CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215310Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 215,310
Review # 1

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: Applicant to insert proposed retest period and storage conditions.

The proposed storage condition and retest period for mobocertinib drug substance is (b) (4) months when stored at (b) (4) °C, with excursions allowable between (b) (4) °C (USP controlled room temperature).

FDA Assessment: Retest period of (b) (4) months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: Applicant to insert proposed shelf life and storage conditions

The proposed storage condition and expiry of mobocertinib drug product is 24 months; Capsules may be stored at room temperature. Do not store above 30°C (86°F). Do not freeze.

FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Mobocertinib/Capsules
Strength	40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have received prior platinum-based chemotherapy.
Applicant	Takeda Pharmaceuticals U.S.A. Inc.
US agent, if applicable	N/A

FDA assessment is indicated in colored fonts

[FDA will complete these sections.]

Submit Date(s)	February 26, 2021
Received Date(s)	February 26, 2021
PDUFA Goal Date	October 26, 2021
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	August 18, 2021
Established Name	Mobocertinib
(Proposed) Trade Name	EXKIVITY
Pharmacologic Class	Kinase inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA submission	*2/26/2021*	*All*
PQAA	*3/15/2021*	*All*
Quality amendment	*4/26/2021*	*OPMA*
Labeling	*4/28/2021*	*DP*
Quality amendment	*4/28/2021*	*Biopharmaceutics*
Labeling	*5/11/2021*	*DP*
Quality amendment	*5/14/2021*	*OPMA*
Quality amendment	*5/18/2021*	*Biopharmaceutics, DP*
Quality amendment	*5/24/2021*	*Biopharmaceutics*
Quality amendment	*5/28/2021*	*DP*
Quality amendment	*6/16/2021*	*DP*
Labeling & Quality amendment	*6/23/2021*	*DP*
Labeling	*6/28/2021*	*DP*
Quality amendment	*7/8/2021*	*DS*
Quality amendment	*7/14/2021*	*DS, DP*
Quality amendment	*7/29/2021*	*DS*
Labeling	*8/9/2021*	*DP*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Paresma Patel
Drug Product	Tefsit Bekele	Anamitro Banerjee
Process and Facility	Huiquan Wu	Rakhi Shah
Microbiology	Huiquan Wu	Rakhi Shah
Biopharmaceutics	Gerlie Gieser	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	

ORBIS Partner Agency Quality Review Team (To be redacted for FOIA)

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
MHRA		
TGA Australia		
ANIVISA		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	IV		(b) (4)	Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs

Other Documents: *IND, RLD, or sister applications*
[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	126,721	Mobocertinib IND

CONSULTS
None

TABLE OF CONTENTS

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

[To the Applicant: Insert text here.] Report any differences in formulation, manufacturing, container closure system, presentation, etc. ***Do not include labeling differences***.

#	FDA (US)	TGA (AUS)	ANVISA (BRA)	HSA (SGP)	SMC (CHE)	MHRA (UK)
1	Container Closure System: Bottles	Blisters	Blisters	Blisters	Blisters	Blisters
2	Packaging Sites: (b) (4) Takeda Bray	Takeda Bray	Takeda Bray	Takeda Bray	Takeda Bray	Takeda Bray

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]

Mobocertinib is a kinase inhibitor indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive metastatic non-small cell lung cancer (NSCLC). The drug substance is mobocertinib monosuccinate salt, which has high solubility across physiologic pH range of pH 1.0 to pH 6.8. (b) (4) Adequate description of the drug substance manufacturing process including CPPs is provided. Characterization data supports the proposed structure of mobocertinib monosuccinate salt. The proposed specifications appear adequate to ensure the identity, strength, and purity of mobocertinib drug substance. Specified and unspecified impurities are limited to ICH Q3A recommended limits. Control of (b) (4) at NMT (b) (4) ppm (b) (4) appears sufficient. The proposed acceptance criteria for particle size distribution (b) (4) (b) (4) are acceptable from drug substance, biopharmaceutics, drug product and manufacturing perspectives. Analytical methods and method validations are found adequate. A retest period of (b) (4) month may be granted when stored under controlled room temperature.

Mobocertinib drug product is an immediate release capsule for oral administration. Mobocertinib capsule contains 40 mg mobocertinib (free base, equivalent to 48.06 mg mobocertinib succinate) without excipients. The commercial manufacturing process of mobocertinib capsules consists (b) (4) The specifications of the drug product are adequate to establish

the drug product's identity, potency, and purity. Individual unspecified impurities are controlled at NMT (b) (4)% each. The specified impurities are also controlled at NMT (b) (4)% each which complies with ICH Q3B limits. The uniformity of dosage unit is tested by weight variation method per USP <905>. The dissolution method and acceptance criterion are found acceptable. Analytical methods and validations are adequate. The overall bridging approach for the Drug-In-Capsule products (DiC-A, DiC-B, and DiC-C) used throughout clinical development of mobocertinib capsules is found adequate. The primary container closure for mobocertinib capsules consists of a 120cc wide mouth, round, white, high-density polyethylene bottle, (b) (4) closure consisting of an outer cap, an inner cap and a foiled induction seal. An expiration dating period of 24 months may be granted when stored at 20°C to 25°C, excursions permitted 15°C to 30°C.

All facilities are recommended for approval based on acceptable compliancy history and relevant manufacturing experience. No pre-approval inspection is identified.

The claim for categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable.

In conclusion, OPQ recommends APPROVAL of NDA 215310.

Life Cycle Considerations:
[FDA ATL to include any life-cycle considerations here]
None

2. APPLICATION BACKGROUND

[Applicant will complete this section.] Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

Mobocertinib has had an active IND Application (126,721) in the US since January 2016, and is not marketed in any region. Mobocertinib was granted the following designations in the US:

- Orphan drug designation was granted on 17 December 2019 for the treatment of NSCLC with genetic alteration in *EGFR* including *EGFR* mutations and/or *EGFR* gene amplification, *HER2* mutations, or BRAF G466V mutations.
- Breakthrough Therapy Designation (BTD) was granted on 23 April 2020 for the treatment of patients with metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.
- Fast Track Designation was granted on 03 June 2020 for the treatment of metastatic NSCLC harboring *EGFR* exon 20 insertion mutations.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

[To the Applicant: Insert text here.] Include CMC meeting dates and any Pre-NDA agreements

A list of relevant regulatory CMC history is provided for IND 126,721 in Table 1.

Table 1 – Summary of Regulatory CMC History for IND 126,721

Date	Description	Reference
25 March 2020	Type C meeting to discuss a waiver request for clinical relative BA/BE study for the intended commercial drug in capsule (DiC) to facilitate drug development. The Agency agreed that the proposal not to conduct an *in-vivo* clinical bioequivalence study to support the proposed decrease in the drug product capsule size for the 40 mg strength from size 1 to size 2 was reasonable. The Agency also agreed that the proposal not to conduct an additional *in-vivo* clinical bioequivalence study to support the bridge between drug substance manufacturing (b) (4) (i.e., via comparative dissolution testing of the earlier clinical DiC-B and the final clinical/stability/proposed commercial DiC-C, and other CMC data) appears reasonable. The meeting was canceled due to the clear feedback provided by the Agency in the Preliminary Comments.	Meeting Request: 7 Jan 2020 Meeting Materials: 7 Feb 2020 FDA Preliminary Comments: 12 March 2020
21 July 2020	Type B CMC End of Phase 2 Meeting to discuss regulatory starting materials, suitability of testing attributes, stability data, dissolution method, and overall quality development plans to support the NDA. **Regulatory Starting Materials:** (b) (4) **Testing Attributes:** FDA agreed with the proposed attributes being tested for release and stability for drug substance. A test for particle size determination has been added to the drug substance release and stability specification in line with FDA suggestion. FDA agreed with the proposed attributes being tested for release and stability for drug product. In line with FDA feedback, uniformity of dosage units by weight	Meeting Request:15 May 2020 Meeting Materials: 16 June 2020 FDA Preliminary Comments: 17 July 2020

	variation has been added to the drug product release specification. **Stability Data:** In line with FDA's feedback, 12 months of long-term drug substance stability data and 6 months of accelerated stability data for three registration batches will be included in the NDA. In addition, supportive stability data supporting the proposed retest period will be provided in the NDA. **Dissolution Method:** Additional dissolution method studies (i.e., open dish) were conducted as suggested by FDA. This data will be included in the NDA.	
17 Dec 2020	Type B Breakthrough Designation Meeting (CMC & Clinical Pharmacology Specific) to discuss the comparative dissolution studies that were conducted as requested in the Type C meeting preliminary feedback as well as the available clinical PK data to support the bridging of the DiC drug product manufactured with DS (b) (4) The Agency agreed with the approach of submitting additional PK bridging data/information in the NDA since the overall results of the comprehensive comparative *in-vitro* dissolution studies (in various pH media) alone do not appear to support comparability of DiC-B and DiC-C. The meeting was canceled due to the clear feedback provided by the Agency in the Preliminary Comments.	Meeting Request: 23 Oct 2020 Meeting Materials: 16 Nov 2020 FDA Preliminary Comments: 10 Dec 2020

The FDA's Assessment: ***Consistent with FDA's records***

[FDA will complete this section.]

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

A claim for categorial exclusion from the preparation of an environmental assessment is made under 21 Code of Federal Regulations (CFR) Part 25.31(b) on the basis that a worst-case Expected Introduction Concentration of the active moiety into the aquatic environment is less than 1 part per billion. To the applicant's knowledge, no extraordinary circumstances exist under 21 CFR Part 25.15(d).

The FDA's Assessment: ***Adequate***

The environmental analysis team was consulted regarding mobocertinib's impact on the environment. Raanan Bloom provided the following statement:

This application has an expected 5th year post approval production volume of (b) (4) *kg. This is a de minimus use level. Language for de minimus levels is provided below (from "Decision Tree" Derived from EA MAPP", item 3a)*

> *The applicant submitted a claim of categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase use, but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included a use amount that is consistent with the claim; the product is substantially lower 1 ppb. Extraordinary circumstances are not indicated, in accordance with 21 CFR 25.15, and the required statement on extraordinary circumstances is provided. Therefore, the claim of categorical exclusion is acceptable.*

5. FACILITIES

[Applicant will complete this section.]
Drug substance manufacturing, packaging and testing facilities are listed below:

(b) (4)

8. BIOPHARMACEUTICS

a. BCS CLASSIFICATION

Applicant to fill:
BCS Classification: None claimed

FDA assessment (FDA to fill):
Not designated

Information to support the BCS Class I designation request, if applicable.
Link: Page#:

The NDA does not include a BCS designation request. However, the mobocertinib drug substance was found to be highly soluble as the highest proposed commercial dose of 160 mg is soluble in 250 mL of aqueous media over the pH range of 1 to 6.8. Mobocertinib is a high permeability compound (apparent permeability coefficient in the apical-to-basolateral direction [$P_{app, A-B}$] of 15.0 x 10^{-6} cm/sec). On the basis of its high permeability and high solubility, mobocertinib exhibits the characteristics of a BCS Class 1 compound at the intended clinical doses.

FDA Comments:
The Applicant did not claim nor seek BCS-1/BCS-3 designation for the mobocertinib succinate drug substance/drug product. Based on the observed *atypical* high solubility behavior of the drug substance, and the inability of the drug product to exhibit rapid to very rapid dissolution in various aqueous pH media in the entire physiologically relevant range, in accordance with the principles set forth in the ICH M9 Guidelines, at this time, mobocertinib succinate capsules is not designated for the purpose of BCS-1 or BCS-3 based biowaivers.

Solubility – *High (per BCS criteria)*
At least 11 mg/mL of mobocertinib (as free base) is soluble in aqueous media across the physiologic pH range of pH 1.0 to pH 6.8, at 37°C (refer to Table 3.b of the 3.2.P.2 PDR-Formulation or Table 3.c of 3.2.S.3). Thus, per BCS criteria, mobocertinib can be technically considered a **high solubility** drug substance within the specified pH range. However, it is important to note that mobocertinib solubility is ***pH-dependent*** as lower amounts of the drug substance are soluble in higher pH (i.e., pH 4.5 and pH 6.8) media, and drastically decreases (0.032 to 0.14 mg/mL is soluble) in pH 7.0 to pH 7.5 at 37°C. Specifically, **in pH 7.0 or 7.5 buffer media, ~8 to 35 mg of the 160 mg clinical dose of mobocertinib will solubilize**. Furthermore, it was noted from the pH-solubility data of mobocertinib succinate at 37°C that lower levels of the parent drug could be quantified which the Applicant attributed to **>10% dimerization** in pH>4.5 media. Note that in the Response to the Biopharmaceutics information request/IR (SN-26), the Applicant provided data to show that 160 mg mobocertinib free base (tested as DS-A, DS-B, and DS-C) would all solubilize completely in 250 mL media [pH 1.2 (dissolution medium for release and stability, KCl/HCl, pH 2.0 Simulated Gastric Fluid (SGF), pH 3.5 Citrate, pH 4.5 Acetate, and pH 6.8 Fasted State Simulated Intestinal Fluid (FaSSIF)], at 37°C.

The (b) (4) is the desired polymorphic form of the drug substance. (b) (4)

(b) (4)

Permeability – *Low to Moderate*

The proposed labeling states that following an oral 160 mg dose, ***1***) the absolute bioavailability (BA) of mobocertinib capsules is 37% (presumably due to extensive first-pass metabolism), and ***2***) in a radiolabeled Mass Balance study, 76% of the administered dose (as mobocertinib solution) was recovered in feces (approximately 6% as unchanged mobocertinib) and 3.57% of the administered dose was recovered in urine (approximately 1% as unchanged mobocertinib) after 18 days of post-dose PK sample collection. This Reviewer notes that the Applicant's GastroPlus® PBPK model suggests that of the almost 100% fraction of the administered dose that permeates the intestinal epithelium, approximately 30% undergoes first-pass gut extraction (i.e., metabolized by the intestinal CYP3A4 enzymes with approximately 1.8% fraction unbound in the enterocytes), which overall explains the ~77% that leaves the gut and enters the portal vein, as well as the low estimated fraction (~36%) that reaches general systemic circulation following oral administration of 160 mg mobocertinib oral capsules. Thus, the available data from *in vivo* clinical studies and PBPK modeling do not appear sufficiently robust to establish the high permeability status of mobocertinib, i.e., on the basis of high systemic absorption. Regardless, this Reviewer acknowledges that high permeability status is no longer required/considered to be eligible for BCS-1 or BCS-3 based biowaivers.

In SN-15, the Applicant explained that (***i***) per the FDA drug-drug interaction guidance, the minimum mobocertinib concentration that should be used for *in vitro* Caco-2 permeability and active efflux assessment is 10.92 µM (i.e., 1/100th of dose ÷ 250 mL); however, (***ii***) to avoid saturation of drug efflux transporters expressed in the Caco-2 cell line, investigational drug concentrations ranging from 1 – 10 µM are typically used for *in vitro* permeability assessments. At test concentrations of 2 µM using the Caco-2 model, the apparent apical-to-basolateral permeability (P_{app} A→B) of mobocertinib parent drug and the two active metabolites did not surpass the reported P_{app} A→B value for the high permeability marker, propranolol (i.e., 4.57 – 15.0 x 10^{-6} cm/sec versus 17.9 x 10^{-6} cm/sec). Additionally, the Applicant concluded that the two active metabolites are also substrates of the P-glycoprotein drug efflux transporter. Furthermore, the effective permeability (P_{eff}) value (predicted by the Applicant's GastroPlus model from *in vitro* Caco-2 permeability data) of mobocertinib was lower than that for propranolol (1.5 x 10^{-4} cm/sec versus 2.91 x 10^{-4} cm/sec). Therefore, based on *in vitro* permeability data and *in*

silico permeability values alone, mobocertinib is conservatively classified as a **low (to moderate) permeability** drug substance.

Note that in SN-15, the Applicant confirmed that mobocertinib dimerization was observed (as a drop in % parent levels at pH exceeding 6.4 and when drug concentrations exceed 14.7 mg/mL freebase) in 'in vitro' solubility studies, and in 'in vivo' animal toxicity studies. The Applicant believes that dimerization poses negligible risk to the clinical bioavailability of mobocertinib because no dimer metabolites were detected in the Human ADME studies. However, because only monomers were being quantified by the bioanalytical method, it is not possible for FDA (Clinical Pharmacology) to confirm whether or not dimers are present in the biological samples obtained from PK studies involving humans.

Dissolution – *Not Rapid Across the Entire Physiologic pH Range*
Note that in 500 mL volumes of pH 4.5, pH 6.5, and pH 6.8 buffer media (USP Apparatus II at 50 rpm; 37 °C), mobocertinib capsules (b) (4) **(i.e., (b) (4) % dissolution within 30 min)**. Refer to Figures 5, 7, and 9 in Section 8d below. Additionally, the drug product does not show rapid dissolution in 500 mL volume of pH 6.8 buffer when using (b) (4) at 100 rpm; refer to Figure 10 in Section 8d below. Note that dissolution data in 900 mL media were not requested by this Reviewer because per the ICH M9 Guidance, it is recommended to use the medium volume for the QC dissolution method, which in this case is 500 mL.

Additional Comments (not directly related to BCS classification):
Effect of gastric pH increasing agents (e.g., proton-pump inhibitors)
Both the solubility of mobocertinib and the dissolution of mobocertinib capsules are pH-dependent, i.e., lower in higher pH media. However, per the Clinical Pharmacology Reviewer (Dr. Kimberly Maxfield), following the decision tree (Figure 1) of the FDA Guidance on Gastric Acid Dependent Drug Interactions, mobocertinib drug solubility at pH 6.8 is not less than 160 mg/250 mL and thus, mobocertinib is considered unlikely to have an *in vivo* drug interaction potential with gastric acidity-reducing agents.

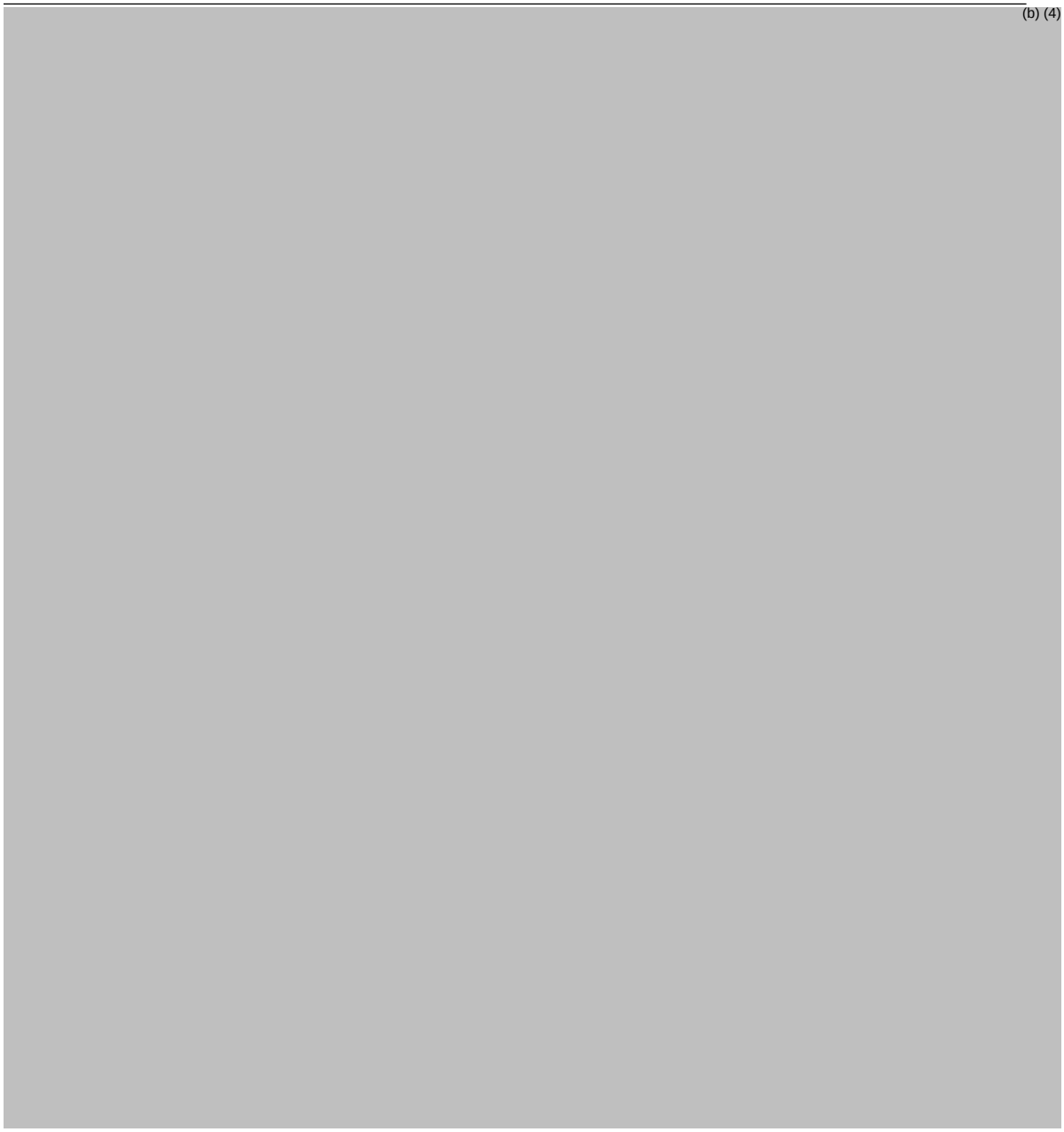
b. DISSOLUTION TEST

[Applicant to fill]

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 RPM	500 mL	37°C	pH 1.2 (b) (4)	Q = (b) (4) at 30 minutes

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



FDA Comments:

Dissolution Method - *Acceptable*

It is noted that the proposed QC dissolution method parameters are not exactly the same as the standard dissolution method conditions recommended for high solubility drug substances (per the FDA Guidance or the ICH M9 Guidance), specifically in terms of the composition of the pH 1.2 dissolution medium.

Discriminating Power/Stability Indicating Potential

The Applicant believes that a discriminating dissolution method is likely not feasible or necessary for mobocertinib capsules.

This Reviewer believes that for drug substances like mobocertinib that exhibit high solubility in pH 1.2 – pH 6.8 dissolution media, discriminating power for changes/differences in CQAs influential to dissolution is not required/expected for the proposed QC dissolution method. However, especially when considering that the proposed drug product does not exhibit rapid/very rapid dissolution across the physiologic pH range, a demonstration of the correct rank-order relationship between the CQA(s) and dissolution, stability-indicating potential (or any other means to support the suitability of the proposed dissolution method for routine QC testing of the finished drug product) would indicate a reliable quality management system for the proposed drug product, and thus, is desirable. Additionally, whenever feasible, the clinical relevance of the proposed dissolution method-generated profiles in terms of rank-order relationship with *in vivo* clinical PK data should be explored.

In SN-15, the Applicant provided the dissolution profile on long-term and accelerated stability data of the two pivotal clinical trial lots that were also used in supporting stability studies (refer to excerpted Figures 1.g and 1.h below). Based on the observed rank-order relationship between mean dissolution values at early sampling time points and storage temperature/time, it appears that (despite the observed high data variability at early dissolution sampling time points) the proposed dissolution method has **stability indicating potential**. This Reviewer notes that for these two supporting stability lots, it appears that the dissolution decreased with storage time (moreso, under accelerated stability conditions) and that the dissolution rate at different stability time points tracked in the opposite direction (b) (4) Nevertheless, as seen in the excerpted figures below, all the stability samples (up to 24 months of long-term and up to 6 months of accelerated stability testing) achieved complete dissolution at 30 minutes.

Figure 1.g Dissolution Profiles for Stability of Lot 228066

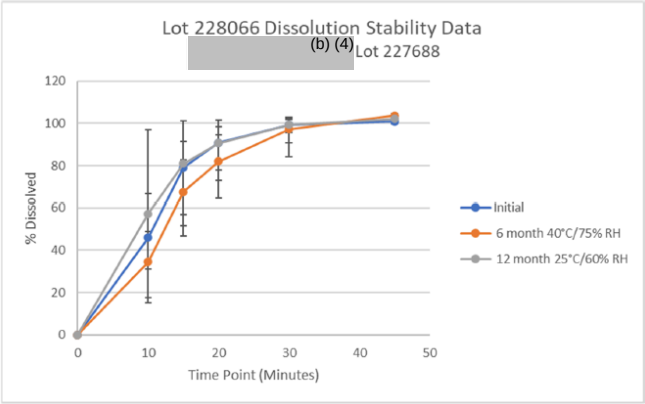
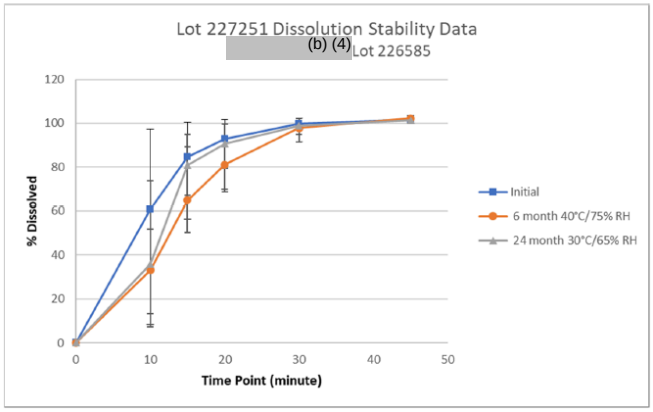


Figure 1.h Dissolution Profiles for Stability of Lot 227251



Both Packaged Lots 228066 and 227251 were used in pivotal Phase 2 clinical trial AP32788-15-101/Part 3. Collectively, the age range at the time of clinical trial use of these two lots is 4 – 17 months. Other lots used in the pivotal Phase 2 clinical trial had ages ranging from 5 – 24 months.

This Reviewer acknowledges the Applicant's conclusion that the proposed dissolution method is not discriminating for changes/differences in API particle size distribution (PSD); (b) (4) . Based on the Applicant's IR Response (SN-30), this Reviewer determines that the apparently counter-intuitive relationship between dissolution rate and API particle size distribution in Figure 3.d is possibly confounded by the intermingling of dissolution profile data from DiC-**B** capsules made with (b) (4) API with those from DiC-**C** capsules made with (b) (4) API, and by the difference in (b) (4)

When focusing only on DiC-**C** capsules (such as shown in Figure 3.j of the same report), it is apparent that the proposed dissolution method shows similar dissolution profiles for lots that were manufactured using (b) (4) DS-C with PSD within the proposed acceptance range and with similar SSA. Additionally, this Reviewer noted that the correct rank-order relationship between (b) (4) **API d_{90} and (early) dissolution rate** was observed for the DiC-C size 2 capsules containing API with the lowest and the highest particle size (b) (4) studied when using the proposed QC dissolution method (figure excerpted below). Overall, the Applicant's inability to observe a clear rank-order relationship between dissolution at early sampling time points and API particle size, and/or greater dissolution profile separations among studied capsule lots was likely precluded/confounded by the following factors: ***1***) the not so perfect inverse correlation between API particle size and specific surface area (SSA) as evidenced by the higher measured SSA of the largest (b) (4) API size variant as compared to the two intermediate (b) (4) API size variants (Table 1.b of the IR Response in SN-15), ***2***) the high observed dissolution data variability at earlier dissolution sampling timepoints, and ***3***) the selection of study variants with API PSD within the proposed API d_{90} acceptance range (b) (4) . Also in SN-15 (as well as in SN-30), it became evident to this Reviewer that (***a***) for assessing the impact of

(b) (4) API PSD on dissolution rate, of the figures included in the report, Figure 3.j is the most appropriate to consider because the target & variant capsule products were manufactured using API material that were sized using the proposed commercial (b) (4) process (thus, guaranteed to be exclusively DS-C), and (***b***) as compared to API d_{90}, the SSA appears to show a better rank-order relationship with dissolution data at early sampling time points.

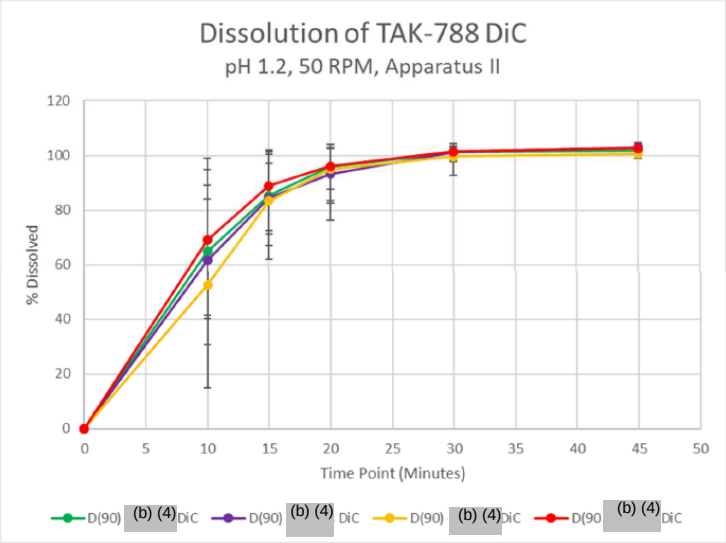


Figure 3.j of the Formulation Development Report

Drug Substance Batch (Output, (b) (4)	D(10)	D(50)	D(90)	SSA
194023 M-7	(b) (4)			
194023 M-2				
194022 M-1				
194021 M-1				

Table 1.b of IR Response in SN-15

That DiC-C capsules containing smaller particle size (and/or higher SSA) input API would be expected to exhibit slightly faster dissolution appears consistent with the numerical PK results of clinical pharmacology studies involving DiC-A, DiC-B, and/or DiC-C capsules, as illustrated by the comparative CMC data and PK data in Reviewer Table 1. Firstly, in Study TAK-788-1001/Part 3, the numerical (yet not statistical) differences in Cmax and AUC following administration of 160 mg doses of DiC-A versus DiC-B capsules can be explained (at least in part) by the relative particle size and SSA of the input API materials used to manufacture the mobocertinib capsules (refer to Table 1.c of the IR response in SN-15 and Table 11.o of the TAK-788-1001 study report or Table 20 of this CMC Assessment Aid). Secondly, in a cross-study comparison of Study 1001/Part 3 (DiC-A size 2, 160 mg) and Study 1005 (DiC-C size 2, 160 mg), the numerically lower parent drug and 'parent drug + metabolites' Cmax and AUC obtained for DiC-A than DiC-C can be explained by the larger particle size of the input API

material in the former than in the latter DiC capsules (refer to Table 1.c of the IR response in SN-15, and Table11.o of the TAK-788-1001 study report for the DiC-A data, as well as the API PSD of DS Lot 227085 on page 9/30 of the IR Response in SN-15 and Table 11.j of the High Fat Meal study report, Treatment A/fasted conditions for the DiC-C data).

Reviewer Table 1

Potential Effect of Input API Particle Size Distribution and Specific Surface Area on Mobocertinib Pharmacokinetic Parameters

PK Study	Drug Product	Dose	(b) (4) Drug Product Lot Number	Input Drug Substance Lot	Drug Substance PSD (µm)	Drug Substance SSA (m^2/g)	Parent Cmax (ng/mL; Geo Mean (%CV))	Parent AUC (ng*h/mL ; Geo Mean (%CV))	Combined Molar Cmax (ng/mL; Geo Mean (%CV)	Combined Molar AUC (ng*h/mL; Geo Mean (%CV))
High-Fat Meal TAK-788-1005	DiC-C, 40 mg, Size 2	160 mg	229161	227085	(b) (4)		56.8 (47.1)	1030 (61.1)	161 (34.2)	3290 (46.4)
Relative BA (DiC-A vs. DiC-B) TAK-788-1001/Part 3	DiC-A, 20 mg, Size 2	160 mg	224847	224723			44.8 (31.5)	739 (25.4)	130 (27.6)	2190 (23.0)
	DiC-B, 40 mg, Size 1	160 mg	226411	226124			41.7 (27.5)	710 (34.9)	121 (24.8)	2080 (30.7)

Note that per the FDA's Clinical Pharmacology Review Team, the resulting drug exposures in healthy subjects following administration of single 160 mg doses (1) are equivalent between DiC-A and DiC-B capsules based on the results of Relative BA Study 1001/Part 3, and (2) appear comparable between DiC-C capsules and DiC-A capsules based on cross-study PK assessment.

Thus, from the Biopharmaceutics perspective, the proposed lower tolerance limit for API d_{90} of (b) (4) µm is reasonable based on the comparative *in vitro* dissolution profile in excerpted Figure 3.j above. Additionally, considering evidence of bioequivalence of DiC-A and DiC-B capsules, and the PK similarity of DiC-A and DiC-C, in addition to the comparative API PSD and SSA data as shown in Reviewer Table 1 above, the proposed upper tolerance limit for API d_{90} of (b) (4) µm is acceptable from the Biopharmaceutics perspective. Note that per the Process Reviewer, drug substance PSD (b) (4) *The acceptability of the proposed particle size distribution for the API, as well as the evaluation of the adequacy of the proposed QC specifications* (b) (4) *will be determined by the CMC Reviewers. Per internal OPQ Review Team discussions, the proposed API particle size acceptance ranges* (b) (4) *were acceptable to the Drug Substance and/or Drug Product Reviewers.*

(b) (4)

Analytical Method Validation
HPLC with UV detection at 325 nm is used to quantify drug in the dissolution samples. The analytical method was evaluated for specificity, accuracy, precision, linearity, solution stability, and robustness. The robustness of the following dissolution method parameters was investigated: paddle rotation speed (50 rpm ± 2 rpm), medium pH (1.2 ± 0.1), medium temperature (37 ± 1 °C), presence/absence of medium deaeration, and sinker type/vendor. Sample solutions stored at 2 - 8°C protected from light were demonstrated to be stable.

In SN-15, per FDA request, the Applicant specified the type/description of the capsule sinker (Steel spring style sinker appropriate for size 2 capsule, or equivalent) in the revised Dissolution Standard Test Procedure. As stated above in Section 7.d of this Assessment Aid, the Drug Product Reviewer considers the analytical methods validation including that for dissolution to be acceptable.

Dissolution Acceptance Criterion – *Acceptable*
The proposed dissolution acceptance criterion is "Q = (b) (4)% at 30 min", apparently based on the dissolution on stability data of two primary stability drug product lots (DP229488 and DP229491) during 6 months of accelerated (30ºC/75% RH) storage, and 12 months of long-term (25ºC/60%), intermediate (30ºC/75% RH) and refrigerated (5ºC) storage, as shown in Figure 1e above.

Based mainly on the dissolution profile data of the pivotal clinical trial lots (e.g., those in excerpted Figures 1.g. and 1.h above), this Reviewer considers the proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) acceptable; Q = (b) (4)% at (b) (4) min is deemed too stringent. The proposed dissolution specification time point (i.e., 30 minutes) is advantageous when considering the observed high data variability at early dissolution sampling time points.

(b) (4)

(b) (4)

Dissolution on Stability
Based on 12 months of long-term and refrigerated stability data as well as 6 months of accelerated stability data from the primary stability batches of the (90-ct and 120-ct bottle) packaged drug product, the proposed expiration dating period for the proposed drug product is 24 months when stored at room temperature not exceeding 30 °C.

Based on the submitted dissolution data at 30 min of the primary stability lots of the DiC-C capsules over 12 months of long-term storage and 6 months of accelerated storage, the stability lots conformed to the Applicant's proposed dissolution acceptance criterion (Q = (b) (4) % at 30 min), and there were no significant trends.

c. BRIDGING THROUGHOUT DRUG PRODUCT DEVELOPMENT (FORMULATION, PROCESS, OR SITE CHANGE)

[To the Applicant: Include a schematic representation of the development of your proposed drug product from initial IND-product to the to-be-marketed product. Include all the formulation/manufacturing/process/etc. changes that occurred throughout development, the studies (in vitro or in vivo) bridging those products, and the PK, clinical, stability-registration studies in which those products were used.
Applicant provide supporting data/Figure(s) here:]

Link: Section 3.2.P.2.2 Formulation Development Page#: 6
Section 3.2.P.2.3 Manufacturing Development Page#: 3

[To the Applicant: Insert text here]

Formulation and Manufacturing Development:

(b) (4)

21 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

9. LABELING

Refer to DMEPA reviews for the most recent USPI and carton/container label. The adequacy of the USPI is currently being evaluated by the clinical division. Below is a brief review of sections 3, 11, 16 and highlight section of the prescribing information.

USPI

Highlights: ***Adequate***

The established name, route of administration, dosage form and strength were provided and found acceptable from the CMC perspective. DMEPA found the proposed proprietary name, Exkivity acceptable.

Section 2 (if relevant): ***Not Applicable***

(Add notes as necessary)

Section 3 Dosage Forms and Strengths: ***Adequate***

The dosage form, strength and description of identifying characteristics of mobocertinib capsules were provided and found acceptable. A minor change was recommended.

Section 11 Description: Choose an item.

If the following excipients used in the drug product, include warning/declaration in the USPI:

(b) (4)

(b) (4)

Description of the drug substance, molecular formula, weight and structure were provided. The pharmacological class, physical/chemical properties, dosage form, strength, and route of administration were provided. A list of capsule components was also provided. The information provided is acceptable. A minor change was recommended.

Section 16 How Supplied/Storage and Handling: ***Adequate***
The applicant initially proposed a storage conditions of (b) (4) . On June 16, 2021, the following information request was sent to the applicant regarding the storage conditions.

Revise the storage conditions under section 16 of the USPI and on the container label to USP controlled room temperature conditions of "20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]."
On June 23, 2021, they responded to the request and agreed to revise the storage conditions to "20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) (See USP Controlled Room Temperature). Another minor change was also recommended under section 16.

Manufacturer Information (Name and Address): ***Provided: Adequate***

Carton/Container Label ***Adequate***
The container/carton label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of the storage conditions in the prescribing information and on container/carton label. The most updated container labels for the two presentations are shown below.

(b) (4)

Final Risk Assessments

[FDA will complete this section.]

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Low	N/A
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	N/A
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Medium		Low	N/A
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	N/A
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	Low		Low	N/A

	• Site		(b) (4)		
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	N/A

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Katherine Windsor, Ph.D. Date: August 10, 2021
Secondary Reviewer: Paresma Patel, Ph.D. Date: August 10, 2021

Drug Product: Approval

Primary Reviewer: Tefsit Bekele, Ph.D. Date: July 15, 2021
Secondary Reviewer: Anamitro Banerjee, Ph.D. Date: August 17, 2021

Process and Facility: Approval

Primary Reviewer: Huiquan Wu, Ph.D. Date: May 18, 2021
Secondary Reviewer: Rakhi Shah, Ph.D. Date: August 16, 2021

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Gieser, Ph.D. Date: August 9, 2021
Secondary Reviewer Banu Zolnik, Ph.D. Date: August 18, 2021

Application Technical Lead: Approval

Xing Wang, Ph.D. Date: August 18, 2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XING WANG
08/18/2021 02:53:22 PM

KATHERINE WINDSOR
08/18/2021 02:59:57 PM

PARESMA R PATEL
08/18/2021 03:01:34 PM

TEFSIT BEKELE
08/18/2021 03:07:31 PM

ANAMITRO BANERJEE
08/18/2021 03:13:18 PM

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BANU S ZOLNIK
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GERLIE GIESER
08/22/2021 08:31:41 PM