CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210498Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210498

Review 1

Drug Name/Dosage Form	MEKTOVI (Binimetinib) Tablet
Strength	15 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Array BioPharma Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA- 0000 (1)	*06/30/2017*	*Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics, and Microbiology*
Amendment – 0013(13, quality response to IR dated 11/03/2017, quality update Module 3 (P.5)	*11/16/2017*	*Drug Product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Charles Jewell	Benjamin Stevens
Drug Product	Olen Stephens	Anamitro Banerjee
Process	Diane Goll	Ying Zhang
Microbiology	Diane Goll	Ying Zhang
Facility	Viviana Matta	Ruth Moore
Biopharmaceutics	Joan (Zhuojun) Zhao	Okpo Eradiri
Regulatory Business Process Manager	Steven Kinsley	NA
Application Technical Lead	Nina Ni	NA
Laboratory (OTR)	NA	NA
ORA Lead	Caryn McNab	
Environmental	Olen Stephens	Anamitro Banerjee

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Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
	Type IV			Adequate	23-SEP-2016	DMF active; reviewed by Dr.

			(b) (4)			Olen Stephens

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Binimetinib (MEK-162, ARRY-438162)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

* Methods Verification (MV) was not requested as the drug substance and drug product reviewers do not have concerns for the analytical methods proposed in this NDA. Based on the OPQ-SOP-0022 effective on 23-Dec-2016, entitled "Procedure for Requesting Method Verification within OPQ", Section 7.4.3, there is no longer a need for reviewers or RBPMs to notify the Methods Verification Program (MVP) Coordinator of a new NME, if there is no concern for method verification.

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Based on the provided stability data, a 36-month expiration dating period is granted for MEKTOVI (binimetinib) tablets in 15 mg strength when stored at USP controlled room temperature 20 - 25ºC (68 - 77ºF); with excursions permitted to 15 - 30ºC (59 - 86ºF).

II. Summary of Quality Assessments

A. Product Overview

(b) (4) was received on 06/30/2017 in the 505b(1) regulatory pathway with FDA orphan drug designation to support MEKTOVI (binimetinib) marketing approval request for the use of binimetinib, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. A reference is made to the encorafenib NDA (NDA 210496; User Fee No. PD3016962), which is also being submitted in parallel to the Division of Oncology Products 2 (DOP2) on 06/30/2017. NDA 210498 has also cross-referenced to (b) (4) and several INDs for developmental data on the oral tablets. (b) (4) There are new and revised quality information submitted in NDA 210498 in Module 3 as summarized in Section 1.4.4.4 in addition to the same quality information as that in the (b) (4). Therefore, this review evaluates the totality of the quality information submitted in NDA 210498.

MEKTOVI contains the active pharmaceutical ingredient (API) binimetinib, a new molecular entity (NME). Binimetinib is a white to slightly yellow powder that is slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and is practically insoluble at pH 4.5 or above. Only one stable crystalline anhydrous form has been identified and the drug substance is non-hygroscopic.

MEKTOVI is formulated as a conventional immediate-release, film-coated, yellow to dark yellow, unscored biconvex ovaloid (capsule shaped) tablet in strength of 15 mg for oral administration. The tablet is debossed with a stylized "A" on one face and "15" on the opposite face.

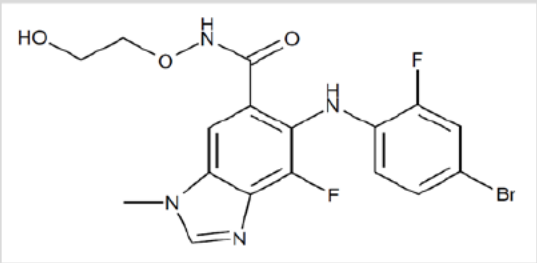
Proposed Indication(s) including Intended Patient Population	Binimetinib is in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	45 mg orally twice daily
Alternative Methods of Administration	NA

B. Quality Assessment Overview

1. Drug Substance [Binimetinib]

The drug substance binimetinib has the following chemical name, structural formula, molecular formula, and molecular weight:

International Non-proprietary Name (INN): binimetinib
Name (IUPAC): 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide
Name (CAS): 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide
(CAS) Registry Number: 606143-89-9
Mol. Formula: $C_{17}H_{15}BrF_2N_4O_3$
Mol. Wt.: 441.23 g/mole
Structural Formula:



Binimetinib is an achiral small molecule in white to slightly yellow powder which is non-hygroscopic. It is isolated as a crystalline anhydrous form (b) (4) the only stable form that has been identified in drug substance batches produced using the commercial drug manufacturing process. Binimetinib is a weak base (pKa=2.50) and exhibits a pH-dependent solubility profile (slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and is practically

insoluble at pH 4.5 or above) and is considered as a BCS Class 4 (low solubility, low permeability) drug.

(b) (4)

Drug substance stability studies on the primary registration batches demonstrated that binimetinib is physico-chemically stable under both conditions: long term 30ºC/75%RH (with 24-month data) and accelerated 40ºC/75%RH (with 6-month data). No significant change or trending has been observed under either storage conditions based on the proposed specification which adequately ensures the quality of binimetinib with respect to identity, purity, and key molecular properties necessary to support its use in the manufacture of the drug product. Confirmative photo-stability study demonstrated the photo-lability of binimetinib. Forced degradation study has established that the UPLC/UV method for assay and purity is stability indicating. The proposed retest date of (b) (4) is acceptable, when stored (b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

[redacted]

2. Drug Product [MEKTOVI (binimetinib) tablets]

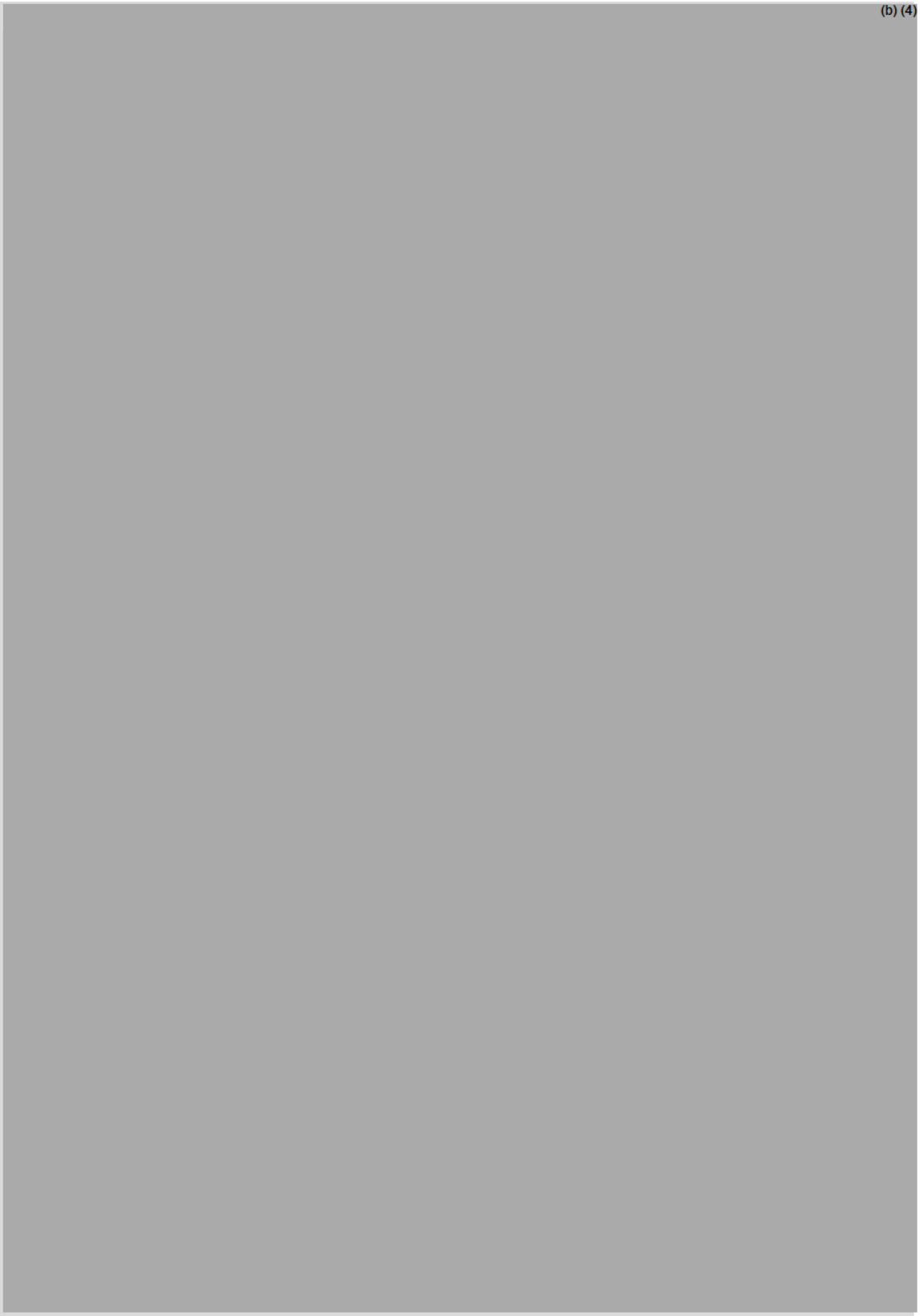
MEKTOVI (binimetinib) tablets are available in 15 mg strength for oral administration. They are film-coated for immediate release, in yellow to dark yellow color, unscored biconvex ovaloid (capsule shaped), debossed with a stylized "A" on one face and "15" on the opposite face. The inactive ingredients are (tablet core): lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate (vegetable source), and (film coating): polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, and ferrosoferric oxide. All excipients are compendial grade. (b) (4) [redacted] he proposed commercial tablet formulation is the same tablet formulation used in the pivotal clinical study and no significant changes to the manufacturing process have been made since the development of the manufacturing process used for production of batches for the pivotal clinical study.

The tablets are packaged in 90 mL high density polyethylene (HDPE) bottles (b) (4) [redacted] induction seal in a 180-ct presentation (for 3 tablets BID x 30 days).

(b) (4)

[redacted]

(b) (4)



The Applicant has adequately demonstrated the suitability of the dissolution method [with an acceptance criterion of NLT (b) (4) % (Q) in 30 minutes] for batch release and stability testing. However, the dissolution method does not discriminate

between binimetinib tablets with varied drug substance particle size distribution, tablet hardness, or other process parameters (b) (4)

Those quality attributes are controlled by the drug substance specification (b) (4) In addition, in vitro/in vivo correlation (IVIVC) has not been established for the drug product.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and labeling) based on Profile.

(b) (4)

3. Special Product Quality Labeling Recommendations (NDA only)

NA

4. Final Risk Assessment (see below)

Attachment - Final Risk Assessment for MEKTOVI (binimetinib) tablets

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 • Raw materials • Process parameters • Scale/equipments • Site • Container closure	Low	Assessed during development and controlled via specifications and container closure	Acceptable	Controls are in place Continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure	Medium	Assessed during development and controlled via specifications and container closure	Acceptable	Controls are in place Continue stability monitoring post approval
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Assessed during development and controlled (b) (4)	Acceptable	Controls are in place
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Assessed during development and controlled via specifications	Acceptable	Controls are in place Continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Assessed during development and controlled (b) (4)	Acceptable	Controls are in place

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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	MEKTOVI™
Dosage form, route of administration	Tablets, 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: 15 mg

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)	NA

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	Tablets
Strengths: in metric system	15 mg
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yellow/dark yellow, unscored biconvex oval (capsule shaped) film-coated tablets debossed with a stylized "A" on one face and "15" 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	MEKTOVI (binimetinib) tablets
Dosage form and route of administration	Tablets, for oral use
Active moiety expression of strength with equivalence statement (if applicable)	NA
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
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Kinase inhibitor
Chemical name, structural formula, molecular weight	Included and adequate
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and practically insoluble at pH 4.5 and above.

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	15 mg tablets
Available units (e.g., bottles of 100 tablets)	Bottles of 180 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yellow/dark yellow, biconvex oval film-coated tablets with a stylized "A" on one face and "15" on the other side
Special handling (e.g., protect from light)	NA
Storage conditions	Store at room temperature 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) *[See USP Controlled Room Temperature]*
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by Array BioPharma Inc.

Reviewer's Assessment of Package Insert: Adequate with minor edit

- ***The applicant will be instructed to amend section 11 with "tablets, for oral use"***

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

2. ***Carton Label***

(b) (4)

[redacted]

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	MEKTOVI™(binimetinib) tablets	MEKTOVI™(binimetinib) tablets
Dosage strength	15 mg	15 mg
Net contents	180 tablets	180 tablets
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Space provided	Space Provided
Storage conditions	Adequate	Adequate
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Distributor stated	Distributor stated
And others, if space is available	NA	NA

Reviewer's Assessment of Labels: Adequate with minor comment:

1. **Indicate an area on the carton label where the lot number and expiration will be printed.**

Review of the package insert will be conducted in coordination with the clinical division.

List of Deficiencies:

1. ***Amend section 11 to state "tablets, for oral use"***
2. ***Indicate an area on the carton label where the lot number and expiration will be printed.***

Overall Assessment and Recommendation: Adequate with minor edits.

Primary Labeling Reviewer Name and Date: Olen M. Stephens; 28-Nov-17

Secondary Reviewer Name and Date: Anamitro Banerjee, December 10, 2017

Olen Stephens

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Anamitro Banerjee

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BIOPHARMACEUTICS

Product Background:

NDA: 210498-ORIG-1 (505(b)(1))

Drug Product Name / Strength: MEKTOVI (binimetinib) Tablets/15 mg

Route of Administration: Oral

Applicant Name: Array BioPharma Inc.

Review Summary:

MEKTOVI (binimetinib) Tablets, 15mg are indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-Approved test. A reference is made to NDA 210496 (encorafenib capsules, 50 and 75 mg), which was submitted in parallel to the Division of Oncology Products 2 (DOP2).

NDA 210498 cross references (b) (4) (binimetinib tablets, 15 mg), (b) (4) was recommended for Approval from the Biopharmaceutics persepctive[1] but the Applicantion was withdrawn by the Applicant (b) (4) NDA 210498 contains the same Biopharmaceutics related content as submitted previously in (b) (4).

The drug substance binimetinib, is a new molecular entity (NME), a potent and selective allosteric, adenosine triphosphate (ATP)-uncompetitive inhibitor of mitogen-activated protein kinase (MEK) 1 and MEK 2. Only one stable crystal form has been identified.

Binimetinib exhibits pH dependent solubility and MEKTOVI is formulated as an immediate release tablet to disintegrate in the stomach and provide rapid dissolution of the drug substance.

Based on the provided dissolution data, the following dissolution method and the acceptance criterion are acceptable:

Method	USP Apparatus II (Paddle) in 900 mL 0.01 N HCl at 75 rpm
Acceptance Criterion	NLT (b) (4)% (Q) in 30 minutes

No formulation bridging is needed as the proposed commercial drug product is the same as the clinical batch (P3-MI).

[1] Panorama (b) (4) 007-IQA-BIOPHARMACEUTICS FINAL.docx

From the Biopharmaceutics perspective, NDA 210498 for binimetinib tablets, 15 mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original Submission	06/30/2017

Highlight Key Outstanding Issues from Last Cycle: N/A (First cycle)

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: Binimetinib is likely a BCS Class 4 (low solubility, low permeability) drug.

Drug Substance Solubility:

Binimetinib is a weak base (pKa=2.50) and exhibits a pH-solubility profile, as shown below:

Table 1 Equilibrium Solubility of Binimetinib in Aqueous Buffered Solutions at 37°C

sis =
vsls =
ins =

Based on the Applicant's calculation, the equilibrium solubility of a 45 mg dose (3×15 mg) of binimetinib is above the BCS high solubility definition at pH 1.0 and in SGF, and below the boundary from pH 2.0 to pH 7.5.

Permeability:

Binimetinib exhibits moderate to high permeability amassed by the Applicant's in vitro Caco-2 system (passive permeability ~63 x10-5 cm·min-1 (Study DM05-042 and Study DM05-042-A1), and the human ADME study indicates that oral bioavailability (%F) was not less than 50% (Study CMEK162A2102).

Drug Substance

Binimetinib base is a non-solvated, anhydrous crystalline solid. (b) (4)

Formulation:

The proposed formulation (b) (4) consisting of lactose monohydrate and microcrystalline cellulose. Croscarmellose sodium (b) (4) colloidal silicon dioxide (b) (4) magnesium stearate (b) (4) acceptable (b) (4) and dissolution.

The proposed drug product formulation used in the pivotal clinical study (shown in Table 2) is the same as that proposed for marketing.

Table 2 Qualitative/Quantitative Drug Product Formulation

(b) (4)

Dissolution Method and Acceptance Criteria

The proposed dissolution method is summarized as follows:

USP Apparatus type	USP II (Paddle)
Rotation (rpm)	75 RPM
Medium	0.01 N HCl (pH 2)
Volume (mL)	900 mL
Temperature	37±0.5 °C
Proposed Sampling Time	30 minutes
Analysis Method	HPLC/UV at 252 nm

In the dissolution method development section (module 3.2.P.2 Drug Product), justification for the choice of dissolution apparatus, dissolution medium, and agitation speed are provided, as detailed below.

The Applicant conducted the dissolution method development in parallel with formulation and process development of the tablet formulation; the dissolution method parameters are listed below:

Table 3 Summary of Dissolution Methods used through the Development of Binimetinib Tablets.

(b) (4)

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Zhuojun Zhao

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Nina Ni

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