CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208772Orig1s000

CHEMISTRY REVIEW(S)

NDA/BLA » NDA 208772

NDA-208772-ORIG-1

Project Owner

Project Actions

Status	Condition	Planned Completion	Percent Complete
Current	At Risk	Apr 28, 2017	85.6%

Project Summary | Project Details | Application Life Cycle | Application History | Inspection View | Tasks | **Submission Facility Status View**

As of Apr 3, 2017 2:33 pm GMT

Submission Overall Manufacturing Facility Status

Overall Inspection Recommendation	Completion Date	Submission Status	Project Name
Approve	1/23/2017	Pending	NDA-208772-ORIG-1

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Associatio
Approve Facility	1/17/2017	NDA-208772-ORIG-1				(b) (4)	CTL CONTROL TESTING LABORATOR...	PENDING
Approve Facility	1/17/2017	NDA-208772-ORIG-1					TCM TABLETS, PROMPT RELEASE	PENDING
Cancelled	11/9/2016	NDA-208772-ORIG-1					TCM TABLETS, PROMPT RELEASE	PENDING
Cancelled	11/8/2016	NDA-208772-ORIG-1					TCM TABLETS, PROMPT RELEASE	PENDING
Cancelled	11/8/2016	NDA-208772-ORIG-1					CTX CONTROL TESTING LABORATOR...	PENDING
Approve Facility	10/6/2016	NDA-208772-ORIG-1	1000370240	226277259	110006142	PENN PHARMACEUTICALS SERVICES LIMITED (b) (4)	TCM TABLETS, PROMPT RELEASE	PENDING
Approve Facility	9/7/2016	NDA-208772-ORIG-1				(b) (4)	CSN NON-STERILE API BY CHEMIC...	PENDING
Approve Facility	9/7/2016	NDA-208772-ORIG-1					CTL CONTROL TESTING LABORATOR...	PENDING
Approve Facility	9/7/2016	NDA-208772-ORIG-1					CTL CONTROL TESTING LABORATOR...	PENDING
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Cancelled	9/7/2016	NDA-208772-ORIG-1					CTL CONTROL TESTING LABORATOR...	PENDING
Approve Facility	9/7/2016	NDA-208772-ORIG-1				(b) (4)	CSN NON-STERILE API BY CHEMIC...	PENDING

Recommendation: Approval from the CMC prospective

NDA 208-772
Review #2

Drug Name/Dosage Form	ALUNBRIG (brigatinib) / Tablet
Strength	30 mg and 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ARIAD Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA- 0002 (2)	*07-28-2016*	*Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics, and Microbiology*
Amendment – 0004 (4), quality response to IR	*08/09/2016*	*Drug Product*
Amendment – 0009 (9), quality information 30day additional stability data	*09/27/2016*	*Drug Substance, Drug Product, Biopharmaceutics, Microbiology*
Amendment – 0010 (10), quality response to IR dated 9/29/2016	*09/30/2016*	*Drug Substance*
Amendment – 0017 (17), quality response to IR dated 11/04/2016	*11/18/2016*	*Drug Product*
Amendment – 0020 (20), quality response to IR dated 11/09/2016	*11/22/2016*	*Drug Product*
Amendment – 0022 (22), quality response to IR dated 11/29/2016	*12/13/2016*	*Drug Substance, Drug Product, Process, Biopharmaceutics*
Amendment – 0023 (23), quality response to IR dated 12/08/2016	*12/14/2016*	*Drug Product*
Amendment – 0027 (27), quality response to IR dated 12/16/2016 & 03/01/2017	*01/05/2017*	*Drug Product, Biopharmaceutics, Process*
Amendment – 0031 (31), quality response to IR dated 01/17/2017,	*01/25/2017*	*Drug Substance*
Amendment – 0033 (32), quality response to IR dated 01/24/2017, update for Module 3 (S.7.3, P.2, & P.7)	*01/26/2017*	*Drug Substance; Drug Product, Biopharmaceutics*
Amendment – 0033 (33), quality update for Module 3 (P.5 & P.8)	*01/27/2017*	*Drug Product, Biopharmaceutics*

Amendment – 0035 (37), Module 2 update for Quality Overall Summary Module 3 (P.8.3) update	*02/02/2017*	*Drug Substance, Drug Product, Biopharmaceutics*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor	OPQ/ONDP/DNDPAPI/BI
Drug Product	Olen Stephens	OPQ/ONDP/DNDPI/BII
Process	Ying Zhang	OPQ/OPF/DPAI/BII
Microbiology	Ying Zhang	OPQ/OPF/DPAI/BII
Facility	Thuy Nguyen/Ruth Moore	OPQ/OPF/DIA/BI
Biopharmaceutics	Joan Zhao/Okpo Eradiri	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Joyce Crich	OPQ/ONDP/DNDPI/BII
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	Olen Stephens	OPQ/ONDP/DNDPI/BII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	Adequate	09/29/2010	DMF active; reviewed by Dr. Danuta Gromek-Woods
	Type III			Adequate	Information provided in NDA	DMF active; supports several approved NDAs & ANDAs
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B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION
IND	110935	ARIAD Pharmaceuticals, Inc.	Brigatinib (AP26113)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/ Toxicology	Complete	Approval	01/25/2017	M Anwar Goheer, Ph.D and Emily Wearne, Ph.D
Methods Verification *	Complete	Acceptable	01/04/2017	David Keire, Ph.D
DMEPA **	Complete with comments for container labels, carton labeling and PI	the proposed proprietary name, Alunbrig, is acceptable	09/06/2016 & 01/06/2017	Janine Stewart, PharmD

*Methods Verification was performed by Division of Pharmaceutical Analysis (DPA) in St. Louis under Office of Testing and Research (OTR)/OPQ/CDER/FDA. See Panorama for the Methods Verification Report Summary.
**DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary

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.

Include the following language in the approval letter:
Based on the provided stability data, a 24-month expiration dating period is granted for 30 mg ALUNBRIG (brigatinib) tablets, and a 18-month expiration dating period is granted for 90 mg ALUNBRIG (brigatinib) tablets, from the date of manufacture of the tablets in the proposed commercial container closure systems when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

II. Summary of Quality Assessments

A. Product Overview

NDA 208-772 was received on August 29, 2016 in the 505b(1) regulatory pathway with FDA breakthrough and FDA orphan drug designations which was granted in October 2014. NDA 208-772 cross references IND 110935 for developmental data on the ALUNBRIG (brigatinib) tablets in the strengths of 30 and 90 mg. Brigatinib is an orally-active tyrosine kinase inhibitor (TKI) that primarily targets activated, mutant forms of ALK and c-ros oncogene 1 (ROS 1), which play roles in NSCLC. ALUNBRIG (brigatinib) tablets are indicated for the treatment of patients with (b) (4) metastatic anaplastic lymphoma kinase positive (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Proposed Indication(s) including Intended Patient Population	For the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Duration of Treatment	90 mg orally once daily for 7 days, followed by 180 mg once daily (continuously). Dose modifications to 60 mg once daily are permitted for management of adverse reactions.
Maximum Daily Dose	180 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

1. Drug Substance [Brigatinib]

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

International Non-proprietary Name (INN): brigatinib

Name (IUPAC): 5-chloro-*N4*-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4 [4-(4-methylpiperazin-1-yl) piperidin-1-yl]phenyl}pyrimidine-2,4-diamine

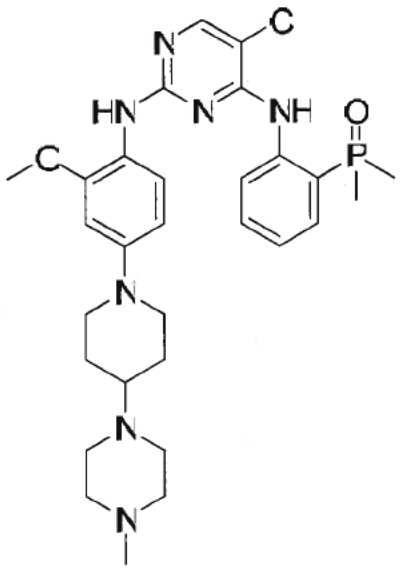
Name (CAS): 2, 4-pyrimidinediamine, 5-chl*oro-N4*-[2-(dimethylphosphinyl)phenyl]-N2-[2-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]-

(CAS) Registry Number: 1197953-54-0

Mol. Formula: $C_{29}H_{39}ClN_7O_2P$

Mol. Wt.: 584.10 g/mole

Structural Formula:



Brigatinib is an achiral small molecule in off-white to beige/tan solid. (b) (4)

(b) (4)

Brigatinib is considered as BCS Class 1 and is highly soluble from pH 1.5 to pH 6.5. However,

drug product ALUNBRIG (brigatinib) tablets is not considered BCS Class 1 because it does not rapidly dissolve to meet the classification.

Brigatinib is manufactured by a proposed commercial process (referred to as "Process B2")

(b) (4)

There are two manufacturers proposed for the commercial production of brigatinib drug substance: (b) (4)

There are slight minor differences in manufacturing equipment, operations, and analytical instrumentation between the two proposed DS manufacturing sites that have been well validated. The provided batch release data and stability data of four registration batches from (b) (4) and three registration batches from (b) (4) demonstrated these two sites are comparable and all batch results well conform to the proposed standard release specifications per ICH guidelines for drug substance to be used in a solid oral dosage form.

Drug substance stability studies demonstrated that brigatinib is physicochemically stable under both long term 25°C/60%RH (18-month data from (b) (4) batches and 12- month data from (b) (4) batches) and accelerated 40°C/75%RH (6-month data from all batches) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that brigatinib is not light sensitive. Forced degradation study has established that the HPLC method for assay and purity is stability indicating. The proposed retest date of (b) (4) stored (b) (4) is acceptable, and in the proposed container closure (b) (4) (b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) and other testing sites (for stability on XRPD, and microbial enumeration). These accepted facilities as listed below are either based on Profile or based on Pre-Approval Inspection.

- (b) (4)

2. Drug Product [ALUNBRIG (brigatinib) tablets]

ALUNBRIG (brigatinib) tablets are available for oral administration in 30 mg and 90 mg dosage strengths. They are off-white, debossed, and film-coated for immediate release. The tablets contain brigatinib as the active pharmaceutical ingredient together with the compendial excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate and hydrophobic colloidal silica), and (b) (4) film coat.

The 30 mg tablets are round and debossed with "U3" on one side; the 90 mg tablets are oval shaped and debossed with "U7" on one side. 30 mg tablets are supplied in 60 ml HDPE bottles (with 1 g desiccant in each) of 21-count presentation and 180-count presentation respectively. 60 mg tablets are supplied in 60 ml HDPE bottles of 7-count presentation and 30-count presentation respectively.

The two dosage strengths (b) (4)

(b) (4)

Two drug product manufacturers selected for commercial manufacture of ALUNBRIG (brigatinib) tablets, (b) (4) Penn Pharmaceuticals, were involved in optimization and validation for formulation and manufacturing process. These two manufacturers use similar equipment and comparable process parameters. Bridging between these two sites in conjunction with two drug substance sites is accomplished through comparison of batches and through the use of both drug substance manufacturers for registration batches. The bridging studies for drug substance manufacturing sites and drug product manufacturing sites also include dissolution studies of the drug product batches manufactured at these sites. The comparable dissolution study results support the comparability establishment of the proposed two drug substance suppliers (b) (4) and two drug product manufacturers ((b) (4) Penn).

For initial commercialization purposes, the 30 mg strength will be manufactured at (b) (4) (b) (4) Both strengths shall be manufactured at Penn Pharmaceuticals in UK.

The applicant submitted the stability data from three primary stability batches (30 mg tablets, at scale of (b) (4)) manufactured at (b) (4) site, up to 18 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. The applicant also

provided the stability data from three primary stability batches for 30 mg tablets (at scale of (b) (4) (b) (4) and three primary stability batches for 90 mg tablets (at scale of (b) (4)) manufactured at Penn site, up to 12 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the 30 mg ALUNBRIG (brigatinib) tablets and 18 months shelf-life for the 90 mg ALUNBRIG (brigatinib) tablets when packaged in the commercial container closure configuration of 60 cc HDPE bottles with desiccant (1g), utilizing any tablet fill count between the bracketed extremes in the stability protocols (30 mg tablets: 14 count through 180 count; 90 mg tablets: 7 count through 60 count). The storage condition supported by the stability protocol is, "USP controlled room temperature, 20°C-25°C (68°F-77°F) with excursions between 15°C-30°C (59°F-86°F)". The submitted photostability study results on the primary batches indicate that the drug product does not require protection from light.

The applicant accepted the Agency's recommended acceptance criterion as "NLT (b) (4)% (Q) in 20 minutes" for the dissolution test in the drug product specifications, as the initially proposed "NLT (b) (4)% (Q) in (b) (4) minutes" is not sufficiently discriminating to assess the relevant quality of the product.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug product manufacturers (for manufacture, release and stability testing, packaging and labeling) and one testing site (for microbial limits testing) as listed below, either based on Profile or based on District Recommendation by Pre-Approval Inspection.

- Penn Pharmaceutical Services (FEI No. 1000370240) in Gwent, UK
- (b) (4)
-

Methods verification was performed by Division of Pharmaceutical Analysis (DPA) in St. Louis under Office of Testing and Research (OTR)/OPQ/CDER/FDA. All the following verified methods for Brigatinib tablets 90mg are acceptable for quality control and regulatory purposes; refer to the Methods Verification Report by DPA dated January 4, 2017 in Panorama. Although the completion of Methods verification is not required for approval of the NDA.

- Analytical Procedures for Assay and Impurities of Drug Substance by HPLC - 3.2. S.4.2. ((b) (4) page 5-13).
- Analytical Procedures-Penn: Identification, Assay and Degradants for Brigatinib tablets 90 mg by RP-HPLC - 3.2. P.5.2.3. (Penn: Page 5-13).
- Analytical Procedures-Penn: Dissolution for Brigatinib tablets 90mg - 3.2. P.5.2.5. (Penn, Page 18-23).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

See Attachment - Final Risk Assessment for ALUNBRIG (brigatinib) tablets (v.2)

Quality Assessment

Purpose

A. This review is to summarize the Amendment 0035 (37) submitted to NDA 208-772 dated 02-Feb-2017, which contains Module 2 update for Quality Overall Summary and Module 3 (P.8.3) update to reflect the stability data collected based on the revised dissolution acceptance criteria of NLT (b)(4)% at 20 minutes. This revision was requested by the biopharmaceutics review team to ensure the dissolution method is discriminating for quality of the drug product. The related sections in 3.2.P.5.2 (Penn), 3.2.P.5.4 (Penn), 3,2, P.5.6 (Penn), 3.2.P.8.1 (Penn) and 3.2.P.8.1 ((b)(4)) for the revised dissolution specification with acceptance criterion of Q= (b)(4)% at 20 minutes have already been updated in the Amendment 0034 (33) dated 27-Jan-2017 as the response to FDA Information Request of 24-Jan-2017. In the updated dissolution data collected at 20 mins through the stability study as formally submitted to Module 3 (P.8.3) in Amendment 0035 (37), none of the registration batches (in both strengths of 30 mg and 90 mg) manufactured from both facilities (Penn (b)(4)) has any Out of Specifications observed or showed any trend at 30°C/75%. There is a lot (#010604 from Penn, which is not a registration batch in 30 mg strength) has (b)(4)% dissolved at 20 minutes at 12 month time point at 30°C/75%, the total stability data of this lot does not show a trend though. Those data have been submitted to the Regional Section prior to this amendment and been evaluated by the review team. This particular data point for Lot # 010604 could be scatter in the data as the acceptance criteria is pushed toward a more discriminating time point (20 minutes vs (b)(4) minutes). Therefore further monitoring the dissolution stability trend is highly recommended post approval to further evaluate the dissolution acceptance criterion and the granted shelf life. Based on the updated quality information included in this amendment, the approval recommendation and shelf life recommendations for ALUNBRIG (brigatinib) tablets (as 24 month for 30 mg strength and 18 month for 90 mg strength at controlled room temperature) filed in the original OPQ IQA still stand. For detailed contents, refer to the enclosed documents entitled *"CMC Memo to File"* by drug product reviewer Dr. Olen Stephens dated 10-Feb-2017 and *"Biopharmceutics Review Notes"* by Dr. Joan Zhao dated 09-Feb-2017 in the next four pages.

B. This review is to correct the typo in the page footer of the previous review documents entitled *"NDA 208772 000 IQA Cover Letter Quality data Review Sheet Executive Summary 28-Jan-2017"* and *"NDA 208772 Alundrig –IQA 31-Jan-2017"* filed in Panorama on 29-Jan-2017 and 31-Jan-2017 respectively. The page footer on right should be read as "Executive Summary & ATL Review - NDA 208-772 Quality Review # 1" for the first nine pages, not "Executive Summary & ATL Review - NDA 208-722 Quality Review # 1".

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CMC Memo to File

Date	10-Feb-17
Applicant:	Ariad
Drug:	Alunbrig™ (brigatinib) tablets, 30 mg and 90 mg
Subject	Amendment review and close-out memo
Reviewer	Olen Stephens, Ph.D.

Amendment 0035 to NDA 208772, submitted to the FDA 2-Feb-17, provides the formal submission of updated stability data to module 3.2.P.8.3 to reflect the revised dissolution acceptance criteria of NLT (b) (4)% at 20 minutes. This revision was negotiated with the biopharmaceutics review team to ensure the dissolution method is discriminating for quality of the drug product. Additionally, the quality overall summary in Module 2 was updated to reflect this change in dissolution acceptance criteria as well as to incorporate drug product lots 011700 and 011701, which were manufactured using drug substance lots (b) (4). These additional lots strengthen bridging of the two drug substance suppliers. These data were reviewed in the OPQ IQA review filed in Panorama and do not change the recommendation by the review team. The stability data demonstrates that the dissolution acceptance criteria is met for all time point on all batches under both long term and accelerated stability conditions. Due to the earlier time point (20 minutes relative to the (b) (4) minutes) there is more variability in the dissolution stability data, which is to be expected. Only one batch (lot 10604 manufactured by Penn) under long term stability conditions (30 degrees C/75% RH) approached the specification limit at a single time point. This data point was (b) (4)% dissolved at the 12 month time point. In aggregate, there was no trend to change the shelf life recommendation in the original IQA review. Also not that this long-term stability data is collected under more rigorous conditions (30°C/75%) compared to the proposed commercial storage conditions of controlled room temperature. Finally, the difference in dissolution at (b) (4) minutes relative to 20 minutes is unlikely to have a meaningful clinical impact; the 20 minute time point was selected to identify manufacturing issues that would be detected upon release.

Conclusion: The approval recommendation and shelf life recommendations filed in the original OPQ IQA stand as written.

Olen Stephens, Ph.D.
Chemistry Acting Branch Chief, ONDP

Anamitro Banerjee, Ph.D.
Chemistry Acting Branch Chief, ONDP

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 2017.12:20:47PM
GUID: 5a757b4700003844b7bc89632228509f

Olen Stephens

Digitally signed by Olen Stephens
Date: 2017 11:55:36AM
GUID: 5a8b571e00029e680c3cf42984dfa0ee

Recommendation: Approval from the CMC prospective

NDA 208-772
Review #1

Drug Name/Dosage Form	ALUNBRIG (brigatinib) / Tablet
Strength	30 mg and 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ARIAD Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
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2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
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II. Summary of Quality Assessments

A. Product Overview

NDA 208-772 was received on August 29, 2016 in the 505b(1) regulatory pathway with FDA breakthrough and FDA orphan drug designations which was granted in October 2014. NDA 208-772 cross references IND 110935 for developmental data on the ALUNBRIG (brigatinib) tablets in the strengths of 30 and 90 mg. Brigatinib is an orally-active tyrosine kinase inhibitor (TKI) that primarily targets activated, mutant forms of ALK and c-ros oncogene 1 (ROS 1), which play roles in NSCLC. ALUNBRIG (brigatinib) tablets are indicated for the treatment of patients with (b) (4) metastatic anaplastic lymphoma kinase positive (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Proposed Indication(s) including Intended Patient Population	For the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Duration of Treatment	90 mg orally once daily for 7 days, followed by 180 mg once daily (continuously). Dose modifications to 60 mg once daily are permitted for management of adverse reactions.
Maximum Daily Dose	180 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

1. Drug Substance [Brigatinib]

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

International Non-proprietary Name (INN): brigatinib

Name (IUPAC): 5-chloro-*N4*-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4 [4-(4-methylpiperazin-1-yl) piperidin-1-yl]phenyl}pyrimidine-2,4-diamine

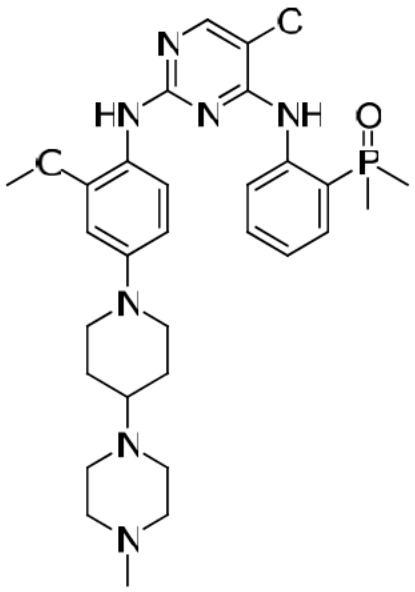
Name (CAS): 2, 4-pyrimidinediamine, 5-chl*oro*-*N4*-[2-(dimethylphosphinyl)phenyl]-N2-[2-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]-

(CAS) Registry Number: 1197953-54-0

Mol. Formula: $C_{29}H_{39}ClN_7O_2P$

Mol. Wt.: 584.10 g/mole

Structural Formula:



Brigatinib is an achiral small molecule in off-white to beige/tan solid. (b) (4)

Brigatinib is considered as BCS Class 1 and is highly soluble from pH 1.5 to pH 6.5. However,

drug product ALUNBRIG (brigatinib) tablets is not considered BCS Class 1 because it does not rapidly dissolve to meet the classification.

Brigatinib is manufactured by a proposed commercial process (referred to as "Process B2")

(b) (4)

There are two manufacturers proposed for the commercial production of brigatinib drug substance: (b) (4) There are slight minor differences in manufacturing equipment, operations, and analytical instrumentation between the two proposed DS manufacturing sites that have been well validated. The provided batch release data and stability data of four registration batches from (b) (4) and three registration batches from (b) (4) demonstrated these two sites are comparable and all batch results well conform to the proposed standard release specifications per ICH guidelines for drug substance to be used in a solid oral dosage form.

Drug substance stability studies demonstrated that brigatinib is physicochemically stable under both long term 25°C/60%RH (18-month data from (b) (4) batches and 12- month data from (b) (4) batches) and accelerated 40°C/75%RH (6-month data from all batches) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that brigatinib is not light sensitive. Forced degradation study has established that the HPLC method for assay and purity is stability indicating. The proposed retest date of (b) (4) stored (b) (4) is acceptable, and in the proposed container closure (b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) and other testing sites (for stability on XRPD, and microbial enumeration). These accepted facilities as listed below are either based on Profile or based on Pre-Approval Inspection.

- (b) (4)
-
-
-
-
-
-

2. Drug Product [ALUNBRIG (brigatinib) tablets]

ALUNBRIG (brigatinib) tablets are available for oral administration in 30 mg and 90 mg dosage strengths. They are off-white, debossed, and film-coated for immediate release. The tablets contain brigatinib as the active pharmaceutical ingredient together with the compendial excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate and hydrophobic colloidal silica), and (b) (4) film coat.

The 30 mg tablets are round and debossed with "U3" on one side; the 90 mg tablets are oval shaped and debossed with "U7" on one side. 30 mg tablets are supplied in 60 ml HDPE bottles (with 1 g desiccant in each) of 21-count presentation and 180-count presentation respectively. 60 mg tablets are supplied in 60 ml HDPE bottles of 7-count presentation and 30-count presentation respectively.

The two dosage strengths (b) (4)

(b) (4)

Two drug product manufacturers selected for commercial manufacture of ALUNBRIG (brigatinib) tablets, (b) (4) Penn Pharmaceuticals, were involved in optimization and validation for formulation and manufacturing process. These two manufacturers use similar equipment and comparable process parameters. Bridging between these two sites in conjunction with two drug substance sites is accomplished through comparison of batches and through the use of both drug substance manufacturers for registration batches. The bridging studies for drug substance manufacturing sites and drug product manufacturing sites also include dissolution studies of the drug product batches manufactured at these sites. The comparable dissolution study results support the comparability establishment of the proposed two drug substance suppliers ((b) (4)) and two drug product manufacturers ((b) (4) Penn).

For initial commercialization purposes, the 30 mg strength will be manufactured at (b) (4) . Both strengths shall be manufactured at Penn Pharmaceuticals in UK.

The applicant submitted the stability data from three primary stability batches (30 mg tablets, at scale of (b) (4)) manufactured at (b) (4) site, up to 18 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. The applicant also

provided the stability data from three primary stability batches for 30 mg tablets (at scale of (b) (4) and three primary stability batches for 90 mg tablets (at scale of (b) (4)) manufactured at Penn site, up to 12 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the 30 mg ALUNBRIG (brigatinib) tablets and 18 months shelf-life for the 90 mg ALUNBRIG (brigatinib) tablets when packaged in the commercial container closure configuration of 60 cc HDPE bottles with desiccant (1g), utilizing any tablet fill count between the bracketed extremes in the stability protocols (30 mg tablets: 14 count through 180 count; 90 mg tablets: 7 count through 60 count). The storage condition supported by the stability protocol is, "USP controlled room temperature, 20°C-25°C (68°F-77°F) with excursions between 15°C-30°C (59°F-86°F)". The submitted photostability study results on the primary batches indicate that the drug product does not require protection from light.

The applicant accepted the Agency's recommended acceptance criterion as "NLT (b) (4)% (Q) in 20 minutes" for the dissolution test in the drug product specifications, as the initially proposed "NLT (b) (4)% (Q) in (b) (4) minutes" is not sufficiently discriminating to assess the relevant quality of the product.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug product manufacturers (for manufacture, release and stability testing, packaging and labeling) and one testing site (for microbial limits testing) as listed below, either based on Profile or based on District Recommendation by Pre-Approval Inspection.

- Penn Pharmaceutical Services (FEI No. 1000370240) in Gwent, UK
- (b) (4)
-

Methods verification was performed by Division of Pharmaceutical Analysis (DPA) in St. Louis under Office of Testing and Research (OTR)/OPQ/CDER/FDA. All the following verified methods for Brigatinib tablets 90mg are acceptable for quality control and regulatory purposes; refer to the Methods Verification Report by DPA dated January 4, 2017 in Panorama. Although the completion of Methods verification is not required for approval of the NDA.

- Analytical Procedures for Assay and Impurities of Drug Substance by HPLC - 3.2. S.4.2. ((b) (4), page 5-13).
- Analytical Procedures-Penn: Identification, Assay and Degradants for Brigatinib tablets 90 mg by RP-HPLC - 3.2. P.5.2.3. (Penn: Page 5-13).
- Analytical Procedures-Penn: Dissolution for Brigatinib tablets 90mg - 3.2. P.5.2.5. (Penn, Page 18-23).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

See Attachment

Memorandum to NDA 208772 Alunbrig-IQA 31-Jan-2017

Purpose

A. This memo is to summarize the Amendment 0035 (37) submitted to NDA 208-772 dated 02-Feb-2017, which contains Module 2 update for Quality Overall Summary and Module 3 (P.8.3) update to reflect the stability data collected based on the revised dissolution acceptance criteria of NLT (b)(4)% at 20 minutes. This revision was requested by the biopharmaceutics review team to ensure the dissolution method is discriminating for quality of the drug product. The related sections in 3.2.P.5.2 (Penn), 3.2.P.5.4 (Penn), 3.2, P.5.6 (Penn), 3.2.P.8.1 (Penn) and 3.2.P.8.1 ((b)(4)) for the revised dissolution specification with acceptance criterion of Q=(b)(4)% at 20 minutes have already been updated in the Amendment 0034 (33) dated 27-Jan-2017 as the response to FDA Information Request of 24-Jan-2017. In the updated dissolution data collected at 20 mins through the stability study as formally submitted to Module 3 (P.8.3) in Amendment 0035 (37), none of the registration batches (in both strengths of 30 mg and 90 mg) manufactured from both facilities (Penn (b)(4)) has any Out of Specifications observed or showed any trend at 30°C/75%. There is a lot (#010604 from Penn, which is not a registration batch in 30 mg strength) has (b)(4)% dissolved at 20 minutes at 12 month time point at 30°C/75%, the total stability data of this lot does not show a trend though. Those data have been submitted to the Regional Section prior to this amendment and been evaluated by the review team. This particular data point for Lot # 010604 could be scatter in the data as the acceptance criteria is pushed toward a more discriminating time point (20 minutes vs (b)(4) minutes). Therefore further monitoring the dissolution stability trend is highly recommended post approval to further evaluate the dissolution acceptance criterion and the granted shelf life. Based on the updated quality information included in this amendment, the approval recommendation and shelf life recommendations for ALUNBRIG (brigatinib) tablets (as 24 month for 30 mg strength and 18 month for 90 mg strength at controlled room temperature) filed in the original OPQ IQA still stand. For detailed contents, refer to the enclosed documents entitled *"CMC Memo to File"* by drug product reviewer Dr. Olen Stephens dated 10-Feb-2017 and *"Biopharmceutics Review Notes"* by Dr. Joan Zhao dated 09-Feb-2017 in the next four pages.

B. This memo updates the Final Risk Assessment for ALUNBRIG (brigatinib) tablets with additional comments for lifecycle considerations regarding to the dissolution test and its revised acceptance criterion. Refer to Attachment: Final Risk Assessment (v2) included in this memo.

C. This review is to correct the typo in the page footer of the previous review documents entitled *"NDA 208772 000 IQA Cover Letter Quality data Review Sheet Executive Summary 28-Jan-2017"* and *"NDA 208772 Alundrig –IQA 31-Jan-2017"* filed in Panorama on 29-Jan-2017 and 31-Jan-2017 respectively. The page footer on right should be read as "Executive Summary & ATL Review - NDA 208-772 Quality Review # 1" for the first nine pages, not "Executive Summary & ATL Review - NDA 208-722 Quality Review # 1".

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CMC Memo to File

Date	10-Feb-17
Applicant:	Ariad
Drug:	Alunbrig™ (brigatinib) tablets, 30 mg and 90 mg
Subject	Amendment review and close-out memo
Reviewer	Olen Stephens, Ph.D.

Amendment 0035 to NDA 208772, submitted to the FDA 2-Feb-17, provides the formal submission of updated stability data to module 3.2.P.8.3 to reflect the revised dissolution acceptance criteria of NLT (b) (4)% at 20 minutes. This revision was negotiated with the biopharmaceutics review team to ensure the dissolution method is discriminating for quality of the drug product. Additionally, the quality overall summary in Module 2 was updated to reflect this change in dissolution acceptance criteria as well as to incorporate drug product lots 011700 and 011701, which were manufactured using drug substance lots (b) (4) These additional lots strengthen bridging of the two drug substance suppliers. These data were reviewed in the OPQ IQA review filed in Panorama and do not change the recommendation by the review team. The stability data demonstrates that the dissolution acceptance criteria is met for all time point on all batches under both long term and accelerated stability conditions. Due to the earlier time point (20 minutes relative to the (b) (4) minutes) there is more variability in the dissolution stability data, which is to be expected. Only one batch (lot 10604 manufactured by Penn) under long term stability conditions (30 degrees C/75% RH) approached the specification limit at a single time point. This data point was (b) (4)% dissolved at the 12 month time point. In aggregate, there was no trend to change the shelf life recommendation in the original IQA review. Also not that this long-term stability data is collected under more rigorous conditions (30^{O}C/75%) compared to the proposed commercial storage conditions of controlled room temperature. Finally, the difference in dissolution at (b) (4) minutes relative to 20 minutes is unlikely to have a meaningful clinical impact; the 20 minute time point was selected to identify manufacturing issues that would be detected upon release.

Conclusion: The approval recommendation and shelf life recommendations filed in the original OPQ IQA stand as written.

_____
Olen Stephens, Ph.D.
Chemistry Acting Branch Chief, ONDP

_____
Anamitro Banerjee, Ph.D.
Chemistry Acting Branch Chief, ONDP

Anamitro Banerjee

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Date: 2017.12 20:47PM
GUID: 5075764700003844b7bc89632228509f

Olen Stephens

Digitally signed by Olen Stephens
Date: 2017.11 55:36AM
GUID: 588da71e00029e680c3cf42984dfa0ee

BIOPHARMACEUTICS REVIEW NOTES ON AMENDMENT TO NDA 208772 – SDN 0037 2/2/2017

Preamble

After completion of the Biopharmaceutics review, the Applicant submitted an amendment to the Application on 2/2/2017. The amendment contains dissolution data on batch # 010604, which show that at 12 months, the mean dissolution at 20 min was (b)(4)% under 30°C/75% RH storage conditions; this indicates that the batch may go to S2 testing or S3 testing. The ATL has requested that the Division of Biopharmaceutics re-evaluate the data to determine if the results are likely to affect the 24-month shelf life of the 30 mg drug product.

Data submitted in the amendment

ARIAD Pharmaceuticals, Inc.

(b) (4)

[redacted]

Biopharmaceutics Assessment

It is noted that the storage conditions, 30°C/75% RH, are more stressed than the long term and intermediate storage conditions. Since the drug product will be stored at ambient temperature and humidity conditions (25°C/60% RH), there is no concern from a Biopharmaceutics perspective; the recommended dissolution acceptance criterion of "Q = (b)(4)% in 20 min" is therefore adequate for quality control and stability assessment of Brigatinib Tablets.

Joan Zhao, PhD 2/9/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP/OPQ

Okpo Eradiri, PhD 2/9/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP/OPQ

Zhuojun Zhao

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Date: 2017/2017 05:22:59PM
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Okponanabofa Eradiri

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Attachment - Final Risk Assessment for ALUNBRIG (brigatinib) tablets (v.2)

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 (with 1 g desiccant)	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 (with 1 g desiccant)	Acceptable	Controls are in place Continue stability monitoring post approval
API Physical Attributes	• Compressibility • Flowability • Segregation	Medium	Formulation development demonstrated low impact of physical properties with current formulation	Acceptable	If drug load increases, evaluate the impact of API's physical properties on drug product manufacturability.
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Assessed during development and controlled via specifications	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, and further evaluate the revised dissolution acceptance criterion (from Q (b)(4)% at (b)(4) mins to Q (b)(4)% at 20 mins)
Moisture Content	• Raw materials • Process parameters • Scale/equipment • Formulation • Container closure • Site	Medium	Assessed during development and controlled via specifications and container closure (with 1 g desiccant)	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 in manufacturing process and storage	Acceptable	Controls are in place

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

This application is recommended for APPROVAL from the CMC perspective.

Joyce Crich, Ph.D.

February 11, 2017

Joyce Crich -S

Digitally signed by Joyce Crich -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Crich -S, 0.9.2342.19200300.100.1.1=2000587292
Date: 2017.02.13 10:05:27 -05'00'

Recommendation: Approval from the CMC prospective

NDA 208-772
Review #1

Drug Name/Dosage Form	ALUNBRIG (brigatinib) / Tablet
Strength	30 mg and 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ARIAD Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA- 0002 (2)	*07-28-2016*	*Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics, and Microbiology*
Amendment – 0004 (4), quality response to IR	*08/09/2016*	*Drug Product*
Amendment – 0009 (9), quality information 30day additional stability data	*09/27/2016*	*Drug Substance, Drug Product, Biopharmaceutics, Microbiology*
Amendment – 0010 (10), quality response to IR dated 9/29/2016	*09/30/2016*	*Drug Substance*
Amendment – 0017 (17), quality response to IR dated 11/04/2016	*11/18/2016*	*Drug Product*
Amendment – 0020 (20), quality response to IR dated 11/09/2016	*11/22/2016*	*Drug Product*
Amendment – 0022 (22), quality response to IR dated 11/29/2016	*12/13/2016*	*Drug Substance, Drug Product, Process, Biopharmaceutics*
Amendment – 0023 (23), quality response to IR dated 12/08/2016	*12/14/2016*	*Drug Product*
Amendment – 0027 (27), quality response to IR dated 12/16/2016 & 03/01/2017	*01/05/2017*	*Drug Product, Biopharmaceutics, Process*
Amendment – 0031 (31), quality response to IR dated 01/17/2017,	*01/25/2017*	*Drug Substance*
Amendment – 0033 (32), quality response to IR dated 01/24/2017, update for Module 3 (S.7.3, P.2, & P.7)	*01/26/2017*	*Drug Substance; Drug Product, Biopharmaceutics*
Amendment – 0033 (33), quality update for Module 3 (P.5 & P.8)	*01/27/2017*	*Drug Product, Biopharmaceutics*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor	OPQ/ONDP/DNDPAPI/BI
Drug Product	Olen Stephens	OPQ/ONDP/DNDPI/BII
Process	Ying Zhang	OPQ/OPF/DPAI/BII
Microbiology	Ying Zhang	OPQ/OPF/DPAI/BII
Facility	Thuy Nguyen/Ruth Moore	OPQ/OPF/DIA/BI
Biopharmaceutics	Joan Zhao/Okpo Eradiri	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Joyce Crich	OPQ/ONDP/DNDPI/BII
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	Olen Stephens	OPQ/ONDP/DNDPI/BII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	Adequate	09/29/2010	DMF active; reviewed by Dr. Danuta Gromek-Woods
	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 II			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

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

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION
IND	110935	ARIAD Pharmaceuticals, Inc.	Brigatinib (AP26113)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/ Toxicology	Complete	Approval	01/25/2017	M Anwar Goheer, Ph.D and Emily Wearne, Ph.D
Methods Verification *	Complete	Acceptable	01/04/2017	David Keire, Ph.D
DMEPA **	Complete with comments for container labels, carton labeling and PI	the proposed proprietary name, Alunbrig, is acceptable	09/06/2016 & 01/06/2017	Janine Stewart, PharmD

*Methods Verification was performed by Division of Pharmaceutical Analysis (DPA) in St. Louis under Office of Testing and Research (OTR)/OPQ/CDER/FDA. See Panorama for the Methods Verification Report Summary.
**DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary

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.

Include the following language in the approval letter:
Based on the provided stability data, a 24-month expiration dating period is granted for 30 mg ALUNBRIG (brigatinib) tablets, and a 18-month expiration dating period is granted for 90 mg ALUNBRIG (brigatinib) tablets, from the date of manufacture of the tablets in the proposed commercial container closure systems when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).

II. Summary of Quality Assessments

A. Product Overview

NDA 208-772 was received on August 29, 2016 in the 505b(1) regulatory pathway with FDA breakthrough and FDA orphan drug designations which was granted in October 2014. NDA 208-772 cross references IND 110935 for developmental data on the ALUNBRIG (brigatinib) tablets in the strengths of 30 and 90 mg. Brigatinib is an orally-active tyrosine kinase inhibitor (TKI) that primarily targets activated, mutant forms of ALK and c-ros oncogene 1 (ROS 1), which play roles in NSCLC. ALUNBRIG (brigatinib) tablets are indicated for the treatment of patients with (b) (4) metastatic anaplastic lymphoma kinase positive (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Proposed Indication(s) including Intended Patient Population	For the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Duration of Treatment	90 mg orally once daily for 7 days, followed by 180 mg once daily (continuously). Dose modifications to 60 mg once daily are permitted for management of adverse reactions.
Maximum Daily Dose	180 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

1. Drug Substance [Brigatinib]

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

International Non-proprietary Name (INN): brigatinib

Name (IUPAC): 5-chloro-*N4*-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4 [4-(4-methylpiperazin-1-yl) piperidin-1-yl]phenyl}pyrimidine-2,4-diamine

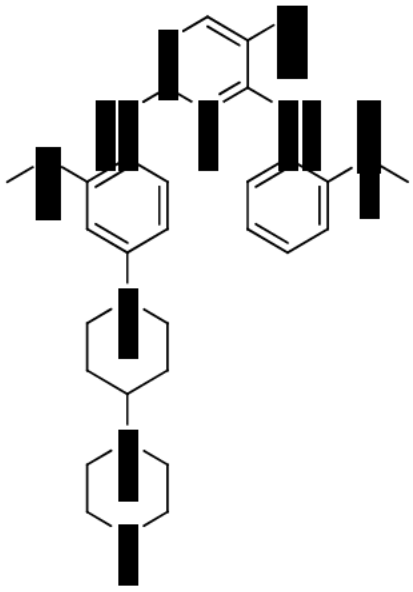
Name (CAS): 2, 4-pyrimidinediamine, 5-chl*oro*-*N4*-[2-(dimethylphosphinyl)phenyl]-N2-[2-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]-

(CAS) Registry Number: 1197953-54-0

Mol. Formula: $C_{29}H_{39}ClN_7O_2P$

Mol. Wt.: 584.10 g/mole

Structural Formula:



Brigatinib is an achiral small molecule in off-white to beige/tan solid. (b) (4)

Brigatinib is considered as BCS Class 1 and is highly soluble from pH 1.5 to pH 6.5. However,

drug product ALUNBRIG (brigatinib) tablets is not considered BCS Class 1 because it does not rapidly dissolve to meet the classification.

Brigatinib is manufactured by a proposed commercial process (referred to as "Process B2")

(b) (4)

There are two manufacturers proposed for the commercial production of brigatinib drug substance: (b) (4)
There are slight minor differences in manufacturing equipment, operations, and analytical instrumentation between the two proposed DS manufacturing sites that have been well validated. The provided batch release data and stability data of four registration batches from (b) (4) and three registration batches from (b) (4) demonstrated these two sites are comparable and all batch results well conform to the proposed standard release specifications per ICH guidelines for drug substance to be used in a solid oral dosage form.

Drug substance stability studies demonstrated that brigatinib is physicochemically stable under both long term 25°C/60%RH (18-month data from (b) (4) batches and 12- month data from (b) (4) batches) and accelerated 40°C/75%RH (6-month data from all batches) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that brigatinib is not light sensitive. Forced degradation study has established that the HPLC method for assay and purity is stability indicating. The proposed retest date of (b) (4) stored (b) (4) is acceptable, and in the proposed container closure (b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) and other testing sites (for stability on XRPD, and microbial enumeration). These accepted facilities as listed below are either based on Profile or based on Pre-Approval Inspection.

- (b) (4)
-
-
-
-
-
-

2. Drug Product [ALUNBRIG (brigatinib) tablets]

ALUNBRIG (brigatinib) tablets are available for oral administration in 30 mg and 90 mg dosage strengths. They are off-white, debossed, and film-coated for immediate release. The tablets contain brigatinib as the active pharmaceutical ingredient together with the compendial excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate and hydrophobic colloidal silica), and (b) (4) film coat.

The 30 mg tablets are round and debossed with "U3" on one side; the 90 mg tablets are oval shaped and debossed with "U7" on one side. 30 mg tablets are supplied in 60 ml HDPE bottles (with 1 g desiccant in each) of 21-count presentation and 180-count presentation respectively. 60 mg tablets are supplied in 60 ml HDPE bottles of 7-count presentation and 30-count presentation respectively.

The two dosage strengths (b) (4)

(b) (4)

Two drug product manufacturers selected for commercial manufacture of ALUNBRIG (brigatinib) tablets, (b) (4) Penn Pharmaceuticals, were involved in optimization and validation for formulation and manufacturing process. These two manufacturers use similar equipment and comparable process parameters. Bridging between these two sites in conjunction with two drug substance sites is accomplished through comparison of batches and through the use of both drug substance manufacturers for registration batches. The bridging studies for drug substance manufacturing sites and drug product manufacturing sites also include dissolution studies of the drug product batches manufactured at these sites. The comparable dissolution study results support the comparability establishment of the proposed two drug substance suppliers ((b) (4)) and two drug product manufacturers ((b) (4) Penn).

For initial commercialization purposes, the 30 mg strength will be manufactured at (b) (4) . Both strengths shall be manufactured at Penn Pharmaceuticals in UK.

The applicant submitted the stability data from three primary stability batches (30 mg tablets, at scale of (b) (4)) manufactured at (b) (4) site, up to 18 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. The applicant also

provided the stability data from three primary stability batches for 30 mg tablets (at scale of (b) (4) and three primary stability batches for 90 mg tablets (at scale of (b) (4)) manufactured at Penn site, up to 12 months at 30°C/65% RH and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the 30 mg ALUNBRIG (brigatinib) tablets and 18 months shelf-life for the 90 mg ALUNBRIG (brigatinib) tablets when packaged in the commercial container closure configuration of 60 cc HDPE bottles with desiccant (1g), utilizing any tablet fill count between the bracketed extremes in the stability protocols (30 mg tablets: 14 count through 180 count; 90 mg tablets: 7 count through 60 count). The storage condition supported by the stability protocol is, "USP controlled room temperature, 20°C-25°C (68°F-77°F) with excursions between 15°C-30°C (59°F-86°F)". The submitted photostability study results on the primary batches indicate that the drug product does not require protection from light.

The applicant accepted the Agency's recommended acceptance criterion as "NLT (b) (4)% (Q) in 20 minutes" for the dissolution test in the drug product specifications, as the initially proposed "NLT (b) (4)% (Q) in (b) (4) minutes" is not sufficiently discriminating to assess the relevant quality of the product.

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for both drug product manufacturers (for manufacture, release and stability testing, packaging and labeling) and one testing site (for microbial limits testing) as listed below, either based on Profile or based on District Recommendation by Pre-Approval Inspection.

- Penn Pharmaceutical Services (FEI No. 1000370240) in Gwent, UK
- (b) (4)
-

Methods verification was performed by Division of Pharmaceutical Analysis (DPA) in St. Louis under Office of Testing and Research (OTR)/OPQ/CDER/FDA. All the following verified methods for Brigatinib tablets 90mg are acceptable for quality control and regulatory purposes; refer to the Methods Verification Report by DPA dated January 4, 2017 in Panorama. Although the completion of Methods verification is not required for approval of the NDA.

- Analytical Procedures for Assay and Impurities of Drug Substance by HPLC - 3.2. S.4.2. ((b) (4) page 5-13).
- Analytical Procedures-Penn: Identification, Assay and Degradants for Brigatinib tablets 90 mg by RP-HPLC - 3.2. P.5.2.3. (Penn: Page 5-13).
- Analytical Procedures-Penn: Dissolution for Brigatinib tablets 90mg - 3.2. P.5.2.5. (Penn, Page 18-23).

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

See Attachment

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LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Immediate Container Label

Reviewer's Assessment: The original bottle labels did not include a lot number or expiry date, but have placeholders "XXXXXX". The applicant was asked to confirm that this space will be used for lot numbers and expiry dates.

The original labels included (b) (4) whereas most labels use barcodes for quick scanning. 21 CFR 201.25 specifically requires bar codes (b) (4)

In amendment 0018 (19) submitted 18-Nov-16, the applicant submitted revised labels that replace the (b) (4) with "For Position Only" (FPO) linear bar codes containing a 14-digit

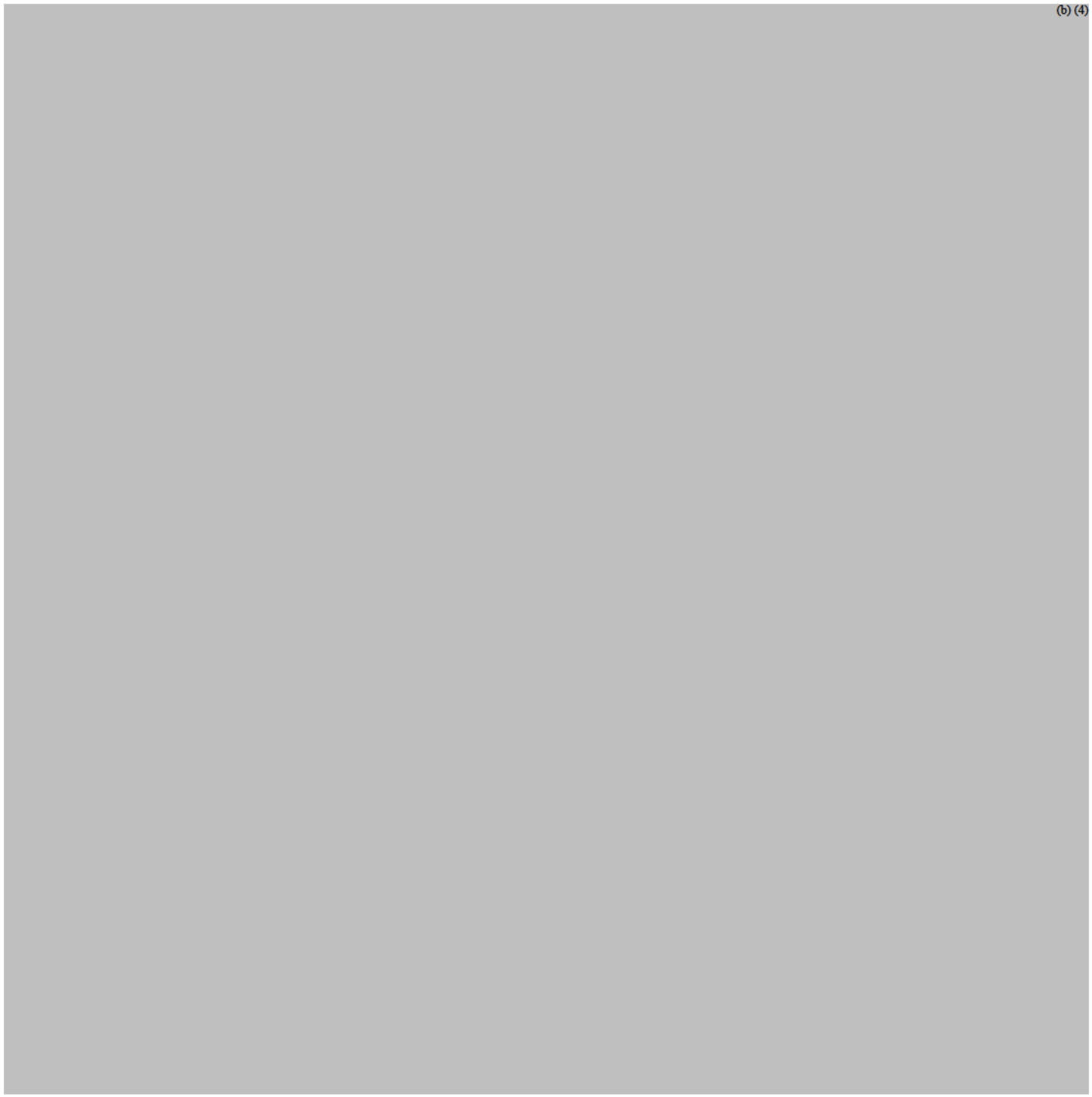
Global Trade Item Number (GTIN). The labels also stipulate area for the lot number and expiry date.

The sponsor also reiterated that (b) (4) as it was originally submitted to the NDA. Only labels with the intended manufacturing and labeling permutations were submitted for review in amendment 0018.

Supportive stability data lacking the 1 g desiccant was submitted to allow pharmacists to distribute the tablets in standard pharmacy bottles without the desiccant for patients that require dose reductions and would not use full bottles of brigatinib in the available count configurations. For that reason, statements in the package insert to, (b) (4) may be removed to avoid complications in the pharmacy.

Carton Labeling

(b) (4)



(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate.***

List of Deficiencies: None; all issues have been addressed

Primary Labeling Reviewer Name and Date: Olen M. Stephens, PhD; 27-Jan-17

Secondary Reviewer Name and Date: Anamitro Banerjee, PhD; 27-Jan-17

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 1/28/2017 03:27:29PM
GUID: 5075764700003844b7bc89632228509f

Olen Stephens

Digitally signed by Olen Stephens
Date: 1/28/2017 02:12:19PM
GUID: 508da71e00029e680c3cf42984dfa0ee

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BIOPHARMACEUTICS

Product Background:

NDA: 208772

Drug Product Name / Strength: ALUNBRIG (Brigatinib) Tablets/30 and 90 mg

Route of Administration: Oral

Applicant Name: ARIAD Pharmaceuticals, Inc.

Review Summary:

The drug substance brigatinib (a new molecular entity), is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Brigatinib exhibits pH dependent solubility; however, the highest strength of the proposed drug product (90 mg) is highly soluble across the physiologic pH range. ALUNBRIG is formulated as an immediate release tablet to rapidly dissolve in gastric fluid.

This review evaluates the proposed dissolution method and acceptance criterion, and the need for bridging.

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

Method	Using USP Apparatus II (Paddle) in 900 mL 0.01 N 50 mM Potassium Phosphate Buffer, pH 7.2 at 70 rpm
Acceptance Criterion	NLT (b)(4)% (Q) in 20 minutes

The Applicant provided comparable dissolution data to support the proposed two drug substance suppliers ((b)(4)) and two drug product manufacturers ((b)(4) Penn). The bridging studies of drug substance manufacturing sites and drug product manufacturing sites are acceptable.

From the Biopharmaceutics perspective, NDA 208772 for Brigatinib tablets, 30 and 90 mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Rolling Submission (Regional/Administrative Information)	06/16/2016
Rolling Submission (CMC portion)	07/28/2016
Rolling Submission (Summary of Biopharmaceutics Studies)	08/29/2016
IR Response (Bridging information for drug substance sites)	12/13/2016
IR Response (Dissolution Acceptance Criterion)	01/05/2017
IR Response (Dissolution Acceptance Criterion)	01/26/2017

Highlight Key Outstanding Issues from Last Cycle: N/A; this is the first review cycle.

Concise Description Outstanding Issues: None

BCS Designation

Reviewer's Assessment: The Sponsor did not submit a BCS classification request as the proposed drug product is not rapidly dissolving as defined by the BCS guidance.

Solubility: *The aqueous solubility of brigatinib was found to be highly sensitive to pH and was studied using multiple experimental designs, including the use of various buffer systems and pH adjusted solutions.*

Table 1. Results of the Quantitative Aqueous Solubility at 25°C

In Buffer System

Buffer[a]	Target pH	Solubility (mg/mL)
Hydrochloric Acid Buffer	1.2	51.5
	2.0	6.9
Acid Phthalate Buffer	2.7	59.8
	4.0	40.9
Neutralized Phthalate Buffer	5.0	21.6
Phosphate Buffer	6.2	15.5
	6.8	4.5
	7.2	2.1
	7.5	0.7

[a] Buffer systems prepared according to USP31/Buffer Solutions

At Different pH Values

Target pH	Final pH	Solubility (mg/mL)[a]
1.5	1.6	>157.1
2.0	2.5	>165.2
4.9	4.5	>355.2
6.5	6.5	218.7
7.0[b]	6.8	7.1
7.0[b]	7.0	3.8
7.0[b]	7.0	2.2
7.5	7.5	2.5
8.0	8.0	0.3
8.5	8.5	0.1
9.0	9.6	0.1

[a] At pH 1 – 4.9, all solids dissolved and the actual solubility is higher than 218.7 mg/mL

[b] The variation in solubility at pH 7.0 is potentially due to the scale at which the experiment is performed and /or sensitivity to slight variation of the final pH (i.e. 6.8 and 7.0) following adjustment.

The highest intended dose of brigatinib is 180 mg per day and the solubility of 180 mg of brigatinib drug substance in 250 ml of aqueous media with a pH range of 1 – 6.8 was evaluated as shown below:

Table 2. Solubility of 180 mg Brigatinib Drug Substance in 250 ml of Aqueous Buffer

pH	Buffer	Measured Concentration
1.0	0.1 N HCl	0.715 mg/ml
3.8	USP Acid phthalate buffer (0.05 M)	0.711 mg/ml
4.8	USP Neutralized phthalate buffer (0.05 M)	0.695 mg/ml
5.8	USP Phosphate buffer (0.05 M)	0.704 mg/ml
6.8	USP Phosphate Buffer (0.05 M)	0.695 mg/ml

Based on the reviewer's calculation, the drug substance is highly soluble from pH 1.0 to 6.8 at the currently proposed highest strength of 90 mg[1].

Permeability: Brigatinib drug substance has been shown to be highly permeable. Permeability assessments of brigatinib are provided in \\cdsesub1\evsprod\nda208772\0001\m2\26-nonclin-sum\pharmkin-written-summary.pdf.

Drug Substance

Brigatinib is a tyrosine kinase inhibitor, which targets activated mutant forms of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1). Brigatinib has no chiral centers. (b) (4)

Formulation:

The proposed commercial tablet formulation (Formulation -3) is the tablet formulation used in the pivotal clinical studies. Brigatinib tablets, 30 mg are white to off-white, round debossed film-coated tablets. Brigatinib tablets, 90 mg are white to off-white, oval debossed film-coated tablets. Both tablet strengths (b) (4) The target composition of brigatinib tablets is shown in Table 3.

Table 3 Composition of Brigatinib Formulations used in Clinical Studies

Component	Drug-in-Capsule	Tablet Formulation-1	Tablet Formulation-2	Tablet Formulation - Formulation-3 (Intended Commercial)
	30 mg	30 mg	30 mg	30 mg / 90 mg[2]
Manufacturers	(b) (4)			Penn
				(b) (4)
Brigatinib				
Lactose monohydrate				
Microcrystalline cellulose				
Sodium starch glycolate (Type A)				
Hydrophobic colloidal silica				
Magnesium stearate				
Total				
Film-coating ((b) (4) White) target weight gain				
Clinical Use (Study No.[4])	101	101	101	101, 102, 103, 105, 106, 109, 201
				(b) (4)

[4] Abbreviated clinical trial codes correspond to the following studies:

Dissolution Method:

The Applicant's proposed dissolution method testing conditions are summarized as follows:

USP Apparatus type	USP II (Paddle)
Rotation Speed (rpm)	70 RPM
Medium	50 mM Potassium Phosphate Buffer, pH 7.2

[1] Draft Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.

Volume (mL)	900 mL
Temperature	37±0.5 °C
Proposed Sampling Time	(b) (4) minutes
Analysis Method	HPLC/UV at 250 nm

The Applicant originally developed a phase-appropriate dissolution procedure, referred to as Dissolution Method-1, for release and stability testing of Phase I brigatinib clinical trial material (Fomulation-1, 30 mg tablets). The used dissolution method parameters are listed below:

Table 4 Comparative Summary of the Applicant's used Dissolution Methods

	The Proposed Method	**Method 1 (Original)**
USP Apparatus type	USP II (Paddle)	(b) (4)
Rotation (rpm)	70 RPM	
Medium	50 mM Potassium Phosphate Buffer, pH 7.2	
Volume (mL)	900 mL	
Temperature	37±0.5 °C	
Proposed Sampling Time	(b) (4)	

Selection of dissolution medium:

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:
These results confirm the robustness of the proposed dissolution method.

Dissolution Method Validation:
The analytical method for the quantitation of brigatinib in dissolution samples was validated for filter compatibility, linearity, accuracy, precision, repeatability, specificity, sample stability, and robustness parameters. All validation acceptance criteria were met. The method validation report (# P166-020A) was provided in the amendment dated 12/13/2016 (\\cdsesub1\evsprod\nda208772\0022\m1\us\rsp-to-29nov2016-rfi-cmc.pdf).

The initial method development and validation for the drug product test procedures of brigatinib tablets, 30 mg and 90 mg was performed at [redacted] (b) (4). Following complete method validation at [redacted] (b) (4), all analytical procedures for brigatinib tablets, 30 mg and

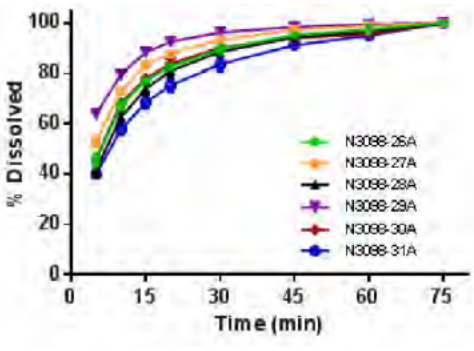
90 mg were transferred to Penn. Method Validation protocol for Penn was also provided in the amendment dated 12/13/2016.

The method validation results are acceptable.

Discriminating Power of the Method:
The Applicant investigated the sensitivity of the proposed dissolution method to intentional changes of the following:

Excipient Content:
The Applicant used the following formulation with variants in (b) (4) :

Table 8 Formulation Variant Study

Study #	Formulation Variant	Dissolution Profiles
Study 1 (30 mg)	(b) (4)	(b) (4)
Study 2 (30 mg, (b) (4) modification in (b) (4)		
Study 3 (90 mg, (b) (4) % modification on amount of (b) (4)		(b) (4) 

Study 4 (30 and 90 mg, particle size and shape)

Drug Product Lot No.	Drug Substance Batch No.	d_{10} (um)	d_{50} (um)	d_{90} (um)	VMD (um)	Morphology
N1008-47	LNB0715178	(b) (4)				
N1008-48	LNB0715180					
N1008-49	LNB0715182					
N1008-50	LNB0715186					

Drug substance particle size distribution tested using dry dispersion laser diffraction

% Dissolved

(b) (4)

Reviewer's Assessment:

The changes in excipient levels in Studies 1 and 2 did not have an effect on the 30 mg tablet manufacturability.

Study 4 (30 and 90 mg) showed that the proposed dissolution method cannot distinguish drug substance particle size distribution change.

Study 3 demonstrated that the proposed dissolution method can detect variability in (b) (4) content ((b) (4)) in 90 mg brigatinib tablets. However, it is noted the used (b) (4) amount variation is (b) (4)% and thus the dissolution method might not be sensitive to detect the (b) (4) variation within (b) (4)%.

Manufacturing Process (b) (4)

(b) (4)

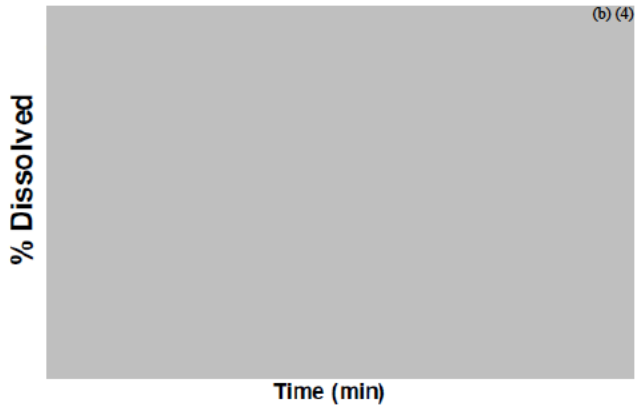
Reviewer's Assessment:

The proposed dissolution method could detect certain differences in the hardness variability at (b) (4) minutes, however the dissolution method is not sensitive to the presence of (b) (4)% change in hardness (i.e. (b) (4)).

Storage Condition

The Applicant performed open-dish stability studies using 30 mg tablets at 40°C/80% RH.

Figure 10. Effects of Accelerated Heat and Humidity on Dissolution of Brigatinib Tablets



Reviewer's Assessment:
As shown above, noticeable slowdown was observed at 10, 15 and 20 minutes time points (e.g. 2 M at 40°C/89% RH). The proposed dissolution method is able to detect changes to tablet performance following drug product exposure to aggressive storage conditions.

Reviewer's Assessment of the dissolution method: ACCEPTABLE[5]
The Applicant has adequately demonstrated the suitability of the dissolution method for batch release and stability testing. The dissolution method shows discriminating power to detect changes under aggressive storage conditions but is not sensitive to meaningful formulation composition and manufacturing process variations.

Dissolution Acceptance Criterion:
The Applicant proposes the acceptance criterion of NLT (b) (4)% in (b) (4) minutes for the current proposed dissolution method. The Applicant provided its statistical analysis using one sided lower tolerance intervals to determine the acceptance criterion based on average dissolution data of each lot (total 11 lots on the 30 mg strength), \\cdsesub1\evsprod\nda208772\0002\m3\32-body-data\32p-drug-prod\brigatinib-tablet-penn\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf. The applicant's proposed dissolution acceptance criterion is not acceptable. The provided dissolution data support (b) (4) acceptance criterion. Based on the submitted data (See the Appendix), we recommend the dissolution acceptance criterion of NLT (b) (4)% in 20 minutes in IR dated 11/29/2016, 12/16/2016 and T-con on 1/25/2017..

In the Applicant's response dated 1/26/2017, the Applicant accepted the acceptance criterion as Q= (b) (4)% at 20 minutes.

Reviewer's Assessment: Acceptable

Bridging of Formulations:

[5] DARRTS: IND 110935 COR-MEET-03 (Meeting Minutes), final date 03/08/2016

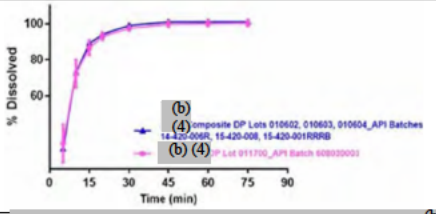
Drug Substance Manufacturing Sites:

Two manufacturers are proposed for the commercial production of brigatinib drug substance: (b) (4)

(b) (4)

In submission 022 to IR dated 11/29/2016, the Applicant provided dissolution comparison of Brigatininb tablets produced using (b) (4) drug substance (Reference) and (b) (4) drug substance (Test) as presented in Table 11. Due to the rapid release, F2 calculation is not applicable to compare the dissolution profiles. Nevertheless, the dissolution data showed comparable profiles using the proposed dissolution method.

Table 11 Process Performance Qualification Plan – Penn

Strength	F2 Comparison	
30 mg		(b) (4) Time Point | (b) (4) | (b) (4) 10 | 73 | 73 15 | 87 | 89 20 | 93 | 94 Similarity Factor (f2) | 89
90 mg	(b) (4)	(b) (4) Time Point | (b) (4) | (b) (4) 10 | 81 | 87 15 | 88 | 92 20 | 91 | 95 Similarity Factor (f2) | 66

In submission 027 to the IR dated 12/16/2016, the applicant submitted data for batch 011700 (30 mg, batch size of (b) (4), using (b) (4) drug substance 60803003) and 011701 (90 mg, batch size of (b) (4), using (b) (4) drug substance 608030002). The batch information was found comparable to those for the primary stability lots and therefore acceptable by the Drug Product Review team.

Reviewer's Assessment: Acceptable.

The data support the bridging between the drug products using two drug substance manufacturers, (b) (4).

Drug Product Manufacturing Sites:

The Applicant states that the 30 mg strength will be manufactured at (b) (4) and both strengths (30 mg and 90 mg) will be manufactured at Penn Pharmaceutical Services Ltd. (Penn) in the UK. The two drug product manufacturers use similar equipment and comparable process parameters (refer to the Process and Facilities review).

Table 12 Comparison of Scale, Lot Numbers, Equipment, and Process used at Each Tablet Manufacturing Site

Parameter	Manufacturing Site		
	(b) (4)	Penn	
Maximum Lot Size	30 mg tablets: (b) (4)	30 mg tablets: (b) (4) 90 mg tablets: (b) (4)	
Dates of Manufacture	Aug 2014 – Oct 2015	Jan 2015 – Jan 2016	
Lot Numbers (Commercial scale and process)	30 mg 140111 140132 140133 140134 140195 150099 150163 150164	30 mg 010133 010602 010603 010604 011867	90 mg 010339 010345 010414 010788 010789 010790 011351 011352 011660
(b) (4)			

The results from 30 mg Brigatinib tablets, manufactured by (b) (4) Penn are consistent (see the Appendix) and comparable. No f2 value is calculated due to rapid release of brigatinib.

Reviewer's Assessment:

The data support the bridging between the two drug product manufacturing sites.

R Regional Information

Comparability Protocols: None

List of Deficiencies: None

RECOMMENDATION

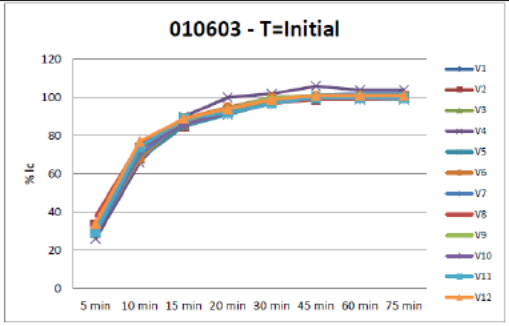
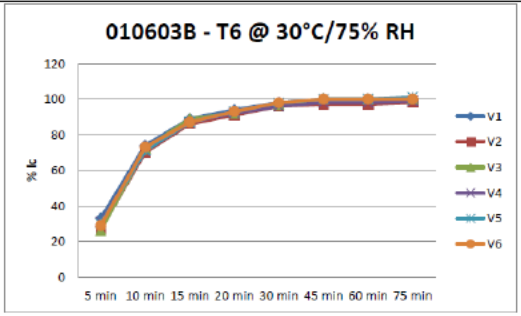
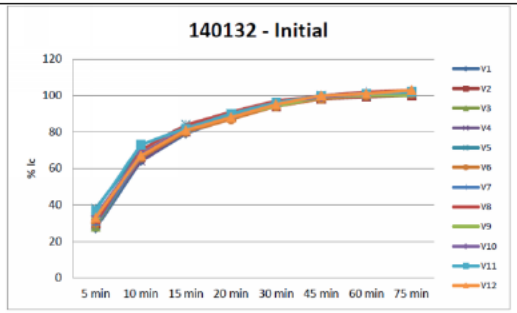
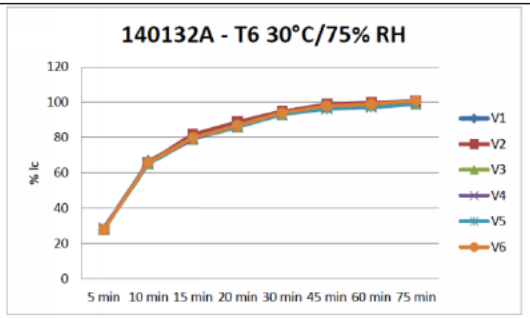
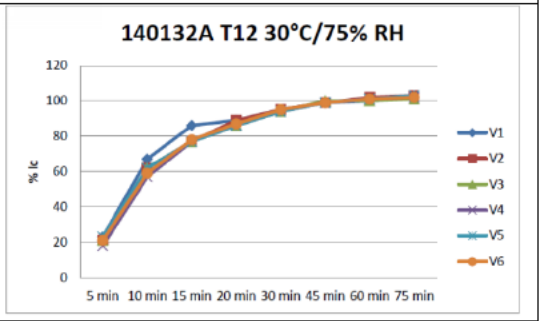
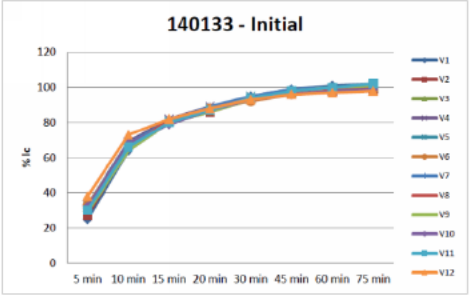
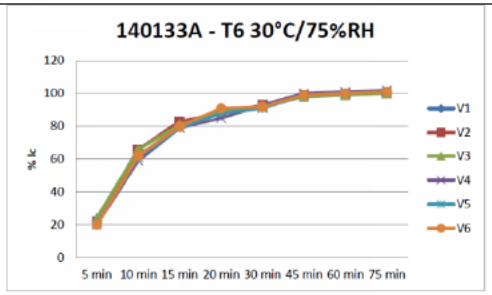
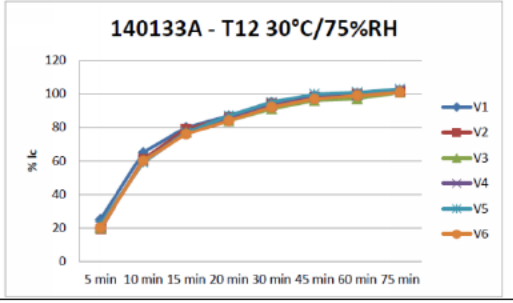
From the Biopharmaceutics perspective, NDA 208772 for Brigatinib tablets, 30 and 90 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Zhao, Ph.D.1/26/2016

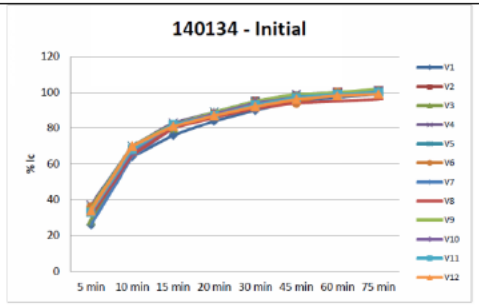
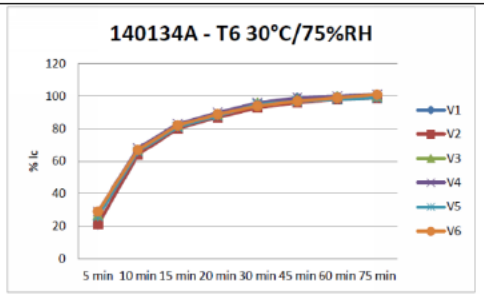
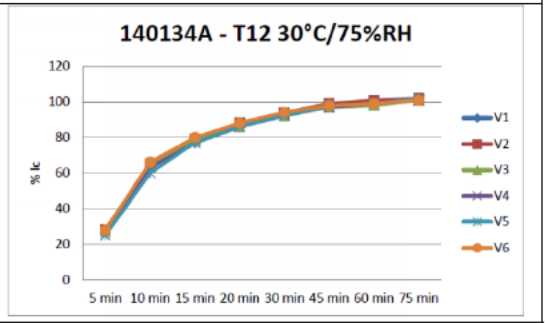
Secondary Reviewer Name and Date: Okpo Eradiri, Ph.D.1/26/2017

APPENDIX: Dissolution Results[6,7]

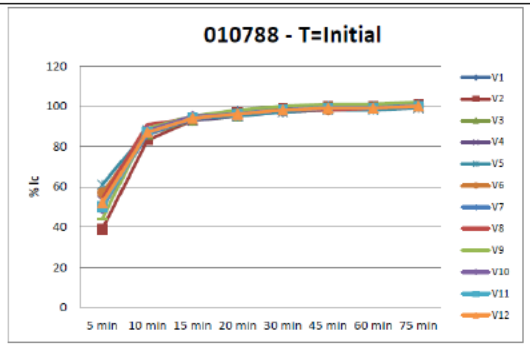
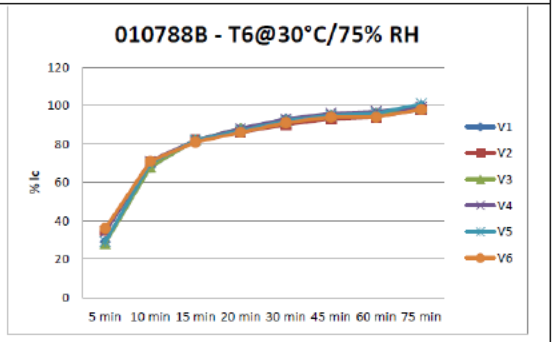
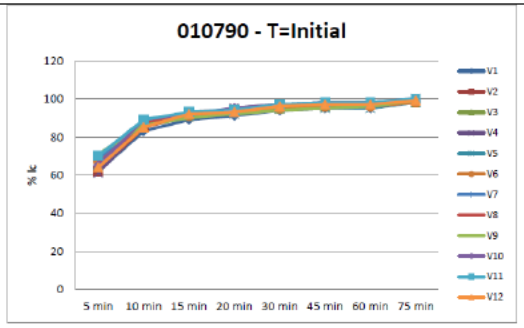
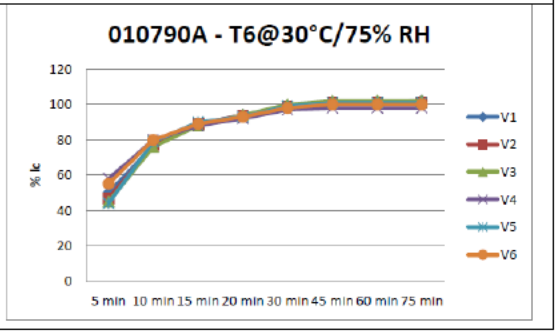
30 mg

Batch # (Manufacturer, Trial #)	Dissolution Data (initial)	Dissolution Data (6 M)	Dissolution Data (12 M)
010603 (Penn, 201, 106)			
140132 (b) (4), 101, 201)			
140133 ((b) (4), 101)			

[6] \\cdsesub1\evsprod\nda208772\0002\m3\32-body-data\32r-reg-info\32r-dissolution-data-penn.pdf
[7] \\cdsesub1\evsprod\nda208772\0002\m3\32-body-data\32r-reg-info\32r-dissolution-data(b) (4).pdf

Batch # (Manufacturer, Trial #)	Dissolution Data (initial)	Dissolution Data (6 M)	Dissolution Data (12 M)
140134 ((b) (4), 101, 105)			

90 mg

Batch # (Trial #)	Dissolution Data (initial)	Dissolution Data (6 M)
010788 (101,201)		
010790 (201,109)		

APPEARS THIS WAY ON APPROVAL

Zhuojun Zhao

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Okponanabofa Eradiri

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Attachment - Final Risk Assessment for ALUNBRIG (brigatinib) 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 (with 1 g desiccant)	Acceptable	Controls are in place and 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 (with 1 g desiccant)	Acceptable	Controls are in place and Continue stability monitoring post approval
API Physical Attributes	• Compressibility • Flowability • Segregation	Medium	Formulation development demonstrated low impact of physical properties with current formulation	Acceptable	If drug load increases, evaluate the impact of API's physical properties on drug product manufacturability.
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Assessed during development and controlled via specifications	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 and Continue stability monitoring post approval
Moisture Content	• Raw materials • Process parameters • Scale/equipment • Formulation • Container closure • Site	Medium	Assessed during development and controlled via specifications and container closure (with 1 g desiccant)	Acceptable	Controls are in place and Continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Assessed during development and controlled in manufacturing process and storage	Acceptable	Controls are in place

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

This application is recommended for APPROVAL from the CMC perspective.

Joyce Crich, Ph.D.

January 29, 2017

Joyce Crich -S

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Attachment - Final Risk Assessment for ALUNBRIG (brigatinib) tablets (v.2)

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 (with 1 g desiccant)	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 (with 1 g desiccant)	Acceptable	Controls are in place Continue stability monitoring post approval
API Physical Attributes	• Compressibility • Flowability • Segregation	Medium	Formulation development demonstrated low impact of physical properties with current formulation	Acceptable	If drug load increases, evaluate the impact of API's physical properties on drug product manufacturability.
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	Assessed during development and controlled via specifications	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, and further evaluate the revised dissolution acceptance criterion (from Q (b)(4)% at (b)(4) mins to Q (b)(4)% at 20 mins)
Moisture Content	• Raw materials • Process parameters • Scale/equipment • Formulation • Container closure • Site	Medium	Assessed during development and controlled via specifications and container closure (with 1 g desiccant)	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 in manufacturing process and storage	Acceptable	Controls are in place

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

This application is recommended for APPROVAL from the CMC perspective.

Joyce Crich, Ph.D.

February 11, 2017

Joyce Crich -S

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BIOPHARMACEUTICS REVIEW NOTES ON AMENDMENT TO NDA 208772 – SDN 0037 2/2/2017

Preamble

After completion of the Biopharmaceutics review, the Applicant submitted an amendment to the Application on 2/2/2017. The amendment contains dissolution data on batch # 010604, which show that at 12 months, the mean dissolution at 20 min was (b)(4)% under 30°C/75% RH storage conditions; this indicates that the batch may go to S2 testing or S3 testing. The ATL has requested that the Division of Biopharmaceutics re-evaluate the data to determine if the results are likely to affect the 24-month shelf life of the 30 mg drug product.

Data submitted in the amendment

ARIAD Pharmaceuticals, Inc.

Biopharmaceutics Assessment

It is noted that the storage conditions, 30°C/75% RH, are more stressed than the long term and intermediate storage conditions. Since the drug product will be stored at ambient temperature and humidity conditions (25°C/60% RH), there is no concern from a Biopharmaceutics perspective; the recommended dissolution acceptance criterion of "Q = (b)(4)% in 20 min" is therefore adequate for quality control and stability assessment of Brigatinib Tablets.

Joan Zhao, PhD 2/9/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP/OPQ

Okpo Eradiri, PhD 2/9/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP/OPQ

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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 208-772	**Established/Proper Name: brigatinib** **Proposed Proprietary Name: ALUNBRIG**
Applicant: ARIAD Pharmaceuticals, Inc.	**Dosage Form: Tablet**
Submission Type: 1 – New Molecular Entity	**Strength(s): 30 mg and 90 mg**
Chemical Type: small molecule	**Cross Referenced Applications: IND 110,935**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			N/A

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

A. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

NDA 208-772 was recevied on August 29, 2016 in the 505b(1) regulatory pathway with FDA breakthrough and FDA orphan drug designations. ALUNBRIG (brigatinib) Tablets (in strengths of 30 and 90 mg) are indicated for the treatment of patients with (b) (4) metastatic anaplastic lymphoma kinase positive (ALK)-positive non-small cell lung cancer (NSCLC) who have progresed on or are intolerant to crizotinib.

NDA 208-772 cross references IND 110,935 for developmental data on the oral tablets. The immediate release brigatinib tablets are white to off-white, debossed, and film-coated. The 30 mg tablets are round and the 90 mg tablets are oval shaped. The two strengths (b) (4) The tablets are packaged in 60 cc HDPE bottles with CR closures, 1 g (b) (4) desiccants, and induction seal. The 30 mg tablets are packaged in 21-count and 180-count presentations; the 90 mg tablet is packaged in a 30-count presentation. These packaging configurations are intended to support a dosing regimen of 90 mg QD for 1 week followed by 180 mg daily. The 30 mg dose strength enables dose reduction. The proposed storage conditions is to store (b) (4) with a proposed shelf life of 24 months.

Brigatinib is an orally-active tyrosine kinase inhibitor (TKI) that primarily targets activated, mutant forms of ALK and c-ros oncogene 1 (ROS 1), which play roles in NSCLC. Brigatinib was granted breakthrough therapy designation in October 2014 and orphan drug designation. Brigatinib has the chemical name 5-chloro-N^4-[2-(dimethylphosphoryl)phenyl)-N^2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2, 4-diamine. Brigatinib is off-white to beige/tan solid, (b) (4). The drug substance does not contain chiral centers (b) (4) the drug product is not hygroscopic. The drug substance is highly soluble from gastric through physiological pH.

Two drug substance and two drug product manufacturing sites have been selected for commercial distribution of ALUNBRIG (brigatinib) tablets. Bridging between these sites is accomplished through comparison of batches and use of both drug substance manufacturers for registration batches. For initial marketing purposes, the Penn Pharmaceuticals Ltd. drug product manufacturer will produce the 30 mg and 90 mg tablets; the second drug product manufacturer, (b) (4) will only manufacture the 30 mg strength.

Refer to the NDA 208-772 Initial Quality Risk Assessment Table attached at the end, for critical product quality review considerations.

B. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	X			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	X			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	X			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	X			A revised 356h form was submitted on 30-Sep-2016 to include (b) (4) manufacturing site, per Agency's request on 29-Sep-2016.
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	X			
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			Additional stability data for drug substance were submitted on 27-Sep-2016 (30 days subsequent to the final component submission of the rolling NDA).
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			Additional stability data for drug product (both 30 mg and 90 mg strengths) were submitted on 27-Sep-2016 (30 days subsequent to the final component submission of the rolling NDA).

B. FILING CONSIDERATIONS					
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?			X	The BE studies will be reviewed by Office of Clinical Pharmacology (OCP).
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	X			The proposed commercial formulation is the tablet formulation evaluated in the Phase I and II clinical studies.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.		X		
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	The proposed drug product is an IR tablet.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	The proposed drug product is an IR tablet.
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?		X		
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X			"Haber 1898", an old organic chemistry paper published in year 1898 in Section 3.3 (Literature References) is written in foreign language. No English version was located in the submission.
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X			EBR is provided for drug product.
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			X	
17.	For Biotech Products, is sufficient information provided in compoliance with 21 CFR 610.9 and 601.2(a)?			X	

NDA 208-772 Initial Quality Risk Assessment Table for ALUNBRIG (brigatinib) tablets

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	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents • Polymorphic conversion	Mod stable drug (3) (The DP Specs set for Single specified degradant NMT (b)(4)%; Single unspecified degradant NMT (b)(4)%, Total degradants NMT (b)(4)%)	2	Release (1)	6
					Stability (3)	18
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Polymorphic conversion • Moisture Content	(b) (4)	BCS I/III (2)	4	32
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Low dose • Particle size/shape • Segregation • Flow property	Med loading (b) (4)	3	4	48
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Moisture • Equipment, process environment	1	2	Release without Spec (5)	10
Dissolution – BCS Class I & III	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• API particle size • Moisture • Tab hardness • Disintegration • Size shape • Film coating	3	2	2	12

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