CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211288Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211288

Review #1

Drug Name/Dosage Form	**Dacomitinib Tablets**
Strength	**15 mg, 30 mg, and 45 mg**
Route of Administration	**Oral**
Rx/OTC Dispensed	**Rx**
Applicant	**Pfizer**
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD 0001 (1)	*January 31, 2018*	*CMC*
SD 0006 (6)	*February 28, 2018*	*DP*
SD 0011 (12)	*March 20, 2018*	*Facility*
SD 0029 (30)	*May 15, 2018*	*CMC*
SD 0033 (33), 0034 (34)	*May 22, 2018*	*DP, EC (Established Conditions)*
SD 0042 (42)	*June 20, 2018*	*Labeling*
SD 0045 (45)	*June 27, 2017*	*EC*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	**Anamitro Banerjee**	**Charles Jewell**
Drug Product	**Rajiv Agarwal**	**Anamitro Banerjee**
Process	**Zhaoyang Meng**	**Rahki Shah**
Microbiology		
Facility	**Zhaoyang Meng**	**Zhihao Peter Qiu**
Biopharmaceutics	**Yang Zhao**	**Banu Zolnik**
Regulatory Business Process Manager	**Steven Kinsley**	
Application Technical Lead	**Thomas Oliver**	
Laboratory (OTR)		
ORA Lead	**Caryn McNab**	
Environmental	**Ron Bloom(EA)**	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		Acceptable		These DMFs are currently referred to in several approved NDA and ANDA for same dosage form.
	Type III			Acceptable		
	Type III			Acceptable		
	Type III			Acceptable		
	Type III			Acceptable		
	Type III			Acceptable		
	Type III			Acceptable		
	Type III			Acceptable		(b) (4)
	Type III			Acceptable		These DMFs were not used.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	72775	Initial IND for PF-00299804
(b) (4)		

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the Quality point of view.

II. Summary of Quality Assessments

A. Product Overview

NDA 211288 was submitted under section 505(b)(1) in support of the use of dacomitinib (Vizimpro™) for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test. The FDA granted priority review for the application. In addition, dacomitinib received an Orphan Drug Designation for treatment of non-small cell lung cancer with epidermal growth factor receptor activating mutations.

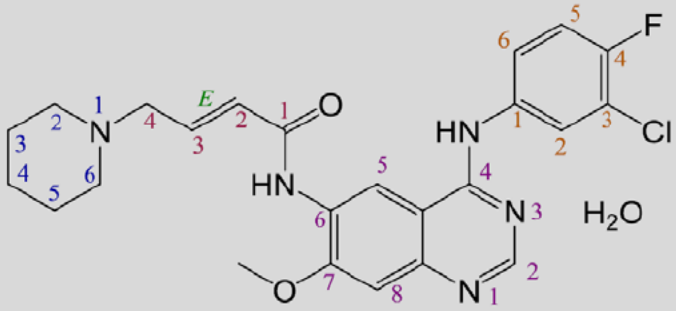
Vizimpro (dacomitinib) Tablets (15, 30 and 45 mg) are manufactured utilizing an immediate release formulation designed for oral administration. The commercial blue film-coated tablets are de-bossed with 'Pfizer' on one side. The 15 mg, 30 mg and 45 mg strengths are differentiated by tablet size (6.35 mm, 7.5 mm, 9.0 mm), and de-bossing of 'DCB 15', 'DCB 30' and 'DCB 45', on the other side. Tablets are packaged in high-density polyethylene (HDPE) bottles, containing 1g desiccant, along with a (b) (4) closure that includes a heat induction seal liner.

Proposed Indication(s) including Intended Patient Population	Vizimpro (dacomitinib) Tablets is indicated for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test
Duration of Treatment	The recommended dose of Dacomitinib Tablets is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. Dose reduction to 30 mg and then 15 mg for adverse events
Maximum Daily Dose	*N/A*
Alternative Methods of Administration	*N/A*

B. Quality Assessment Overview

Drug Substance:

Dacomitinib is a white to pale yellow, non-hygroscopic powder that is soluble in water at pH 1 at 25°C, with solubility decreasing to less than 0.001 mg/mL at pH 8. The drug substance is crystalline, with three known polymorphs. The thermodynamically favored (b) (4) (melting point 115.6°C) was used throughout the clinical development and is proposed for commercial manufacturing of the proposed product.



(2*E*)-*N*-{4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate

Chemical Formula: $C_{24}H_{27}ClFN_5O_3$

Molecular Weight: 487.96

(b) (4)

manufacturing process or the dissolution. The crystal form is not controlled as the applicant demonstrated that under all the conditions studied in the IND and this NDA, (b) (4) The applicant provided a risk assessment for elemental impurities consistent with ICH Q3D and is evaluated by the drug product reviewer. The analytical methods and the validation data presented by the applicant appear to be appropriate for this product and establish adequate controls for the quality of the drug product. The applicant provided batch release data for several clinical batches and three clinical batches. All the batches conform to the proposed specifications and show minimal impurities or degradants. (b) (4) The applicant confirmed that all the ingredients used in the container closure system conform to the relevant sections in the CFR for food contact. The applicant provided 48-month stability data for three registration batches of the drug substance under long term storage conditions and 6 months of data under accelerated conditions. No changes or trends are observed. The applicant included assay in the stability testing protocol in response to the IR dated May 01, 2018. (b) (4) stability was found acceptable. Based on the data provided in this submission, the proposed retest period of (b) (4) months when stored at (b) (4) %RH in the proposed container closure is acceptable.

Drug Product:

Vizimpro (dacomitinib) Tablets (15, 30 and 45 mg) are comprised of an immediate release blue film-coated formulation for oral administration. (b) (4) The proposed commercial tablets are de-bossed with 'Pfizer' on one side. The 15 mg, 30 mg and 45 mg strengths are differentiated by tablet size (6.35 mm, 7.5 mm, 9.0 mm), and de-bossing of 'DCB 15', 'DCB 30' and 'DCB 45', on the other side. Only compendial excipients [microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, Opadry II Blue 85F30716 (containing polyvinyl alcohol—partially hydrolyzed, talc, titanium dioxide, macrogol/PEG 3350 and FD&C Blue #2/Indigo Carmine Aluminum Lake) common for oral formulations are used for the manufacture of tablets. Tablets are packaged in high-density polyethylene (HDPE) bottles containing 1g desiccant with (b) (4) closure that includes a heat induction seal liner. The container closure system utilized for the 30 count bottles for dacomitinib 15 mg, 30 mg and 45 mg film-coated tablets comply with the standards set by the Consumer Product Safety Commission (CPSC) in 16 CFR 1700.

(b) (4)

The proposed commercial configuration of 30 count in 60 mL bottle that was not studied in the registration stability is bracketed by the 7 count in 45 mL bottle and the 100 count in

60 mL bottle. Dacomitinib 15 mg, 30 mg and 45 mg tablet strengths are made (b) (4) Three batches of the lowest (15 mg) and highest strengths (45 mg) were placed on stability, bracketing a single batch of the middle strength (30 mg). Bracketing was also implemented for bottle counts with only the 7 and 100 count bottles being tested. The lowest and highest bottle counts have the highest and lowest (b) (4) /tablet (respectively), thus representing the extremes in terms of (b) (4) per dosage unit. The 28-count bottle was bracketed and no active testing was performed. The matrix testing approach (1/3 reduced testing as described in ICH Q1D) is detailed in the application and was reviewed in Section P.8 of this review. Per recommendation in Pre-NDA CMC specific meeting dated 14-JUL-2017, applicant provided a risk assessment per ICD Q3D for Elemental Impurities (EI). The acceptable levels for the individual EIs are set based on ICH Q3D PDEs.

Drug product is release tested for: Appearance, Identification, Assay, Impurities, Dissolution, Content Uniformity (b) (4) Per ICH Q1A(R2), a primary stability program consisting of dacomitinib 15 mg, 30 mg and 45 mg tablets packaged in HDPE bottles with desiccant, was completed through 48 months at the storage condition of 30ºC/75% RH and 6 months at the accelerated storage condition of 40ºC/75 % RH. One of the stability batches was also used in the stress and the photostability testing. The stress testing was conducted to evaluate the impact of environmental stress such as temperature and humidity to the product quality. The photostability testing was conducted per ICH Q1B guideline "Stability Testing: Photostability Testing of New Drug Substances and Products". All results support the proposed acceptance criteria of assay and impurity. (b) (4) Based on the 48-months stability data for 7 batches from the primary program, the proposed expiration period is 48-months when stored at controlled room temperature for all three product strengths packaged in HDPE bottles with desiccant (see table in section P.8 under Reviewer's Assessment). A 48-month shelf-life (at Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) may be granted.

Facilities:

The drug substance (dacomitinib) is manufactured and tested by **Pfizer Ireland Pharmaceuticals (FEI #3002807852)**. The site was last inspected by FDA on 01/2018 and was classified as VAI. The facility was determined to be acceptable based on file review.

The drug product [Vizimpro (dacomitinib) Tablets (15, 30 and 45 mg)] is manufactured, release tested and packaged (primary: bottles) by **Pfizer Manufacturing Deutschland GmbH (FEI: 3002807097)**. The site was last inspected by FDA and classified as NAI with the drug profile classes covered "CHG", "**TCM**" and "TCT". The site was determined to be acceptable based on file review.

Pfizer Pharmaceuticals LLC (FEI: 2623619), (b) (4) listed as both performing secondary packaging and overseeing final product release. No further evaluation needed for these two sites as Pfizer Manufacturing

Deutschland GmbH (FEI: 3002807097) is the only site responsible for batch release (drug product release testing and issuance of the certificate of analysis) and secondary packaging is viewed as low risk process.

Biopharmaceutics:
The applicant established acceptable bridging between the non-film coated formulation, white film-coated formulation and the final target blue film-coated using a relative bioavailability (BA) study and comparative dissolution testing. Dacomitinib is classified as a BCS Class II (low solubility and high permeability) compound.

The approved dissolution method utilizes a USP Apparatus 2 with paddles rotating at 75 rpm. The media (900 mL) consists of sodium acetate buffer (pH 4.5) at 37°C.

The release and stability dissolution specification is Q= (b)(4)% dissolved in 15 minutes.

Established Conditions:
Pfizer submitted a proposal to incorporate Established Conditions (ICH Q12) into their original NDA application. In a T-CON held on June 13, 2018, the Agency informed Pfizer that due to the limited timeframe left in the review cycle and the concerns remaining with the proposed Established Conditions that the NDA would not be able to be approved with the current Established Conditions proposal.

Pfizer amended their application (25-JUN-18) to modify their prior proposal and instead rely on only implicit EC's that is, that Pfizer will rely on existing regulations and guidance to guide their approach to post approval changes (implicit ECs do not have to be specifically called out).

Upon approval of the dacomitinib NDA, Pfizer plans to submit a prior approval supplement (PAS) and request a pre-submission meeting to have a more thorough discussion on the proposed established conditions submitted on May 22, 2018. This pre-submission meeting should include representation from ONDP, OLDP, OPF, OPPQ and OPRO. Until approval of this prior approval supplement (established conditions), Pfizer will maintain the Established Conditions (implicit) outlined in the NDA in accordance with existing regulations and guidance.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

I. Drug Substance Deficiencies
1) None

II. Drug Product Deficiencies
1) None

III. Environmental Deficiencies
1) None

IV. Labeling Deficiencies
1) None

V. Process Deficiencies
1) None

VI. Facilities Deficiencies
1) None

VII. Biopharmaceutics Deficiencies
1) None

VIII. Microbiology Deficiencies
1) None

IX. Other Deficiencies (specify discipline)
1) None

Application Technical Lead Name and Date: Thomas F. Oliver, PhD 7/3/2018

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LABELING

R Regional Information

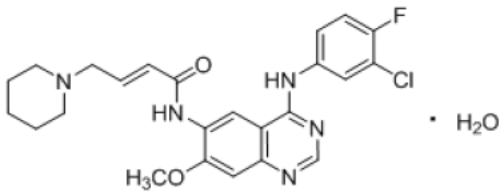
1.14 Labeling

Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

Dacomitinib is an oral kinase inhibitor with a molecular formula of $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$ and a molecular weight of 487.95 Daltons. The chemical name is: (2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate and its structural formula is:



Dacomitinib is a white to pale yellow powder [redacted] (b) (4)

VIZIMPRO tablets contain 45, 30, or 15 mg of dacomitinib with the following inactive ingredients in the tablet core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating consists of Opadry II® Blue 85F30716 containing: Polyvinyl alcohol – partially hydrolyzed, Talc, Titanium dioxide, Macrogol/PEG 3350, and FD&C Blue #2/Indigo Carmine Aluminum Lake.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

VIZIMPRO is supplied in strengths and package configurations as described in Table 6 below:

Table 6. VIZIMPRO strengths and package configurations

VIZIMPRO Tablets			
Package Configuration	**Tablet Strength (mg)**	**NDC**	**Tablet Description**
30 Count Bottle with a child-resistant closure	15	0069-0197-30	Blue film-coated, immediate release, round biconvex tablet, debossed with "Pfizer" on one side and "DCB15" on the other side.
30 Count Bottle with a child-resistant closure	30	0069-(b) (4)-30	Blue film-coated immediate release, round biconvex tablet, debossed with "Pfizer" on one side and "DCB30" on the other side.
30 Count Bottle with a child-resistant closure	45	0069-(b) (4)-30	Blue film-coated immediate release, round biconvex tablet, debossed with "Pfizer" on one side and "DCB45" on the other side.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2.2 Recommended Dosage

The recommended dosage of VIZIMPRO is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. VIZIMPRO can be taken with or without food *[see Dosage and Administration (2.4, (b) (4) Clinical Pharmacology (12.3)]*.

Take VIZIMPRO the same time each day. If the patient vomits or misses a dose, do not take an additional dose or make up missed dose but continue with the next scheduled dose.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☐ Yes ☐ No ☒ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Commercial packaging:

Immediate Container Label (15 mg):

Immediate Container Label (30 mg):

Immediate Container Label (45 mg):

Reviewer's Assessment: *The applicant responsed to deficiency and revised the container labels as recommended. Adequate.*

Reviewer's Assessment:

The labeling of the PI and container labels is revised per labelling tools and https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM569607.pdf *guidance to have the most current information of the labels.*

The deficiencies on PI are identified and will be communicated to the applicant by DDMAC/OND.

At the request of the ATL, an information request was sent to the applicant on 15-JUN-2018 to delete (b) (4) *from the container labels. An amendment was submitted on 21-*

JUN-2018 with the color mock-ups of the revised labels. The container labeling and PI are now adequate from a CMC stand point.

A final version of the agreed upon PI and container labels will be reviewed by the ATL and included in their memo.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 21-JUN-2018

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

Anamitro Banerjee, PhD,

Rajiv Agarwal

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Date: 6/21/2018 03:29:45PM
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Anamitro Banerjee

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Date: 6/21/2018 04:51:32PM
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BIOPHARMACEUTICS

Application No: NDA 211288-ORIG-1

Drug Product Name/Strengths: Dacomitinib Tablets/15 mg, 30 mg, and 45 mg

Route of Administration: Oral

Applicant Name: Pfizer

List Submissions being Reviewed: Original NDA-211288 submission dated 1/31/2018

Review Recommendation: **ADEQUATE**

Review Summary:

Submission: Pfizer submitted this NDA seeking approval for Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Review Objective: The Biopharmaceutics Review evaluates the adequacy of (1) the proposed dissolution method and acceptance criterion for routine QC testing of the proposed drug product at batch release and during stability, and (2) bridging of different formulations used in clinical studies.

Dissolution Method and Acceptance Criterion: The following Applicant's proposed dissolution method and dissolution acceptance criterion are acceptable for batch release and stability testing of the proposed Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg.

Final dissolution method and acceptance criterion for Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg

USP Apparatus	Speed (rpms)	Medium/Temp	Volume (mL)	Acceptance Criterion
2 (paddle)	75	Sodium acetate buffer, pH 4.5/37 °C	900	Q = (b)(4)% dissolved in 15 minutes

Bridging of Formulations: The Applicant established the bridging between the non film-coated formulation, white film-coated formulation, and the final target blue film-coated tablets using relative bioavailability (BA) study and comparative dissolution testing. The bridging is acceptable.

Biowaiver Request: Biowaiver Request is not submitted nor required.

Overall Review Recommendation: From the Biopharmaceutics perspective, NDA-211288 for Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg is recommended for **APPROVAL**.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, PhD 5/14/2018
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

Secondary Reviewer Name and Date:

Banu S Zolnik, PhD 5/22/2018
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

BIOPHARMACEUTICS ASSESSMENT

Dacomitinib Tablets is a kinase inhibitor indicated for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations as detected by an FDA-approved test. The recommended dose of Dacomitinib Tablets is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs.

1. DRUG SUBSTANCE:

1.1 Solubility:

Dacomitinib is a non-hygroscopic, white to pale yellow powder. The Applicant reported that dacomitinib is a low water-solubility drug (Table 1). Although, the Applicant stated that the drug substance meets the criterion in FDA guidance for 'highly soluble' at pH 4 or lower, where the highest dose strength (45 mg) is soluble in 250 mL [0.23 mg/mL (at pH 4.0) × 250 mL = 57.5 mg], the Applicant's assessment is not correct because a drug substance is considered highly soluble when the highest strength is soluble in 250 mL of aqueous media within the pH range of 1–6.8 at 37°C, as the solubility of dacotinib in pH 6 is 0.006 mg/mL, only 1.5 mg of dacotinib will be soluble in pH 6

Table 1. Aqueous solubility of dacomitinib at room temperature

1.2 Permeability:

The Applicant evaluated the permeability of dacomitinib based on human absolute oral bioavailability (BA) study [Study A7471046, mean absolute BA of dacomitinib after oral administration relative to intravenous administration reported to be 80.0% (90% CI: 74.9%–85.5%)], human absorption, distribution, metabolism and excretion (ADME) study (Study A7471020), rat single pass intestinal perfusion study [SPIP, intestinal Apparent Permeability (Papp): 140–249×10^{-6} cm/sec, greater than the high permeability standard of metoprolol with Papp of 23–60×10^{-6} cm/sec) and Caco-2 permeability assessment ($Papp_{A\rightarrow B}$: 2.6–8×10^{-6} cm/sec, $Papp_{B\rightarrow A}$: 2.5–4.5×10^{-6} cm/sec, efflux ratio ranging from 0.53–1.28).

1.3 BCS designation:

The Applicant stated that dacomitinib is classified as BCS Class II (low solubility and high permeability) compound.

2. DRUG PRODUCT:

The proposed commercial formulation of Dacomitinib Tablets is an immediate release (IR) tablet available in three strengths: 15 mg, 30 mg and 45 mg blue film-coated tablets, (b) (4)

(b) (4)

The proposed commercial tablets are de-bossed with 'Pfizer' on one side. The 15 mg, 30 mg and 45 mg strengths are differentiated by tablet size (6.35 mm, 7.5 mm, 9.0 mm), and de-bossing of 'DCB 15', 'DCB 30' and 'DCB 45', respectively. The tablets are packaged in high density polyethylene (HDPE) bottles containing desiccant with an induction seal and closure (b) (4).

3. PROPOSED DISSOLUTION METHOD AND DISSOLUTION ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for Dacomitinib Tablets, 15 mg, 30 mg and 45 mg are as follows:

Proposed dissolution method and acceptance criterion for Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg

USP Apparatus	Speed (rpms)	Medium/Temp	Volume (mL)	Acceptance Criterion
2 (paddle)	75	USP 4.5 sodium acetate buffer/37 °C	900	Q = (b) (4) % dissolved in 15 minutes

(b) (4)

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3.4 Dissolution profiles for Dacomitinib Tablets using the proposed dissolution method:

The Applicant provided the dissolution profiles for Dacomitinib Tablets registration batches (**blue film-coated** tablets), using the proposed dissolution method (Figure 3).

Figure 3. Dissolution profiles for Dacomitinib Tablets registration batches (Batches No. 9811433000/9811433001/9811433002, 9811533000/9811533001/9811533002, and 9811633000/9811633001/9811633002 for 15-mg, 30-mg, and 45 mg-strength, respectively)

3.5 Discriminating ability of the proposed dissolution method:

3.5.1 Drug substance particle size:

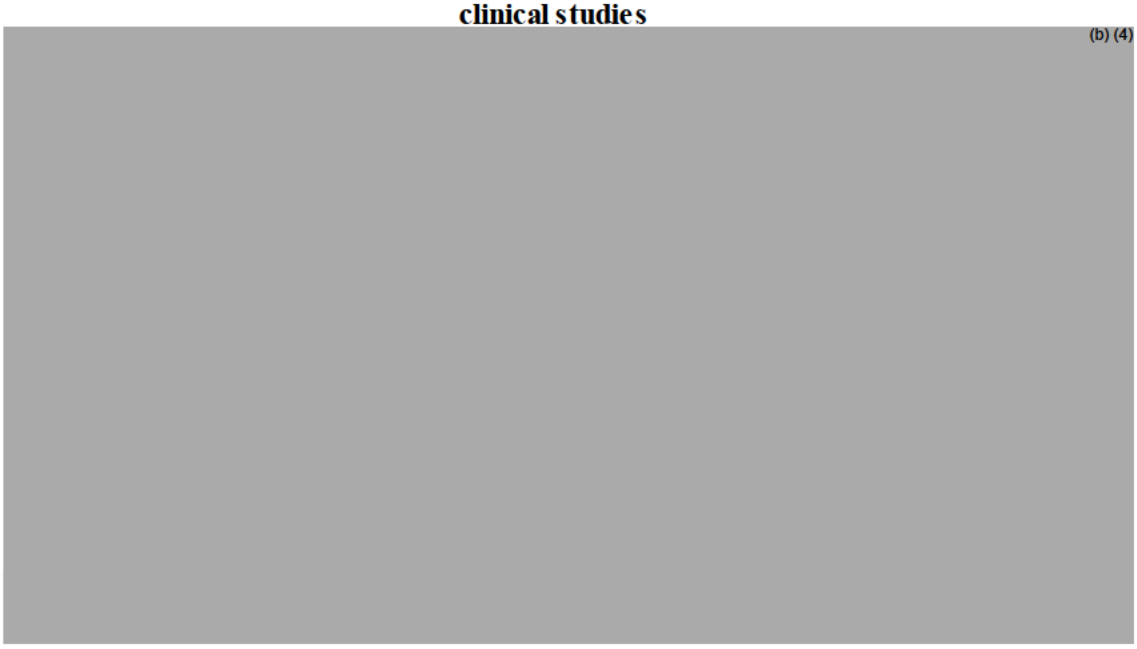
It is demonstrated that the proposed dissolution method is not discriminating towards the changes in drug substance particle sizes used for the manufacture of Dacomitinib Tablets (D_{90} range tested: (b) (4) µm) (Figure 4).

The Applicant reported that a range of drug substance particle distributions up to D_{90} of (b) (4) µm were used to support clinical studies (used in Studies of A7471009, A7471042, A7471047), including the relative bioavailability study (A7471022) where equivalence in AUC was confirmed between tablets manufactured with drug substance with D_{90} of (b) (4) µm and (b) (4) µm (Figure 5).

In addition, the Applicant demonstrated that, in the food effect study of A7471015, dosing of Dacomitinib Tablets manufactured with drug substance of particle size D_{90} of (b) (4) µm in fed state did not have a significant impact on drug exposure level compared to that in fasted state [$AUC_{0-\infty}$ ratio 114.2% (90% CI: 104.7%, 124.5%)]. The study results of A7471015 will be assessed by the Office of Clinical Pharmacology Reviewers.

Figure 4. Dissolution profiles for Dacomitinib Tablets manufactured with drug substance of different particle sizes using the proposed QC dissolution method

Figure 5. Drug substance particle size distribution for Dacomitinib Tablets batches used in clinical studies



The Applicant reported that the proposed particle size specification for dacomitinib drug substance is D_{90} NMT (b) (4) µm. The proposed particle size specification for dacomitinib drug substance will be determined by the assigned Drug Substance Reviewer.

3.5.2 Formulation variants:

It is demonstrated that the proposed dissolution method is discriminating towards the changes in (b) (4) The results indicate that two formulation changes (b) (4) have a significant impact on the dissolution rate (Figure 6).

Table 2. Formulation variants evaluated for Dacomitinib Tablets

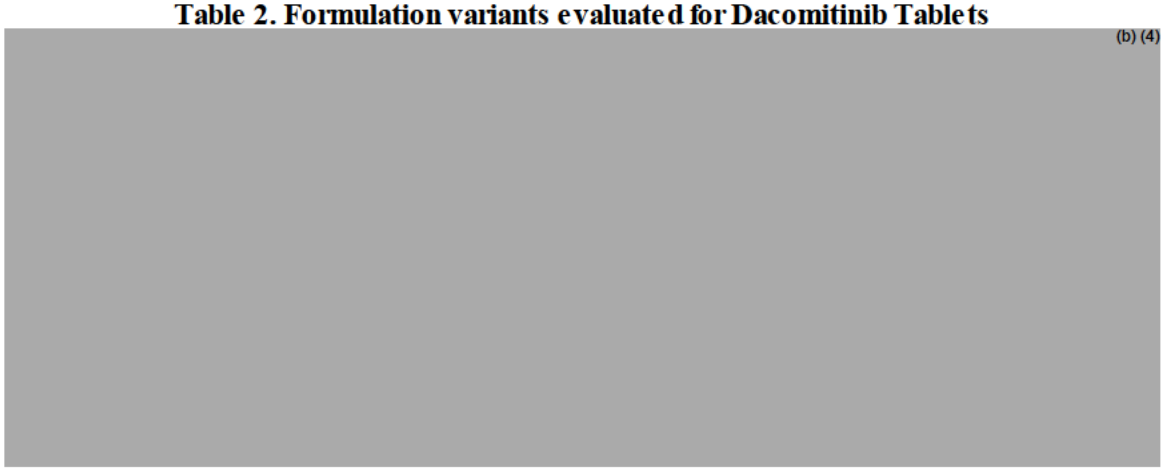


Figure 6. Dissolution profiles for Dacomitinib Tablets manufactured with different formulation variants using the proposed dissolution method (b) (4)

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Reviewer's Assessment: The proposed dissolution method [*USP apparatus 2 (Paddle) at 75 rpm, 900 mL of pH 4.5 sodium acetate buffer at 37 ºC*] is shown to be discriminating towards (b) (4) The proposed dissolution method is acceptable for batch release and stability testing of Dacomitinib Tablets, 15 mg, 30 mg, and 45 mg. The Applicant's proposed dissolution acceptance criterion of "Q = (b) (4) % dissolved in 15 minutes" is acceptable.

4. BRIDGING OF FORMULATIONS:

4.1 Different clinical formulations:

Clinical formulations consisted of non-film-coated (b) (4) tablets, plain white film-coated (b) (4) tablets and debossed blue film-coated tablets. The debossed blue film coated tablets are proposed commercial drug product (Tables 3 and 4).

Early Phase 1, Phase 2 clinical studies, and the BR26/A7471011 Phase 3 study were supported using (b) (4) **non-film-coated tablets** (0.5 mg, 5 mg, 15 mg and 20 mg dosage strengths). (b) (4)

The Phase 3 study A7471009 (referred to as Study 1009) and other Phase 1 and Phase 2 studies were supported by (b) (4) **white film-coated tablets** (15 mg, 30 mg and 45 mg dosage strengths with the (b) (4) film-coat). (b) (4)

(b) (4)% w/w in the formulation was required to (b) (4) of 30 mg and 45 mg while maintaining appropriate tablet size. The manufacturing process (b) (4)

Registration stability, Phase 3 study DP312804/A7471050 (referred to as Study 1050), other Phase 1 and Phase 2 studies, and the proposed commercial drug product were supported by (b) (4) **debossed blue film-coated tablets** (15 mg, 30 mg and 45 mg dosage strengths with the Blue Opadry® II 85F30716 film-coat). The tablet core remained the same as that of the white film-coated tablets, and differed in tablet size (tablet diameter was changed (b) (4) mm for the 30-mg tablet), debossing and film-coat color.

Table 3. Summary of Dacomitinib Tablets formulations used in clinical studies

[a] Phase III
[b] Relative
[c] Mass bal

Table 4. Composition of 0.5 mg, 5 mg, 15 mg, 20 mg, 30 mg and 45 mg Dacomitinib Tablets used in clinical studies and proposed commercial formulation

(b) (4)

(b) (4)

(b) (4)

4.2 Bridging strategy:

The Applicant submitted a relative bioavailability (BA) study and comparative dissolution data to support the bridging between the non film-coated formulation and white film-coated formulation (different drug loading and different excipient levels). The Applicant submitted comparative dissolution data to support the bridging between the white film-coated and the final target blue film-coated tablets (b) (4) (Figure 10).

Table 5. Different Dacomitinib Tablets 45 mg using in the bridging of the formulations

Tablet
Debossed E
Coated Tab

[1] The same

Figure 10. Applicant's bridging strategy for Dacomitinib Tablets 15 mg, 30 mg and 45 mg different formulations

4.3 Relative bioavailability between the non film-coated and white film-coated formulations:

Based on the results of the clinical relative bioavailability study (A7471022) between the non film-coated and white film-coated tablets, similar PK between the two formulations appeared to be demonstrated, however the assessment of the equivalency will be made by the OCP reviewer (Table 6).

Table 6. Statistical summary of treatment comparisons for Dacomitinib non film-coated and white film-coated tablets

C_{max} (n

[1] The ratios

N=32

4.4 Comparative dissolution profiles between Bridging between the non film-coated, white film-coated and final blue film-coated tablets:

All non film-coated, white film-coated and final blue film-coated tablets generated similar dissolution profiles in multi-pH media (Figures 11–13).

Figure 11. Dissolution of different Dacomitinib formulations in 0.1M HCl medium

Figure 12. Dissolution of different Dacomitinib formulations in pH 4.5 medium

Figure 13. Dissolution of different Dacomitinib formulations in pH 6.8 medium

Reviewer's Assessment: The Applicant established the bridging between the non film-coated formulation, white film-coated formulation, and the final target blue film-coated tablets using relative bioavailability (BA) study and comparative dissolution testing. This Reviewer considers the bridging among different formulations are adequately established.

5. BIOWAIVER REQUEST:

Biowaiver Request is not submitted nor required.

Yang Zhao

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Assessed during Development	Acceptable	Controls are in place.
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	Assessed during Development	Acceptable	No specifications, justification in the NDA.
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
					(b) (4)
					(b) (4)

Rajiv Agarwal

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