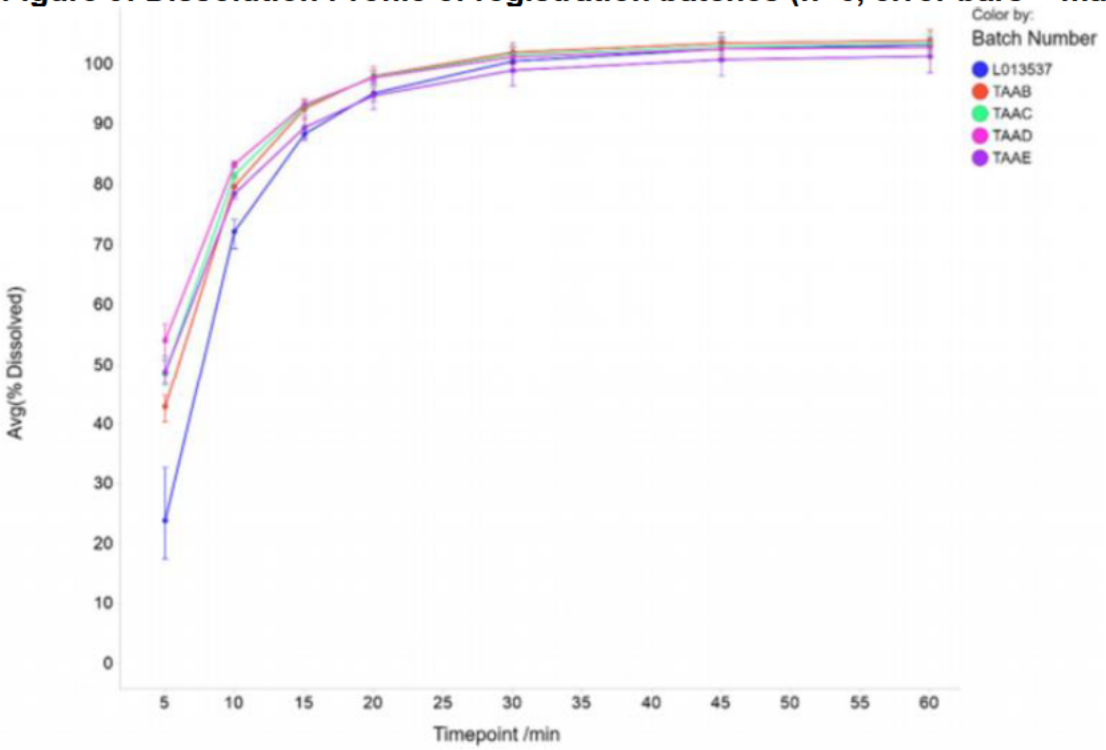


Table 7: Registration batches

Batch number	Tablet strength (mg)	Batch size (nominal granulation size – kg)	Batch number of drug substance	Date of manufacture	Site of production	Use
TAAB	100	(b) (4)	19600T0004	November 2019	AstraZeneca AB, Södertälje, Sweden	Clinical and stability
TAAC	100		19600T0003	November 2019	AstraZeneca AB, Södertälje, Sweden	Clinical and stability
TAAD	100		19600T0005	November 2019	AstraZeneca AB, Södertälje, Sweden	Stability
L013537	100		19600T0006	November 2019	AstraZeneca AB, Gothenburg, Sweden	Clinical
TAAE	100		19600T0002 19600T0003	October 2020	AstraZeneca AB, Södertälje, Sweden	Stability

Reviewer's Comments:

The Applicant has submitted the Physiologically Based Biopharmaceutics Model (PBBM) to support their initially proposed dissolution acceptance criterion, "Q=(b) (4)% in

(b) (4) min". However, as described below in Section B.5., the PBBM results (as presented) were found to be inadequate to support the Applicant's proposal. Therefore, the dissolution acceptance criterion was set based on the in vitro dissolution profile data (Figure 9 and Table 7) of the clinical batches that were shown to be bioequivalent to the approved acalabrutinib capsules in Study HV-115. The FDA requested that the Applicant tighten the proposed dissolution acceptance criterion from "Q=(b) (4)% in (b) (4) min" to "Q=(b) (4)% in 20 min" in IR #2 dated 3/25/22. In the Applicant's response dated 4/8/22, the dissolution acceptance criterion was revised to "Q=(b) (4)% in 20 min" and the specifications have been updated accordingly.

B.3 PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODEL (PBBM)[4,5]:

Assessment: Inadequate to Support Q = (b) (4)% at (b) (4) min

(b) (4)

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B.12 PRODUCT BRIDGING

Assessment: Adequate

The formulation of the clinical drug product (Batches TAAB/TAAC/L013700 AstraZeneca AB, Sweden) is the same as the formulation of the proposed commercial drug product (Batch TAAB AstraZeneca AB, Sweden). There were no changes to the manufacturing process, nor manufacturing site in the current submission. Therefore, no bridging studies are needed between the clinical and the to-be-marketed drug products.

B.13 BIOWAIVER REQUEST

Assessment: A biowaiver is not requested nor required

This NDA does not contain a biowaiver request. Only one dosage strength (100 mg) is being sought for approval, and thus, a biowaiver request is not applicable to this application.

R. REGIONAL INFORMATION

Comparability Protocol[9] for the addition of drug product's manufacturing site:
The Applicant is proposing to add an alternative manufacturing site, AstraZeneca Pharmaceuticals LP, Mount Vernon, US for the manufacture and QC testing of AMT (**Table 11**). As part of the proposal, the Applicant indicates that they will provide a comparative dissolution testing using the QC dissolution method to demonstrate that the drug product's in vitro dissolution performance is not compromised by the change of manufacturing site. Refer to the Drug Product review for additional CMC information.

[9] M.3.2.R: Comparability Protocol for the Drug Product: docubridge://open/Server=CDER-PRODUCTION&Id=F9ecad5004cb24931a2f818857478df0e&NodeId=Ndb8261525a9d4c4186cbe696e1b6b9ef&Page=0

Table 11: Present and Proposed (future) Drug Product Manufacturers

Present	Proposed
AstraZeneca AB Gärtunavägen 151 85 Södertälje Sweden (Drug product manufacture, QC testing, stability testing and primary and secondary packing)	AstraZeneca AB Gärtunavägen 151 85 Södertälje Sweden (Drug product manufacture, QC testing, stability testing and primary and secondary packing)
AstraZeneca AB Forskargatan 18 151 85 Södertälje Sweden (QC testing and stability testing)	AstraZeneca AB Forskargatan 18 151 85 Södertälje Sweden (QC testing and stability testing)
AstraZeneca Pharmaceuticals LP 587 Old Baltimore Pike Newark Delaware 19702 United States of America (Primary and secondary packing)	AstraZeneca Pharmaceuticals LP 587 Old Baltimore Pike Newark Delaware 19702 United States of America (Primary and secondary packing)
	AstraZeneca Pharmaceuticals LP **4601 Highway 62 East** **Mount Vernon** **Indiana 47620** **United States of America** **FEI number: 1825662** **(Drug product manufacture, QC testing)**

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Min (Sammie) Kang

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Date: 6/28/2022 09:53:22AM
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Qi Zhang

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