CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213591Orig1s000

PRODUCT QUALITY REVIEW(S)

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 213591 is recommended for approval from OPQ. All manufacturing and labeling sites are adequate and there are no pending review issues nor any recommended PMR/PMC actions from OPQ. A shelf life of 24 months is granted when the tablets are stored under "Controlled room temperature: 20°–25° (68°–77° F); excursions permitted between 15°C and 30°C (59°F and 86°F); store in the original container with the desiccant cartridge". The shelf life includes a 6 week in-use period to be labeled on the container closure.

The NDA includes one comparability protocol regarding the (b) (4) **. The action letter should include the following language:**

"FDA acknowledges the comparability protocol for the re-validation procedures and the proposed reporting category of the changes likely to occur during the lifecycle of this product. The comparability protocol is approved."

II. Summary of Quality Assessments

A. Product Overview

Tabrecta (capmatinib) tablets are indicated for MET-mutated advanced non-small cell lung cancer (NSCLC). The proposed mechanism of action is by inhibition of the MET receptor tyrosine kinase. The drug substance is a new molecular entity. The drug product are oral film coated tablets available in 150 mg and 200 mg strengths. The tablets are manufactured using (b) (4) **and formulated with excipients that meet NF/USP quality standards. The tablets are packaged in HDPE bottles with an aluminum induction seal and** (b) (4) **2 g desiccant. The applicant cross references INDs** (b) (4) **, 116,691 and 124,033 for product development information. Capmatinib was granted Breakthrough Therapy Designation on 18-Apr-2019 and Orphan Drug designation 15-Mar-2019. The recommended dose is between 200 mg and 400 mg twice daily. The two dosage strengths allow dose reductions in 100 mg increments as described in the package insert.**

Proposed Indication(s) including Intended Patient Population	**MET-mutated advanced non-small cell lung cancer (NSCLC)**
Duration of Treatment	**Through disease progression until dose limited toxicity as determined by specific adverse events**

Maximum Daily Dose	**800 mg**
Alternative Methods of Administration	**No alternative methods allowed by the package insert**

B. Quality Assessment Overview

The drug substance is capmatinib hydrochloride. Three crystal forms were identified in development, but the commercial synthesis only yields crystalline (b) (4), which is used in the drug product manufacturing process. The drug substance (b) (4).

No impurities with mutagenic potential are expected to be impurities in the capmatinib hydrochloride drug substance. A retest period of (b) (4) months is supported by stability data with stored (b) (4) and stored in the proposed container closure.

The drug product is manufactured from conventional excipients using conventional manufacturing unit operations. The drug substance is (b) (4) (b) (4) (b) (4)

Capmatinib tablets, 150 mg and 200 mg are dose proportional and are (b) (4) (b) (4) The biopharmaceutics review team determined the dissolution method is acceptable as a QC method for the 150 mg and 200 mg tablets and that the acceptance criterial of "NLT (b) (4)% in 20 minutes" is able to reject (b) (4) in the manufacturing process. No scale up is proposed. (b) (4) The commercial batch size is same as registration batches.

The applicant proposes to implement (b) (4) (b) (4) (b) (4)

Both impurities (b) (4) to support a 6-week in-use period. The nonclinical

review team has verified that these impurities are controlled within qualified limits for their stability specifications.

The drug substance and drug product manufacturing facilities are approvable based on acceptable compliance history, District file review and Final ORA recommendation. Novartis Pharma Produktions GmbH is responsible for manufacture of the drug product, analytical testing of the drug product and excipients. Novartis Ringaskiddy Pharma Ltd. is listed as the drug substance manufacturer and tester for the subject application. (b) (4) is listed as primary packaging site for the DP and packaging component tester. No PAIs were recommended/performed for these facilities. Four drug substance and product testing facilities were also listed in the application which are approvable based on profile.

C. Special Product Quality Labeling Recommendations (NDA only)

(b) (4)

The action letter should include the following language:

"FDA acknowledges the comparability protocol for the re-validation procedures and the proposed reporting category of the changes likely to occur during the lifecycle of this product. The comparability protocol is approved."

D. Final Risk Assessment (see Attachment)

The final risk assessment remains unchanged from the initial risk assessment. The inherent chemical stability of the drug substance, tight specifications for assay, and adequate in vitro release method address primary failure modes. The desiccant in the container closure and printed in-use period on the product label address (b) (4) (b) (4). Beyond the 24 month shelf life and 6 week in-use period, (b) (4) is observed, so shelf life extension and in-use period extension should consider the early developmental data that identified the (b) (4)

(b) (4). **There were no new product quality concerns identified for the drug substance, drug product, manufacturing process, or in vitro release.**

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	(b) (4)	3	2	Release (1)	6
					Stability (3)	18
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		2	3	4	24
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		2	3	4	24
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		1	2	Release with spec (3)	6
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site		4	2	3	24

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Tabrecta (Capmatinib) tablets
Dosage form, route of administration	For oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 150 mg and 200 mg
Maximum Daily Dose	400 mg PO

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Tabrecta should be swallowed whole and should not be broken, chewed, or crushed.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Film-coated tablets: 150 mg and 200 mg capmatinib
Strengths: in metric system	150 mg and 200 mg
Active moiety expression of strength with equivalence statement (if applicable)	Salt equivalence statement noted on the product label and section 11; not required here.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	150 mg: pale orange brown, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side 200 mg: yellow, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Tabrecta (capmatinib)
Dosage form and route of administration	Tablet for oral use
Active moiety expression of strength with equivalence statement (if applicable)	Salt equivalence statement provided for both dosage strengths
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA; qualitative composition provided only.
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Receptor tyrosine kinase inhibitor
Chemical name, structural formula, molecular weight	Adequate; provided
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Capmatinib is a yellow powder with a pKa_1 of 0.9 (calculated) and pKa_2 of 4.5 (experimentally). Capmatinib hydrochloride is slightly soluble in acidic aqueous solutions at pH 1 and 2 and further decreasing solubility towards neutral condition. The log of the distribution coefficient (n-octanol/acetate buffer pH 4.0) is 1.2

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	150 mg and 200 mg film-coated tablets
Available units (e.g., bottles of 100 tablets)	Bottles of 56 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Same descriptions as in section 3
Special handling (e.g., protect from light)	Dispense in the original package with the desiccant cartridge; Protect from moisture; Discard any unused TABRECTA remaining after 6 weeks of first opening the bottle
Storage conditions	Store at 20^{O}C to 25^{O}C (68^{O}F to 77^{O}F), excursions permitted between 15^{O}C and 30^{O}C (59^{O}F and 86^{O}F) *[see USP Controlled Room Temperature]*
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

Reviewer's Assessment of Package Insert: Adequate

II. Labels:

1. *Container and Carton Labels*

(b) (4)

2. *Carton Label*

None

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tabrecta® (capmatinib); prominence is adequate
Dosage strength	150 mg and 200 mg
Net contents	56 film-coated tablets
"Rx only" displayed prominently on the main panel	Present
NDC number (21 CFR 207.35(b)(3)(i))	Space reserved for NDC number
Lot number and expiration date (21 CFR 201.17)	Space indicated on label
Storage conditions	USP Room Temperature language used; Special instruction to protect from moisture, maintain desiccant, and discard after 6 weeks; Statement to keep out of reach of children;
Bar code (21CFR 201.25)	Present
Name of manufacturer/distributor	Present
And others, if space is available	Product of Ireland claim present; physician sample labels are available that contain commensurate information. Salt equivalence statement provided; (b) (4)

Reviewer's Assessment of Labels: Adequate

List of Deficiencies: **None**

Overall Assessment and Recommendation: **Adequate with the recommended changes communicated through the clinical RPM. The applicant was instructed to move the salt equivalence statement to the side panel. Revised labels are forthcoming.**

Primary Labeling Reviewer Name and Date: **Olen Stephens, 4/13/2020**

Secondary Reviewer Name and Date: **Anamitro Banerjee, 4/13/20**

Appears this way on original

Olen Stephens

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Anamitro Banerjee

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BIOPHARMACEUTICS

Application No: NDA 213591; TABRECTA® **(**capmatinib) film-coated tablets, 150 mg and 200 mg
Route of Administration: Oral
Applicant Name: Novartis Pharmaceuticals Corporation
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

Background:

The Applicant is seeking approval for NDA 213591 Tabrecta® (capmatinib/INC280) film-coated tablets, 150 mg and 200 mg for the treatment of advanced non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation *via* the 505 (b)(1) regulatory pathway. The recommended daily dose for the proposed tablet drug product is 200 mg to 400 mg orally twice a day.

Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg are immediate-release, film-coated tablets that received a Breakthrough Therapy Designation on 04/18/2019 for the treatment of patients with metastatic non-small cell lung cancer with a MET exon 14 skipping mutation with disease progression on or following platinum-based chemotherapy. This NDA also received a Breakthrough Therapy Designation on 07/30/2019 for first-line treatment of patients with metastatic non-small cell lung cancer with a MET exon 14 skipping mutation. Additionally, an Orphan Drug Designation was granted to Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg on 03/15/2019 for treatment of patients with metastatic non-small cell lung cancer with a MET genomic tumor aberration.

Phase II safety and efficacy study, CINC280A2201 (GEOMETRY mono-1 study A2201) is the basis for approval for this application in which 400 mg dose (administered as 4× 100 mg or 2× 200 mg strength) capmatinib tablets were administered twice daily.

REVIEW SUMMARY:

The objective of this Biopharmaceutics Review is to evaluate the overall dissolution profile data to support **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, and **3)** the need for bridging drug product manufacturing sites, and film-coating color for the 150 mg commercial drug product.

- ***Proposed Dissolution Method:***

The Applicant provided dissolution profile data in support of the following quality control (QC) dissolution method for dissolution testing of the proposed drug product:

Parameters	Dissolution Method **ACCEPTABLE**
Apparatus/Speed	USP Apparatus 1 (basket)/75 rpm
Media/Volume	0.01M HCl, pH 2.0/900 mL
Bath temperature	37.0±0.5 C

Based on the aforementioned dissolution data, the proposed dissolution method is deemed **ACCEPTABLE** as a QC method for the 150 mg and 200 mg strengths of the proposed drug product.

- ***Dissolution Acceptance Criterion***:

The Applicant proposed '*NLT* (b) (4)*% (Q) in 20 minutes'* as the dissolution acceptance criterion for batch release and stability testing of Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg drug product. The proposed acceptance criterion is acceptable as the dissolution method and the proposed acceptance criterion is able to reject (b) (4) 150 mg and 200 mg drug product batches.

- ***Bridging Clinical Development and Final Market Image Batches:***

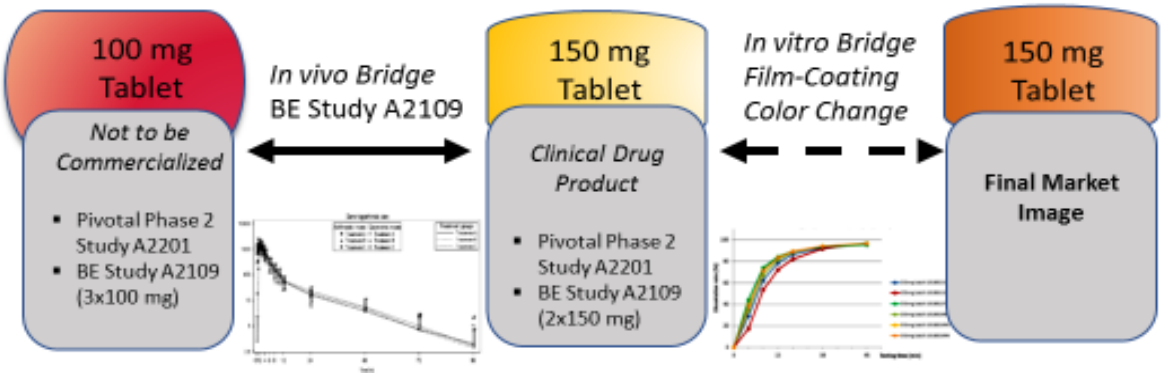
a) Bridging Batches of Different Strengths:

During the pivotal Phase II safety and efficacy study A2201, 150 mg film-coated tablets were introduced, in addition to the 100 mg and 200 mg strengths. It should be noted that the 100 mg drug product will not be commercialized. A bioequivalence (BE) study A2109 was conducted with a single 300 mg (as 3×100 mg and 2×150 mg) dose of the drug product in healthy subjects to provide a bridge between the 100 mg and 150 mg tablet drug products.

b) Bridging of Batches with Film-Coating Color Change

The Final Market Image (FMI) for the 150 mg tablet drug product is pale orange brown color.

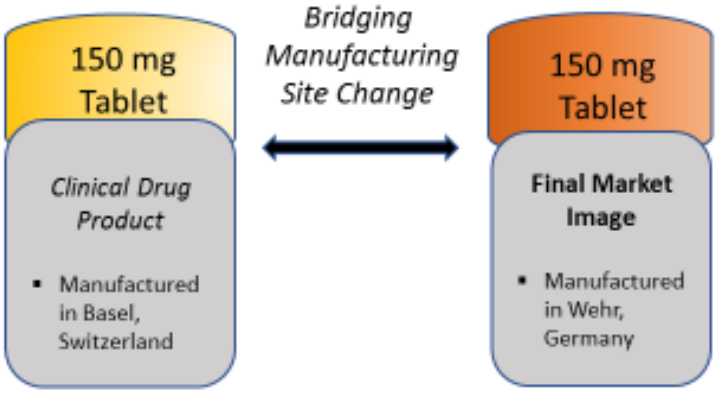
The film-coating color for the 150 mg tablet drug product was changed from light-yellow to pale orange brown color. The light-yellow 150 mg tablet drug product was dosed in the Phase 2 clinical study A2201. Dissolution profile data for the light-yellow 150 mg tablet drug product batches dosed in the pivotal clinical study A2201 and the pale orange brown color FMI of the 150 mg drug product are similar and provide a 'bridge' between the two different film-coating colors of the150 mg drug product.



c) Bridging of Batches due to Manufacturing Site Change for the Drug Product:

The Applicant identified Novartis Pharma Produktions GmbH, Wehr, Germany as the commercial manufacturing site for the 150 mg and 200 mg tablet drug product.

Initally drug products (100 mg, 150 mg and 200 mg) used in the clinical study A2201, were manufactured at pilot scale at the clinical manufacturing unit, **Novartis Pharma AG, Basel, Switzerland**. Later, the Applicant manufactured these strengths at the commercial manufacturing site at **Novartis Pharma Produktions GmbH, Wehr, Germany** and used these batches in the Phase 2 clinical study A2201. The dissolution profile data for the 100 mg, 150 mg, 200 mg drug product batches manufactured at the two manufacturing sites are > (b) (4)% in 20 minutes and provide a 'bridge' between the two manufacturing sites.



- ***Biowaiver for 150 mg strength:***

The 150 mg and 200 mg tablet drug product are bridged based on the following data: (i) 150 mg tablet drug product is compositionally proportional to the 200 mg drug product with respect to capmatinib, the active pharmaceutical ingredient (API) and excipients, (ii) pharmacokinetic (PK) profile for 200 mg strenght is obtained from the Study X2103, (iii) 150 mg strength drug product demonstrate similar mean dissolution profile data to the 200 mg drug product at batch release (with > (b) (4)% release of capmatinib in 20 minutes), using the acceptable dissolution method.

It should be noted BE Study A2109 characterized PK profile of 150 mg strength. In this review, biowaiver for 150 mg strength is evaluated because the PK profiles for 150 mg and 200 mg strenghts were obtained from two separate PK studies, A2109 and X2103, respectively.

- ***Biopharmaceutics Risk Assessment:***

The proposed QC dissolution method [*USP Apparatus 1 at 75 rpm basket speed with 900 mL 0.01M HCl, pH 2.0 at 37.0° C*] and the dissolution acceptance criterion of '*NLT* (b) (4)*% (Q) in 20 minutes'* together is able to reject abberant 150 mg and 200 mg drug product batches with respect to the particle size distribution of the drug substance, (b) (4) (b) (4) (b) (4)

OVERALL REVIEW RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 213591 for Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS REVIEWED:

Submissions Reviewed	Reference ID
IND 124033 Type C Preliminary Meeting Minutes	Dated 01/29/2017, DAARTS (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80422de5)
IND 124033 Type C Teleconference Meeting Minutes	Dated 02/03/2017, DAARTS (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804245c4)
IND 124033 Type C Teleconference Preliminary Meeting Minutes	Dated 09/14/2018, DAARTS (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b58b1)
IND 124033 Type C Teleconference Meeting Minutes	Dated 09/24/2018, DAARTS (https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b84a1)
Original NDA 213591 Submission	Dated 12/10/2019, SDN 2 (\\cdsesub1\evsprod\nda213591\0000\m2\27-clin-sum\summary-biopharm-nsclc.pdf)

➢ *DRUG SUBSTANCE*

The active ingredient in the proposed drug product is capmatinib dihydrochloride monohydrate (molecular weight of the dihydrochloride salt form=503.37 grams/mole; free base=412.43 grams/mole), an yellow crystalline (needle-shaped), slightly (b) (4) (b) (4) achiral drug substance. The drug substance exhibits several polymorphic forms. The crystalline form, (b) (4) is the (b) (4) form obtained during drug substance manufacture. Other forms include (b) (4)

- ***Solubility:***

The equilibrium solubility of capmatinib dihydrochloride monohydrate was conducted in buffer solutions across the physiological pH range 1.0-7.50 at 25 C and 37 C following stirring for 24 hours and is provided in **Table 1**.

Table 1. Equilibrium solubility of capmatinib dihydrochloride monohydrate at 25 C and 37 C following stirring for 24 hours

Solvent	Temperature (°C)	Solubility (mg/mL) [a]
pH 1.0 (HCl 0.1N)	25	12.0 [b]
pH 2.0 (HCl 0.01N)	25	10.3 [b]
Methanol	25	47.5
Ethanol absolute	25	3.7
n-Octanol	25	0.03
Acetonitrile/water/85% phosphoric acid (50/50/0.1)	25	> 101.1
Water	37	1.464
pH 1.0 (HCl 0.1N)	37	4.176
pH 2.0 citrate buffer	37	4.227
pH 3.0 citrate buffer	37	0.234
pH 4.0 acetate buffer	37	< LOQ *
pH 6.8 phosphate buffer	37	< LOQ *
pH 7.5 phosphate buffer	37	< LOQ *

[a] Equilibrium solubility determined after 24 hours stirring. Solubility is measured for the dihydrochloride monohydrate form (b) (4)

* Limit of quantification (13.6 µg/mL)

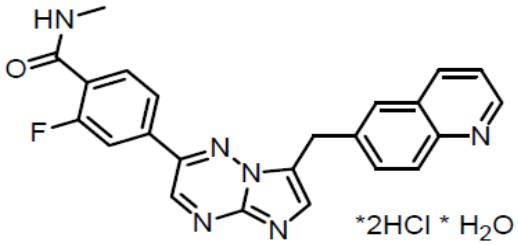
Reviewer's Assessment of Drug Substance Solubility:

The free base exhibits pH-dependent high solubility (4.176 mg/mL) in 0.1N HCl, pH 1.0 and very low solubility (<13.6 µg/mL) in acetate buffer, pH 4.0 and phosphate buffer, pH 6.8-7.5 following stirring for 24 hours at 37 C (see **Table 1**). However, following equilibration of the drug substance for 24 hours at 25 C, capmatinib exhibits comparatively high solubility (12.00 mg/mL and 10.3 mg/mL in 0.1N HCl and 0.01N HCl, respectively) with partial or complete dissociation of the dihydrochloride salt. The Applicant noted that partial dissociation of the salt leads to (b) (4) in aqueous buffer solutions at pH≤3.0.

- ***Permeability/Absorption:***

Capmatinib dihydrochloride monohydrate (see **Figure 1**) drug substance exhibits two (2) pKa's: pKa_1=0.9 (theoretically calculated) and pKa_2=4.5, which was experimentally determined. The LogD of capmatinib dihydrochloride monohydrate was experimentally determined to be 1.2 at pH 4.0.

Figure 1. Chemical structure of capmatinib dihydrochloride monohydrate



The apparent permeability (P_{app}) of capmatinib dihydrochloride monohydrate was demonstrated to be 25×10^{-6} cm/sec in human intestinal epithelial monolayers (Caco-2 cells) and found to be greater than the high permeability positive control, metoprolol ($P_{app}=14\times10^{-6}$ cm/sec). The efflux ratio (B-A/A-B ratio) was determined to 2.63, suggesting capmatinib to be likely a P-glycoprotein substrate.

The oral absorption of capmatinib tablets is higher (>70%) with median time to reach maximum concentration (T_{max}) of approximately 1-2 hours. Capmatinib was found to be extensively (>96%) bound to plasma proteins and distributed in the body with a high apparent volume of distribution, $V_z/F=525$ L. It is eliminated from the body with a terminal median half-life ($t_{1/2}$) of 8.23 hours and a median clearance, CL/F=40.3 L/hour.

Reviewer's Assessment of BCS classification:

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

- ***Particle Size Distribution (PSD) of the Drug Substance:***

As the drug substance is needle-shaped, crystalline material that exhibits pH-dependent low solubility profile in buffer solutions, pH 1.0-7.5, (b) (4) (b) (4) (b) (4) The effect of drug substance PSD on the dissolution of the drug product will be discussed under '*Discriminating Ability of the Proposed Dissolution Method'*.

- ***DRUG PRODUCT:***

The to-be-marketed (TBM) drug product is an immediate-release, film-coated, 150 mg (pale orange brown) and 200 mg (yellow) ovaloid, curved, unscored, debossed capmatinib tablet drug product. The composition of the 150 mg and 200 mg drug product is provided in **Table 2**. The 150 mg and 200 mg drug product are manufactured from a (b) (4) (b) (4) and are dose proportional. Initially, the 50 mg capsule drug product and 50 mg, 100 mg, and 200 mg tablet drug product were manufactured and dosed in clinical studies. The 150 mg tablet drug product was introduced later during the clinical development. The 100 mg drug product was used for process scale-up and for establishing bioequivalence (BE) with the 150 mg drug product; however, the 100 mg drug product will not be commercialized.

Capmatinib is needle-shaped, crystalline drug substance that exhibits pH-dependent low solubility profile in buffer solutions, pH 1.0-7.5. Additionally, the drug substance (b) (4) (b) (4)

Table 2. Composition of Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg

Ingredient	Amount per unit dose of tablet [mg]		Function
	150 mg	200 mg	
Tablet Core			
Capmatinib hydrochloride (b) (4)	176.550	235.400	Active substance
Microcrystalline cellulose [2]			(b) (4)
Mannitol			
Crospovidone (b) (4)			
Povidone (b) (4)			
Magnesium stearate[3]			
Colloidal silicon dioxide			
Sodium lauryl sulfate			
(b) (4)			
Total core tablet weight			
Film- coating			
(b) (4)			(b) (4)
	-	-	(b) (4)
Total film-coating weight		(b) (4)	
Total film-coated tablet weight	**770.000**	**1026.000**	

(b) (4)

[redacted]

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

The manufacturing sites used in the manufacture of the laboratory scale, pilot scale, various clinical studies, and the commercial to-be-marketed (TBM) Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg is provided in **Table 3**.

Table 3. Commercial manufacturing sites for Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg

Batch type(s)	Manufacturing site(s)	Testing site(s)
Laboratory scale development:	Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland	Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India
Pilot scale development:	Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany	Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland
Phase IIa/IIb clinical supplies:	Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany	Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India

Batch type(s)	Manufacturing site(s)	Testing site(s)
		Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland
Bioavailability (BA) / Bioequivalence (BE):	Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland	Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland

Batch type(s)	Manufacturing site(s)	Testing site(s)
Manufacturing process verification at full scale (Also termed as 'Pre-validation'):	Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany	Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein, Switzerland
Process Performance Qualification (Also termed as 'Process validation'):	Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany	Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein, Switzerland
Primary stability (Also termed as 'Registration stability'):	Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland Novartis Pharma Produktions GmbH Oeflinger Str. 44 79664 Wehr, Germany	Novartis Healthcare Pvt. Ltd. Plot no. 4, Survey no's 101 and 101/2 Lalgadi Malakpet Shameerpet Hyderabad-500101 India Novartis Pharma AG Lichtstrasse 35 4056 Basel Switzerland

It should be noted that two batches each of the 100 mg and 200 mg and one batch of the 150 mg drug product was manufactured at pilot scale at the clinical manufacturing unit, Novartis Pharma AG, Basel, Switzerland (see **Table 3**). Other clinical batches were manufactured at the commercial manufacturing site at Novartis Pharma Produktions GmbH, Wehr, Germany (see **Table 3**). The Applicant provided dissolution profile data and conducted in vivo bioavailability/bioequivalence (BA/BE) studies to 'bridge' the two manufacturing sites that will discussed under "*Bridging of Formulations, Manufacturing Sites, and Film-Coating Color of the 150 mg Drug Product"*.

- ***DISSOLUTION INFORMATION:***

Dissolution testing was utilized as a [redacted] and bridge (i) the 150 mg and 200 mg tablet drug product, (ii) film-coating color of the 150 mg drug product, and (iii) the manufacturing sites for the 150 mg and 200 mg commercial drug product.

- ***DISSOLUTION METHOD:***

The dissolution method proposed for quality control of the proposed drug product is provided in **Table 4**.

Table 4. Proposed dissolution method for quality control (QC) of Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg

Parameters	Method
Apparatus/Speed	USP Apparatus 1 (basket)/75 rpm
Media/Volume	0.01M HCl, pH 2.0/900 mL
Bath temperature	37.0±0.5 C

The dissolution method development was performed with the 50 mg, 100 mg, 150 mg, and 200 mg drug product batches.

Selection of Dissolution Medium and Volume:

[redacted]

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(b) (4)

Discriminating Ability of the Proposed Dissolution Method:

Capmatinib is needle-shaped, crystalline drug substance that exhibits pH-dependent low solubility profile in buffer solutions, pH 1.0-7.5. (b) (4)

(b) (4)

(b) (4)

The Applicant identified the following CMA and CPP (see **Table 6**) and provided dissolution profile data to support the discriminating ability of the proposed dissolution method:

Table 6. Critical Quality Attributes (CQA) evaluated to support the discriminating ability of the proposed dissolution method

Critical Process Parameters
(b) (4)

(b) (4)

The Applicant noted that drug substance with larger PSD (D_{90}) demonstrated a (b) (4)

The following PSD of the drug substance were evaluated during product development and for manufacturing the clinical and registration batches (see **Table 7**).

Table 7. Details of the particle size distribution (PSD) of various 100 mg, 150 mg, and 200 mg drug product batches

Tablet strength [mg]	Drug product batch nos.	Drug substance particle size		
		X_{10} [µm]	X_{50} [µm]	X_{90} [µm]
	Laboratory phase batches			
100	ORA-0025-001	(b) (4)		
100	ORA-0025-002			
100	ORA-0042-001			
100	ORA-0025-003			
	Pilot phase batches			
100	X220IM (BE study)			
200	X221IM			
150	1010011115 (BE study)			
150	1010012759 (BE study)			
150	1010011511			
150	1010011512			

Two different 150 mg drug product batches were manufactured with different particle size distribution under identical (b) (4) process: Batch **1010011115** [with D_{10} (b) (4) µm, D_{50}= (b) (4) µm, D_{90} (b) (4) µm of the drug substance] and Batch **1010012759** [with D10= (b) (4) µm, D50 (b) (4) µm, D90= (b) (4) µm of the drug substance].

Batch **1010011115** with larger particle size exhibited slower dissolution as compared to Batch **1010012759** (see **Figure 5).** The similarity factor '*f2*' between the dissolution profile data of the 150 mg drug product batch 1010011115 and the 150 mg drug product batch 1010012759 using the Automation Tool is 37.05 (<50), suggesting that the dissolution profiles are dissimilar. These two batches were also used in the BE Study A2109 and were compared to 100 mg drug product batch X220IM.

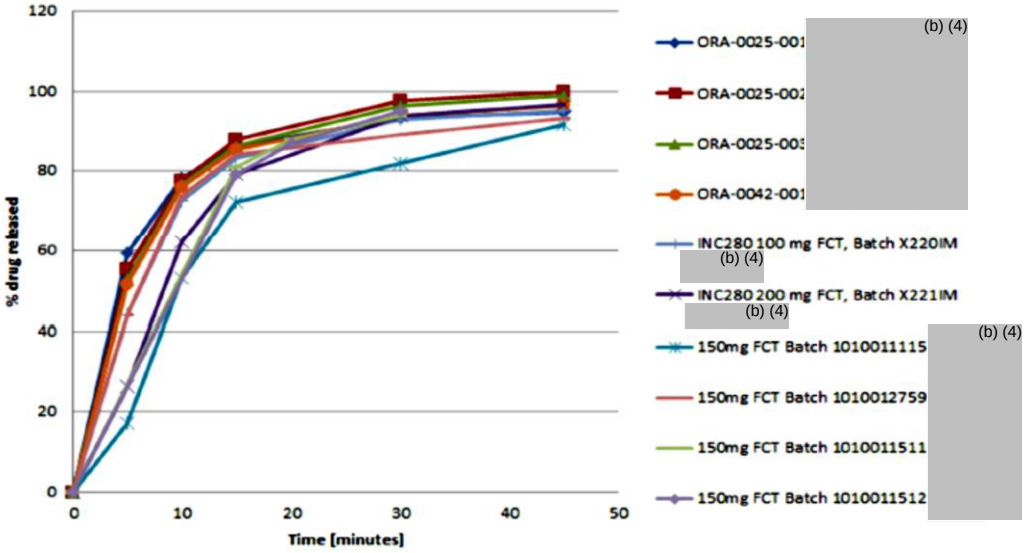
In the BE study, it was concluded that Batch **1010011115** was not BE to the 100 mg strength whereas Batch **1010012759** was BE to the 100 mg strength as shown in Appendix 1. In this review, the data in Appendix 1 is represented in a way to show comparision of geometric mean of Cmax (ng/mL) and AUCinf (ng*hr/mL) of these two batches. The larger particle size batch (1010011115) shows slower dissolution and lower Cmax as compared to the smaller particle size batch with faster dissolution and higher Cmax (see **Table 8**). Although this should not be construed as an in vitro in vivo correlation, but it appears that there may be a rank order relationship between the batches with slower dissolution and lower Cmax.

The Applicant attributed the slower dissolution of batch 1010011115 [with higher D_{90}] to (b) (4) due to the tendency of (b) (4) . However, this trend was not seen for the batches, 1010011511 and 1010011512 with higher D_{90}= (b) (4) μm; these batches exhibited faster dissolution (see **Figure 5**).

Table 8. Comparative geometric mean pharmacokinetic data for two 150 mg tablet drug product batches: Batch 1010011115 and Batch 1010012759 manufactured with different particle size distribution under identical (b) (4) process

150 mg		
	Batch 1010011115	**Batch 1010012759**
	d90: (b) (4) µm	d:90 (b) (4) µm
Cmax (ng/mL)	1480	1870
AUC inf (ng.hr/mL)	5900	6650

Figure 5. Effect of drug substance PSD on the dissolution of various 100 mg, 150 mg, and 200 mg drug product batches



Based on the overall dissolution data generated using product development, clinical, and registration batches to evaluate the effect of PSD of the drug substance on the dissolution of the 100 mg, 150 mg, and 200 mg drug product batches, the Applicant proposed a two-tier PSD for the drug substance: $D_{90} \leq$ (b) (4) μm, $D_{50} \geq$ (b) (4) μm.

It should be noted that the Applicant first manufactured a capsule formulation that exhibited lower exposure in the relative bioavailability (BA) Study X2103 (**Table 9**) and slow dissolution (see **Figure 6**). Based on these findings, it can be conclude that the proposed dissolution method is able to discriminate batches with lower exposure. Based on these findings, this capsule formulation was replaced with the proposed film-coated tablet formulation.

Figure 6. Comparative mean dissolution profile data for the N=12 units of the 50 mg, capsule and 50 mg, 100 mg, 150 mg, 200 mg tablet drug product batches to 'bridge' the two drug products using the proposed dissolution method

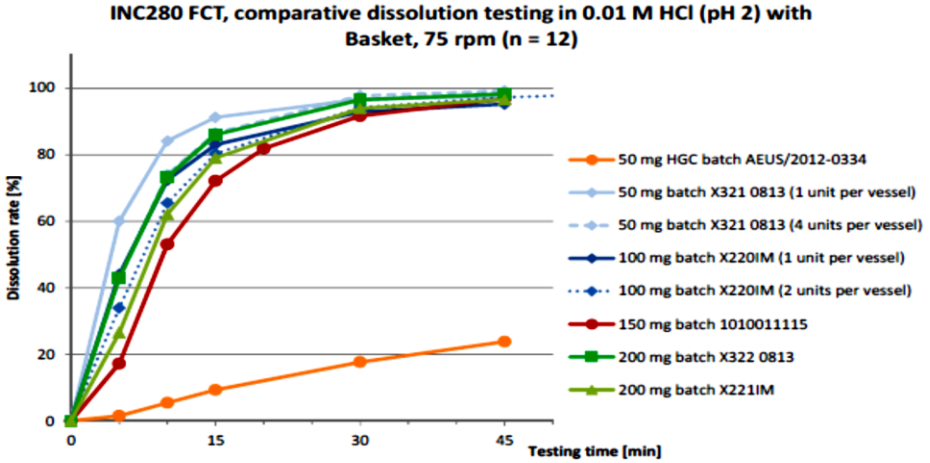


Table 9. Geometric mean ratios for pharmacokinetic parameters for capmatinib when dosed 3×200 mg tablet drug product X332 0813 (Treatment B) and 12×50 mg capsule drug product, AEUS/2012-0334 (Treatment A) in the relative bioavailability (BA) Study X2103

PK Parameter [unit]	Treatment	Adjusted Geo-mean	Geo-mean Ratio
C_{max} [ng/mL]	A	1680	3.01
	B	5040	
AUC_{last} [ng·hr/mL]	A	6600	2.37
	B	15600	
AUC_{inf} [ng·hr/mL]	A	6330	2.49
	B	15800	

Treatment A = 12 x 50 mg capmatinib hard gelatin capsules under fasted conditions;
Treatment B = 3 × 200 mg capmatinib film-coated tablets under fasted conditions.

Source: Section 2.1.1 of [Summary of Biopharmaceutic Studies and Associated Analytical Methods] for Study 2103 – Table 2-2

- ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed "*Q=* (b) (4) *% in 20 minutes"* as the dissolution acceptance criterion for batch release and stability testing of Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg drug product, which is acceptable.

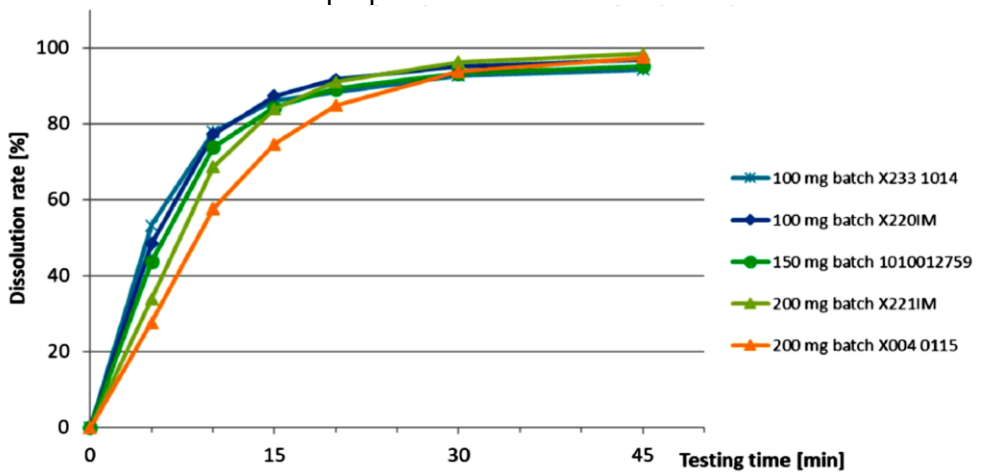
Dissolution Data at Batch Release:

The mean dissolution profile data for the 100 mg, 150 mg, and 200 mg drug product batches (see **Table 10**) dosed in the pivotal safety and efficacy study A2201 and in the bioequivalence study A2109 at batch release using the proposed dissolution method is provided in **Figure 7**.

Table 10. 100 mg, 150 mg, and 200 mg drug product batches used in the pivotal clinical study A2201 and BE study A2109

Batch #	**X220IM**	**1010012759**	**1010015993**	**X221IM**
Strength	100 mg	150 mg (light yellow)	150 mg (pale orange brown)	200 mg
Date of manufacture	Oct-2015	Jan-2017	Aug-2017	Oct-2015
Place of manufacture	Novartis Pharma Produktions GmbH, Wehr, Germany			
Batch size	(b) (4)			
Type of batch	Production scale	Production scale	Production scale	Production scale
Batch #	**X220IM**	**1010012759**	**1010015993**	**X221IM**
Use of batch	Registration stability, Pivotal clinical and BE study	Registration stability, Pivotal clinical and BE study	Registration stability (color change to pale orange brown)	Registration stability, Pivotal clinical study
Batch record	[X220IM English]	[1010012759 English]	[1010015993 English]	[X221IM English]
	[X220IM German]	[1010012759 German]	[1010015993 German]	[X221IM German]

Figure 7. Mean dissolution profile data for the N=12 units of the clinical batches of 100 mg (X220IM), 150 mg (1010012759), and 200 mg drug product (X221IM and X004 0115) used in the pivotal clinical study A2201 and in the bioequiv alence study A2109 at batch release using the proposed dissolution method



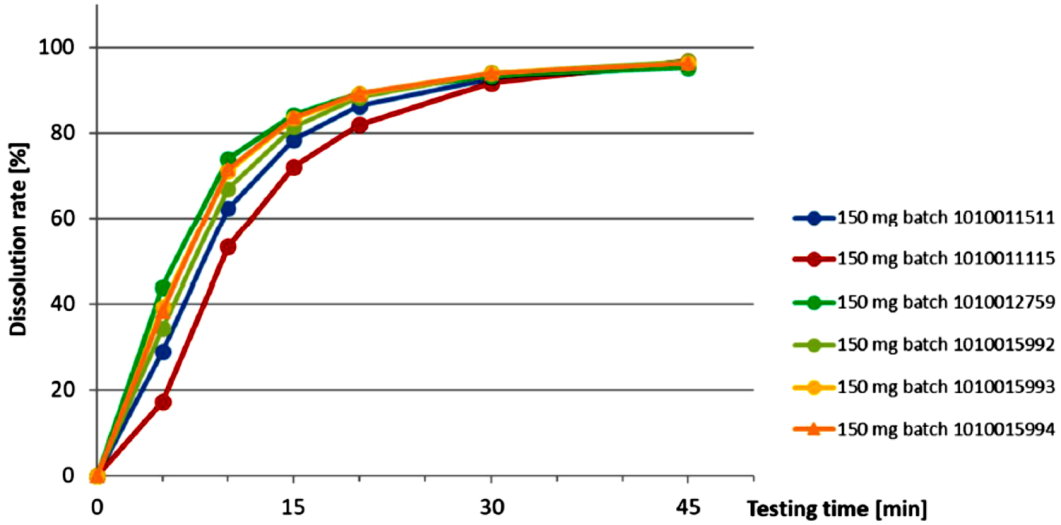
From the dissolution profile data provided in **Figure 7**, greater than 80% capmatinib is released in 20 minutes for all the registration/clinical batches.

Dissolution Data on Long-Term Stability Conditions:

The dissolution profile data for the 150 mg drug product on long-term stability is provided in **Figure 8a**. Although it shows 150 mg batch 1010011115 demonstrates slower dissolution as

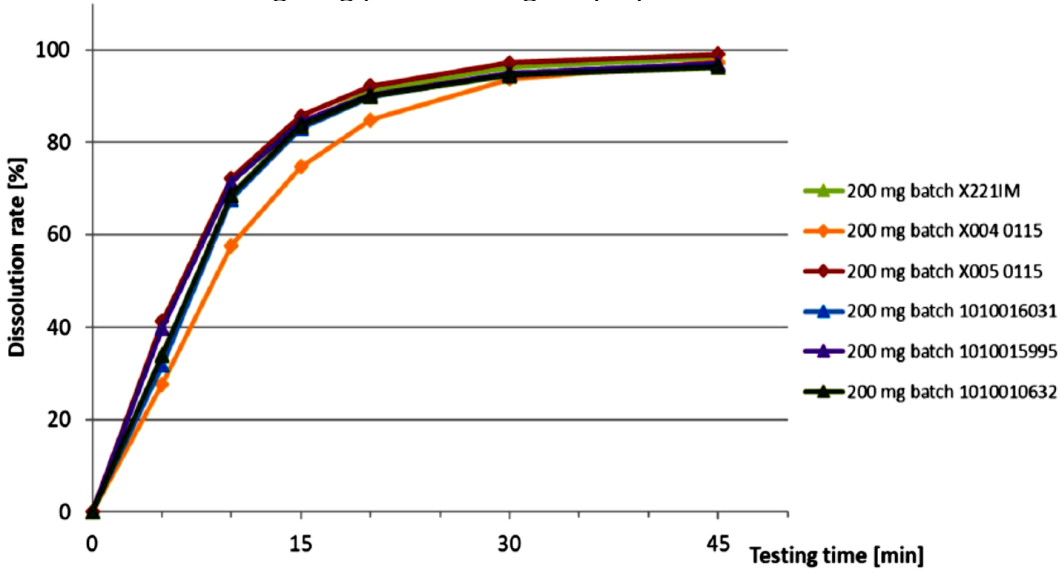
compared to other registration batches of the 150 mg drug product, this batch has been used in the clinical study and found BE to the 100 mg batch

Figure 8a. Mean dissolution profile data for the N=12 units of the clinical and registration batches of 150 mg drug product using the proposed dissolution method



The dissolution profile data for the 200 mg drug product on long-term stability is provided in **Figure 8b**. The 200 mg batch X005 0115 demonstrates slower dissolution as compared to other registration batches of the 200 mg drug product, however it still meets the proposed acceptance criterion.

Figure 8b. Mean dissolution profile data for the N=12 units of the clinical and registration batches of 200 mg drug product using the proposed dissolution method



***Reviewer's Assessment** of the Proposed Dissolution Acceptance Criterion*:
Based on the totality of the dissolution data at batch release and on stability, the proposed dissolution acceptance criterion "*Q=* (b) (4) *% in 20 minutes*" is acceptable for each strength of the drug product as the dissolution method demonstrates the ability to reject certain 150 mg and 200 mg drug product batches at this specification due to (b) (4).

Bridging of Clinical Development and Final Market Image Batches:

The details about the batches and manufacturing sites are shown in **Table 1** in Appendix 2.

***a) Bridging Batches of Different Strengths*:**
During the pivotal Phase II safety and efficacy study A2201, 150 mg film-coated tablet was introduced, in addition to the 100 mg and 200 mg strengths. It should be noted that the 100 mg drug product will not be commercialized. A bioequivalence (BE) study A2109 was conducted with a single 300 mg (as 3×100 mg and 2×150 mg) dose of the drug product in healthy subjects to provide a bridge between the 100 mg and 150 mg tablet drug product.

b) Bridging Batches with Film-Coating Color Change:
The Final Market Image (FMI) for the 150 mg tablet drug product is pale orange brown color.

The film-coating color for the 150 mg tablet drug product was changed from light-yellow to pale orange brown color. The light-yellow 150 mg tablet drug product was dosed in the Phase 2 clinical study A2201. Dissolution profile data for the light-yellow 150 mg tablet drug product batches dosed in the pivotal clinical study A2201 and the pale orange brown color FMI of the 150 mg drug product are similar and provide a 'bridge' between the two different film-coating colors of the150 mg drug product (see **Figure 9**).

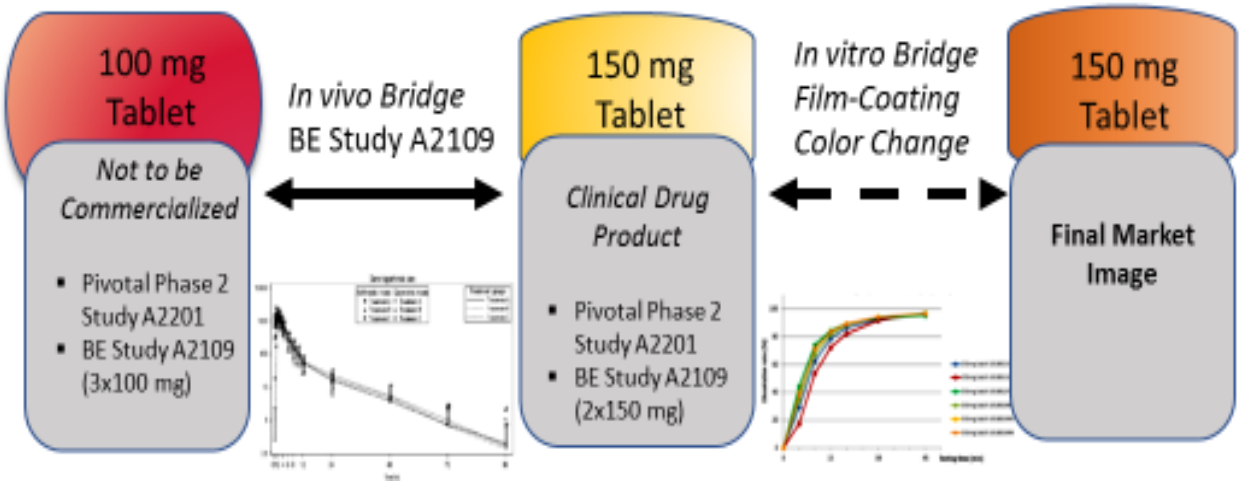
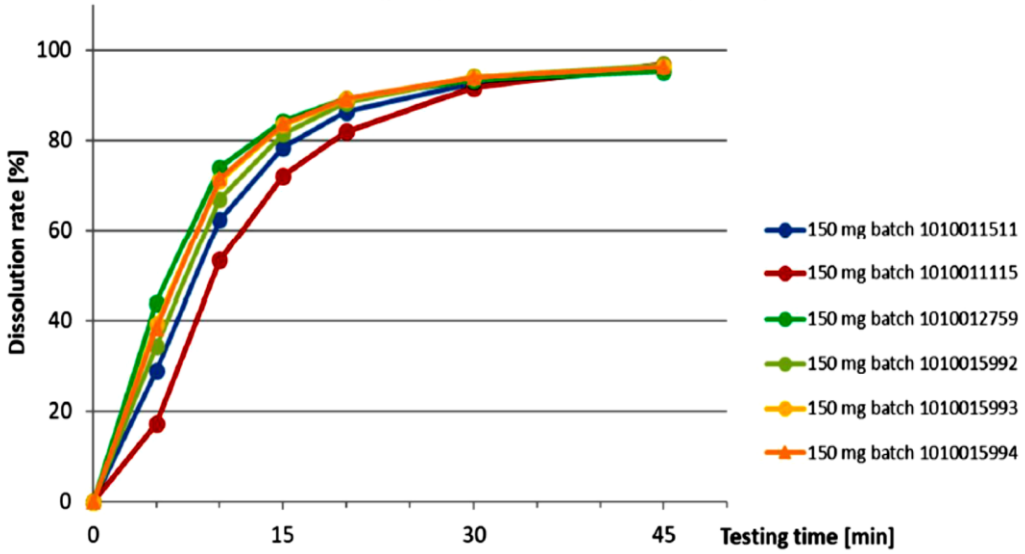


Figure 9. Comparative mean dissolution profile data for the N=12 units to 'bridge' the light-yellow colored 150 mg tablet drug product and the pale orange brown Final Market Image (FMI) of the 150 mg tablet drug product batches using the proposed dissolution method



***c) Bridging of Batches due to Manufacturing Site Change for the Drug Product*:**

The Applicant identified Novartis Pharma Produktions GmbH, Wehr, Germany as the commercial manufacturing site for the 150 mg and 200 mg tablet drug product.

Initally drug products (100 mg, 150 mg and 200 mg) used in the clinical study A2201, were manufactured at pilot scale at the clinical manufacturing unit, **Novartis Pharma AG, Basel, Switzerland**. Later, the Applicant manufactured these strengths at the commercial manufacturing site **at Novartis Pharma Produktions GmbH, Wehr, Germany** and used these batches in the Phase 2 clinical study A2201. The dissolution profile data for the 100 mg, 150 mg, 200 mg drug product batches administered in the Phase 2 clinical study A2201 and manufactured at the two manufacturing sites are > (b) (4)% in 20 minutes and provide a 'bridge' between the two manufacturing sites (see **Figure 10**).

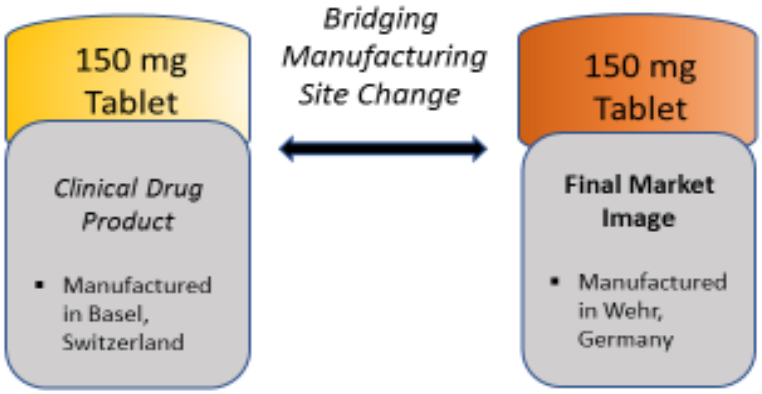
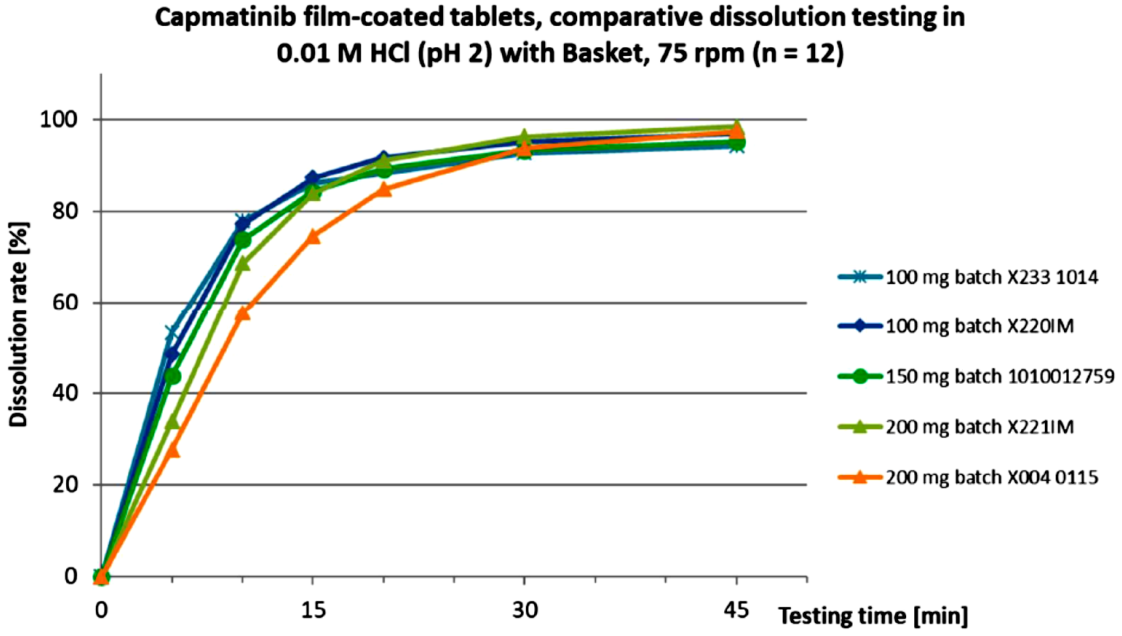


Figure 10. Comparative mean dissolution profile data for the N=12 units of the 100 mg, 150 mg, 200 mg drug product batches to 'bridge' the two manufacturing sites: the clinical manufacturing unit, Novartis Pharma AG, Basel, Switzerland and at the commercial manufacturing site at Novartis Pharma Produktions GmbH, Wehr, Germany using the proposed dissolution method

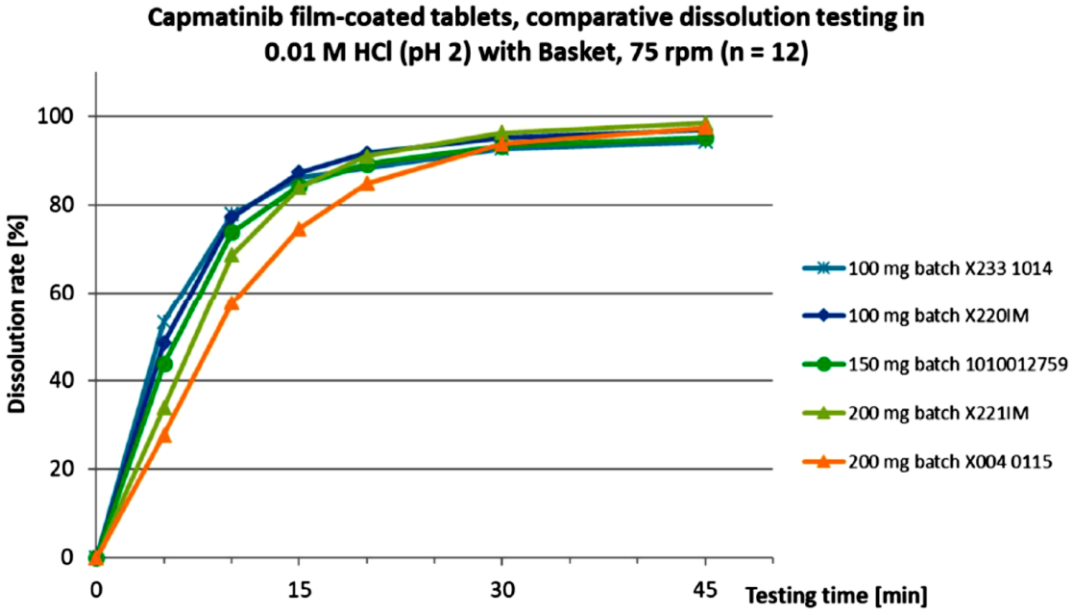


- ***Biowaiver for 150 mg strenght:***

The 150 mg and 200 mg tablet drug product are bridged based on the following: (i) 150 mg tablet drug product is compositionally proportional to the 200 mg drug product with respect to capmatinib, the active pharmaceutical ingredient (API) and excipients, (ii) PK profile for 200 mg strenght is obtained from the Study X2103, (iii) 150 mg strength drug product demonstrate similar mean dissolution profile data to the 200 mg drug product at batch release (with >85% release of capmatinib in 20 minutes), using the acceptable dissolution method (see **Figure 11**).

It should be noted BE Study A2109 characterized PK profile of 150 mg strength. In this review, biowaiver for 150 mg strength is evaluated because the PK profiles for 150 mg and 200 mg strenghts were obtained from two separate PK studies, A2109 and X2103, respectively.

Figure 11. Comparative mean dissolution profile data for the N=12 units of the 150 mg, 200 mg drug product batches dosed in the pivotal clinical trial A2201 to 'bridge' the 150 mg and 200 mg drug product using the proposed dissolution method



- ***POST-APPROVAL COMMITMENTS:*** **None**

- ***LIST OF DEFICIENCIES:*** **None**

- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 213591 for Tabrecta® (capmatinib) film-coated tablets, 150 mg and 200 mg is recommended for **APPROVAL.**

APPENDIX 1

Table 1a. Geometric mean ratios for pharmacokinetic parameters for capmatinib when dosed 150 mg drug product batch 1010011115 (Treatment C) and 100 mg drug product batch X220IM (Treatment A) in the BE Study A2109

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	N[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	A	76	1930	C:A	0.770	0.697	0.850
	C	76	1480				
AUClast (ng·hr/mL)	A	76	6710	C:A	0.870	0.815	0.929
	C	76	5840				
AUCinf (ng·hr/mL)	A	75	6790	C:A	0.869	0.815	0.927
	C	76	5900				
Tmax (hr)[2]	A	76	1.01	C-A	-0.00625	-2.02	5.08
	C	76	1.01				

Treatment A – Reference (batch number X220IM) - Single oral dose of capmatinib at 300 mg (3 x 100 mg) using 100 mg FMI tablet

Treatment C - Test 2 (batch number 1010011115) - Single oral dose of capmatinib at 300 mg (2x150 mg) using 150 mg FMI tablet full scale commercial batch

[1] N = number of observations used for analysis.

[2] For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Source: [Study A2109 –Table 14.2-1.2], [Study A2109- Table 9-2]

Table 1b. Geometric mean ratios for pharmacokinetic parameters for capmatinib when dosed 150 mg drug product batch 1010012759 (Treatment B) and 100 mg drug product batch X220IM (Treatment A) in the BE Study A2109

					Treatment Comparison		
						95% CI	
PK Parameter (unit)	Treatment	N[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	A	76	1920	B:A	0.971	0.887	1.06
	B	76	1870				
AUClast (ng·hr/mL)	A	76	6700	B:A	0.977	0.914	1.04
	B	76	6550				
AUCinf (ng·hr/mL)	A	75	6760	B:A	0.984	0.921	1.05
	B	73	6650				
Tmax (hr)[2]	A	76	1.01	B-A	-0.00625	-2.47	3.98
	B	76	1.01				

Treatment A - Reference (batch number X220IM) - Single oral dose of capmatinib at 300 mg (3 x 100 mg) using 100 mg FMI tablet

Treatment B - Test 1 (batch number 1010012759) - Single oral dose of capmatinib at 300 mg (2 x 150 mg) using 150 mg FMI tablet full scale commercial batch

[1] N = number of observations used for analysis.

[2] For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio'and minimum and maximum differences under 95% CI.

Source: [Study A2109 –Table14.2-2.1], [Study A2109- Table 9-2]

APPENDIX 2

Table 1. Product development, clinical and registration batches manufactured at the various manufacturing sites

Study number INC280	Formulation identifier	Dosage form and strength	Batch number	Batch size [units]	Site of manufacture	Date of manufacture	Drug substance batch number
CINC280X2103 (Relative bioavailability study)	(b) (4)	INC280 hard gelatin capsules, 50 mg	AEUS/2012-0334	(b) (4)	Novartis East Hanover	Feb-2013	(b) (4)
		INC280 film-coated tablets, 200 mg	X322 0813		Novartis Pharma AG, Basel	Aug-2013	
CINC280A2109 (BA/BE study)		INC280 film-coated tablets, 150 mg	1010011115		Novartis Pharma Produktions GmbH, Wehr	Jul-2016	
		INC280 film-coated tablets, 100 mg	X220IM		Novartis Pharma Produktions GmbH, Wehr	Oct-2015	
		INC280 film-coated tablets, 150 mg	1010012759		Novartis Pharma Produktions GmbH, Wehr	Jan-2017	

Study number INC280	Formulation identifier	Dosage form and strength	Batch number	Batch size [units]	Site of manufacture	Date of manufacture	Drug substance batch number
CINC280A2201 (Pivotal study)	(b) (4)	INC280 film-coated tablets, 200 mg	1010009729	(b) (4)	Novartis Pharma Produktions GmbH, Wehr	Apr-2016	(b) (4)
		INC280 film-coated tablets, 200 mg	1010011116		Novartis Pharma Produktions GmbH, Wehr	Jul-2016	
		INC280 film-coated tablets, 200 mg	1010012299		Novartis Pharma Produktions GmbH, Wehr	Dec-2016	
		INC280 film-coated tablets, 150 mg	1010012759		Novartis Pharma Produktions GmbH, Wehr	Jan-2017	
		INC280 film-coated tablets, 200 mg	X004 0115		Novartis Pharma AG, Basel	Feb-2015	
		INC280 film-coated tablets, 100 mg	X060 0315		Novartis Pharma AG, Basel	Mar-2015	
		INC280 film-coated tablets, 100 mg	X062 0315		Novartis Pharma AG, Basel	Mar-2015	
		INC280 film-coated tablets, 200 mg	X094 0415		Novartis Pharma AG, Basel	May-2015	
		INC280 film-coated tablets, 100 mg	X220IM		Novartis Pharma Produktions GmbH, Wehr	Oct-2015	

Study number INC280	Formulation identifier	Dosage form and strength	Batch number	Batch size [units]	Site of manufacture	Date of manufacture	Drug substance batch number
CINC280A2201 (Pivotal study)	(b) (4)	INC280 film-coated tablets, 200 mg	X221IM	(b) (4)	Novartis Pharma Produktions GmbH, Wehr	Oct-2015	(b) (4)
		INC280 film-coated tablets, 100 mg	X232 1014		Novartis Pharma AG, Basel	Oct-2014	
		INC280 film-coated tablets, 100 mg	X233 1014		Novartis Pharma AG, Basel	Oct-2014	
		INC280 film-coated tablets, 100 mg	X251 1114		Novartis Pharma AG, Basel	Nov-2014	
		INC280 film-coated tablets, 200 mg	1010013774		Novartis Pharma Produktions GmbH, Wehr	Apr-2017	
		INC280 film-coated tablets, 150 mg	1010015992		Novartis Pharma Produktions GmbH, Wehr	Aug-2017	

Novartis East Hanover	Novartis Pharmaceuticals Corporation, East Hanover
Novartis Pharma AG, Basel	Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland
Novartis Pharma Produktions GmbH, Wehr	Novartis Pharma Produktions GmbH, Oeflinger Str. 44, 79664 Wehr, Germany

Parnali Chatterjee

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Banu Zolnik

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/s/

OLEN M STEPHENS
04/13/2020 03:00:38 PM
OPQ Recommendation: approve Shelf life: 2 years with a 6 week in-use period after first opening. Comparability protocol can be approved.