CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208065Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208065
Review # 1

Drug Name/Dosage Form	**osimertinib**
Strength	**40mg and 80mg**
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	**AstraZeneca Pharmaceuticals LP**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Multiple Categories 0002	05-Jun-15	CMC portion of rolling review
Proprietary Name 0005	31-Mar-15	ATL
Proprietary Name 0006	13-Apr-15	ATL
Proprietary Name 0008	29-May-15	ATL
Response to IR 0009	16-Jun-15	Process and Biopharm
Amendment 0011	02-Jul-15	Drug Substance and Drug Product
Response to IR 0018	10-Jul-15	DS, DP, Facilities
Amendment 0021	22-Jul-15	Drug Substance
Response to IR 0029	14-Aug-15	Drug Substance and Drug Product
Response to IR 0033	08-Sep-15	Facility, Biopharm, Micro, DP
Labeling 0035	08-Oct-15	DP and ATL
Response to IR 0036	08-Oct-15	Process
Response to IR 0040	13-Oct-15	Process
Response to IR 0041	20-Oct-15	DP, Process
Tcon	21-Oct-15	DP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Charles Jewell**	**OPQ/ONDP/DNDPAPI/BI**
Drug Product	**William (Mike) Adams**	**OPQ/ONDP/DNDPI/BII**
Process	**Ying Zhang**	**OPQ/OPF/DPAI/BII**
Microbiology	**Ying Zhang**	**OPQ/OPF/DPAI/BII**
Facility	**Thuy Nguyen**	**OPQ/OPF/DIA/BI**
Biopharmaceutics	**Gerlie Gieser** **Okpo Eradiri**	**OPQ/ONDP/DB/BI**
Regulatory Business Process Manager	**Steve Kinsley**	**OPQ/OPRO/RBPMI/BI**
Application Technical Lead	**Liang Zhou**	**OPQ/ONDP/DNDPI/BII**
Laboratory (OTR)		
ORA Lead	**Paul Perdue Jr**	**OGROP/ORA/OO/OMPTO/DMPTPO/MDTP**
Environmental Assessment (EA)	**Olen Stephens**	**OPQ/ONDP/DNDPI/BII**

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETE	COMMENT
(b) (4)	Type IV		(b) (4)	4		
	Type III			4		
	Type III			4		
	Type III			4		
	Type III			4		
	Type III			4		
	Type III			4		
	Type III			4		
	Type III			4		

4: sufficient information provided in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	117,879	IND
Pre-Phase III Type C Meeting	117,879	14 January 2014
Informal Teleconference – CMC	117,879	12 August 2014
Breakthrough Therapy Designation Type B Meeting	117,879	02 October 2014
Breakthrough Therapy Designation Type B Meeting - CMC	117,879	07 October 2014
Pre-NDA Type B Meeting	117,879	09 December 2014
Informal Teleconference – CMC	117,879	28 April 2015

2. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality recommends NDA 208-065 for "approval" as there are no pending review or inspection issues. The manufacturing and testing facilities received an overall "acceptable" evaluation from the Office of Process and Facilities (04-Oct-15). An initial shelf life of 12 months in the finished package is granted when stored at USP controlled temperature (20 ^{O}C to 25 ^{O}C (68 ^{O}F to 77 ^{O}F). The initiation of shelf life is designated (b) (4)

The applicant proposed a comparability protocol to change the (b) (4) The approval letter should include the following language, "The comparability protocol to change the (b) (4) is acceptable, but this change must be reported as a CBE 30 and not a CBE 0."

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Due to the accelerated development of this product, a complete protocol to support the worst case scenario of (b) (4) has not been completed. The applicant commits to complete a long term stability study to establish the effect of an (b) (4) on the stability of the finished product, which is to be submitted as a prior approval supplement. This is not a post-marketing commitment, rather a protocol to generate additional data to improve the overall quality control of the product.

II. Summary of Quality Assessments

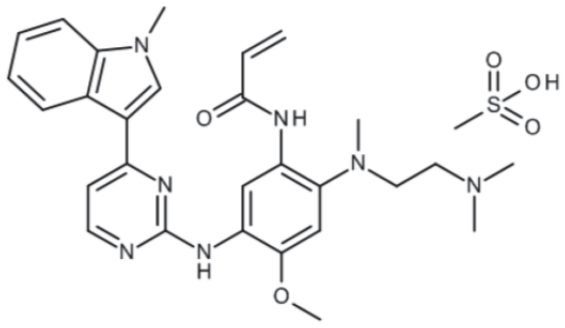
A. Drug Substance [Osimertinib] Quality Summary

Osimertinib is the drug substance for this NDA. Throughout this review, the drug substance is referred to interchangeably as AZD9291, its laboratory code. (b) (4) . Osimertinib is an irreversible inhibitor of the mutant EGFR receptor (EGFRm) and a specific version of the EGRFm (EGFRm/T790M). (b) (4)

The drug substance is produced by a (b) (4)

(b) (4) Four impurities are specified in the drug substance, and one mutagenic impurity is specified. For this drug substance with this patient population the Agency is accepting a threshold of toxicological concern (TTC) for mutagenic impurities of (b) (4) ppm, based in part on ICH S9 and the dosing schedule. The manufacturing process has demonstrated the ability to limit potential mutagenic impurities to below (b) (4)% of the TTC in all cases, so only the most prevalent mutagenic impurity is specified (b) (4) is the only solvent specified. Water content in all development and commercial batches is below (b) (4)%, so microbial testing is not necessary for this drug substance on release, though microbial growth is monitored in stability testing. The drug substance is stable for (b) (4) months at long term storage and (b) (4) months under accelerated storage. This reduced stability set was accepted based on accelerated development of this break-through designated product and not actual stability demonstration. Supportive stability data supports a re-test period of around (b) (4) months when stored in (b) (4) (b) (4) stored in rigid outer containers at (b) (4)

The applicant proposed a comparability protocol to change the (b) (4) The proposed protocol would report this change as a CBE (0). The protocol is acceptable, based on the potential for improvement in the process, with no perceived quality cost. The approval letter should include language to approve this comparability protocol, but the reporting should be a CBE 30 instead of CBE (0).



- AZD9291 mesylate
- $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$
- MW: (b) (4) (mesylate salt)
- MW: (b) (4) (free base)
- CAS registry #: 1421373-66-1
- (b) (4)
- pKa: 9.5 and 4.4
- (b) (4)
- melting onset: 248°C (DSC)
- (b) (4)

IUPAC Name: (b) (4)

B. Drug Product [Tagrisso (osimertinib) tablets] Quality Summary

Tagrisso is osimertinib mesylate formulated as 40 mg or 80 mg free base (equivalent to 47.7 and 95.4 mg mesylate, respectively) film-coated tablets (b) (4) The 40mg tablet is 9mm round, biconvex, beige and debossed with 'AZ' over '40' on one side and plain on the reverse. The 80 mg tablet is 7.25x14.5mm oval, biconvex, beige and debossed with 'AZ 80' on one side and plain on the reverse. The tablet core is composed of mannitol, microcrystalline cellulose, low-substituted hydroxpropyl cellulose and sodium stearyl fumarate. Both tablets use the same film-coating which is composed of polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

The bulk tablets are manufactured in (b) (4) The bulk tablets (b) (4) package for bulk tablets (b) (4) composed of (b) (4), (b) (4) Bulk tablet are to be stored at (b) (4) The finished package for both tablet strengths is a 30-count HDPE bottle with (b) (4) screw cap, aluminum induction innerseal (b) (4)

The controls and specification for excipients, the manufacturing process, bulk tablets and finished product are described in sufficient detail. The tests and criteria in the regulatory specification are justified. The analytical methods are described in sufficient detail and validated appropriately. The protocol for post approval stability studies is acceptable. **The recommended initial expiry period is 12 months in the finished package when stored at USP controlled temperature (20 ^{O}C to 25 ^{O}C (68 ^{O}F to 77 ^{O}F)**. The tablets are not sensitive to light or moisture.

Manufacturing process: (b) (4) has been used throughout the development of AZD 9291 film-coated tablets. (b) (4) The overall manufacturing process has been studied and optimized for risks posed by (b) (4) For each unit operation, the applicant identified the failure mode and related quality attributes of drug product.

Microbiology: For drug product, the applicant did not include the microbial control in the release specifications. They included microbial control (TAMC, TYMC and absence of *E. Coli*.) in the primary stability studies under long-term

conditions, and stated such control will be monitored annually until the end of these studies (statement provided on Page 15 in Module 3.2.P.5.6).

Biopharmaceutics: The Biopharmaceutics review of this NDA focused on (1) the proposed dissolution method and acceptance criteria, and (2) the bridging of the proposed commercial film-coated tablets to various osimertinib formulations used in the AURA (Expansion and Extension) and the AURA 2 Studies. Overall, it can be concluded that debossing did not negatively impact the complete release of osimertinib from the 40 mg tablets and the 80 mg tablet cores used in this development study. The Applicant proposes not to use disintegration in lieu of dissolution testing as a routine QC test since there was no observed correlation between dissolution and disintegration rates of osimertinib tablets. Furthermore, there was no observed link between tablet core hardness and disintegration time.

The proposed dissolution method exhibits discriminating capability as it was able to detect differences in (b) (4) to and/or tablet hardness of different clinical batches of 40 mg tablets. The apparent limited influence of manufacturing and formulation variables on the dissolution profiles of osimertinib tablets could be explained at least in part by the high solubility of the drug substance over a wide pH range. The proposed dissolution method is adequate to assure batch-to-batch variability via monitoring complete dissolution of osimertinib tablets at the time of manufacturing release and during stability testing.

Judging from the findings of the relative BA study (Study 5), the oral bioavailability of osimertinib is not expected to be negatively impacted when administered as an aqueous dispersion of the tablet either orally or via a nasogastric tube, because the oral bioavailability of the intact oral tablet is comparable to that of the oral solution. Some lung cancer patients who had developed difficulty swallowing tablets received osimertinib as a pre-dispersed tablet in the clinical studies conducted. Chemical stability of an aqueous dispersion was reported to be acceptable over (b) (4), and the transfer of dispersed tablets through nasogastric tubes was shown to be suitable for administration using appropriate commercially available tubes. (b) (4) However, use of heat or ultrasonication to prepare the dispersion was not compatible with this formulation and this information has been captured in the package insert.

Both 40 mg and 80 mg strengths of the proposed commercial osimertinib *debossed* film coated tablets have comparable *in vitro* dissolution characteristics [and thus are not expected to behave differently (in terms of efficacy)] to the *non-debossed* film-coated tablets evaluated in the pivotal Phase 2 clinical Studies AURA Extension and AURA2. There is adequate bridging between the clinical research and the proposed commercial formulations of osimertinib tablets.

The applicant requested to use clinical lots formulated with lots of API campaign 4 for commercial launch drug product. The applicant confirmed that the campaign 4 drug substance batches intended to be used for launch was manufactured at the (b) (4) as listed on 356h. All batches met the proposed commercial specification, including debossing design. There is no additional risk for distributing the clinical lots manufactured at the same proposed API site as the product met all proposed commercial specification. Therefore, the firm was informed that it would be acceptable to launch commercial supplies with the following drug product batches: CAAB, CAAC, AAAB, AAAC, AAAD.

An overall "approval" recommendation has been rendered by the Office of Pharmaceutical Quality. There are no pending review issues and the manufacturing and testing facilities received an overall "acceptable" evaluation from the Office of Process and Facilities (04-Oct-15). An initial shelf life of 12 months in the finished package is granted when stored at USP controlled temperature (20 ^{O}C to 25 ^{O}C (68 ^{O}F to 77 ^{O}F). The approval letter should include the following language, "The comparability protocol to change the (b) (4) is acceptable, but this change must be reported as a CBE30 and not a CBE0."

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Tagrisso tablets
Non Proprietary Name of the Drug Product	Osimertinib tablets
Non Proprietary Name of the Drug Substance	Osimertinib
Proposed Indication(s) including Intended Patient Population	for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.
Duration of Treatment	Until disease progression
Maximum Daily Dose	80 mg
Alternative Methods of Administration	An extemporaneously prepared dispersion made by stirring in water may be administered orally or by nasogastric tube. (b) (4)

D. Biopharmaceutics Considerations

1. BCS Classification:
    - *Drug Substance:* Osimertinib exhibits high solubility and higher than moderate permeability (based on Caco-2 system and human

radiolabelled ADME Study 11), (b) (4) In the ADME study using 20 mg oral solution, ~80% of the radioactivity was associated with metabolites and other by-products in feces and urine, and an additional 2% was attributed to the unchanged drug.

- *Drug Product:* Osimertinib tablets are very rapidly dissolving (on average, ≥(b) (4)% dissolved in (b) (4)).

2. Biowaivers/Biostudies
   - *Biowaiver Requests* - none
   - *PK substudies:* AURA expansion versus AURA extension (refer to Clinical Pharmacology review for the assessment of these PK substudies)
   - *IVIVC:* none

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: The label allows for preparation of an extemporaneous aqueous dispersion for patients who have difficulty swallowing tablets

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: I recommend this NDA for approval.
Olen Stephens, PhD
Application Technical Lead
Acting Branch Chief, ONDP

Olen Stephens -S
Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.10.22 10:10:04 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

Executive Summary of Drug Substance

AZD9291 mesylate is the drug substance for this NDA. It is the mesylate salt of an irreversible inhibitor of the mutant EGFR receptor (EGFRm) and a specific version of the EGRFm (EGFRm/T790M). (b) (4)

The drug substance is produced by a process using (b) (4)

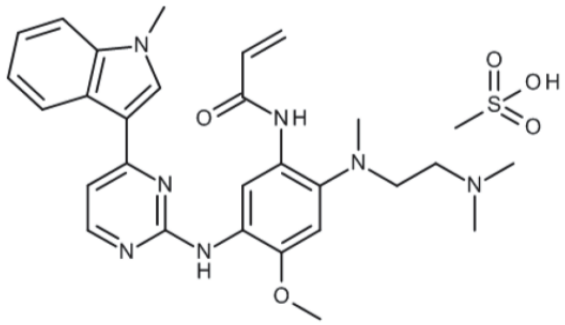
Ultimately, four impurities are specified in the drug substance, and additionally one mutagenic impurity is specified. For this drug substance in this application the Agency is accepting a threshold of toxicological concern (TTC) for mutagenic impurities of (b) (4) ppm. The manufacturing process has demonstrated limiting potential mutagenic impurities to below (b) (4)% of the TTC in all cases, so only the highest mutagenic impurity is specified. (b) (4) is the only solvent specified. Water content in all development and commercial batches is below (b) (4)%, so microbial testing is not necessary for this drug substance on release. Microbial growth is monitored in stability testing. The drug substance is demonstrated to be stable for (b) (4) months at long term storage and (b) (4) months under accelerated storage. This shorter than normal level is based on accelerated development and not actual stability demonstration. Supportive stability data supports a re-test period of around (b) (4) months. This is likely to increase when registration stability studies are completed and commercial batches undergo stability studies.

The applicant proposed a comparability protocol which covers a change in (b) (4)

They proposed a reporting of CBE (0). It is recommended that this protocol be accepted, based on the potential for improvement in the process, with no perceived quality cost. Although the reporting should be at CBE (30) instead of CBE (0).

2.3.S.1 General Information

Applicant's Response:



- AZDD9291 mesylate
- $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$
- MW: (b) (4) (mesylate salt)
- MW: (b) (4) (free base)
- CAS registry #: 1421373-66-1
- (b) (4)
- pKa: 9.5 and 4.4
- (b) (4)
- melting onset: 248°C (DSC)
- (b) (4)

IUPAC Name: (b) (4)

Reviewer's Assessment: No issues, solubility is high for purposes of the bioclassification system. Permeability is low based on numbers, but actual permeability is moderately high, and applicant studies imply no bioavailability issues dependent on formulation (oral solution, tablet, capsule). (b) (4)

2.3.S.2 Manufacture

- Drug Substance Manufacture and Quality Control Testing
  - (b) (4)
- Quality Control Testing
  - AstraZeneca AB; Gärtunavägen; SE-151 85; Södertälje; SWEDEN
- Performance of Stability Testing
  - (b) (4)

S.2.2 Description of the Manufacturing Process and Controls

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?

2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

Applicant's Response:
Summary of Synthetic Manufacturing Process (Reviewer Drawn)

(b) (4)

[redacted]

Reviewer's Assessment: This scheme is drawn by the reviewer to capture relative amounts of material used in each step, in-process controls and yields. The process appears to be well understood and well controlled. Two things to note. (b) (4) **The applicant is also requesting a comparability protocol to change the** (b) (4) **Their proposed testing scheme is adequate, so I recommend accepting the comparability protocol with an acceptable supplement review criteria. They request CBE-0, I recommend telling them CBE-30, so we have an opportunity to look at the data before approval.**

Control of Critical Steps and Intermediates

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?
4. Are intermediates controlled adequately to assure the structure and impurity profile of the final drug substance?

Applicant's Response:

Information on Starting Materials and other Raw Materials (example C of A's provided in application)

Starting Materials (typical suppliers: (b) (4)

(b) (4)

(b) (4)

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(b) (4)

-
-
-

Reviewer's Assessment: This specification is considered adequate, even though the applicant has decided (b) (4) **The justification by the applicant to not include these was reviewed and the argument was deemed to be reasonable and supported by manufacturing experience. This included additional requested data for justification of** (b) (4) **requested in an information request sent 21 August 2015 (response received 08 September 2015. It is noted that they originally planned to** (b) (4) **but re-instated this by amendment during the review cycle, due to** (b) (4) **of the manufacturing process that** (b) (4) **This is acceptable. There were no examples of ROI exceeding** (b) (4) **% throughout the development process in the drug substance stage. It should also be noted that there**

we no examples of mutagenic impurity (b) (4) reaching the level of (b) (4) %, even though the suggested acceptance criteria is NMT (b) (4) %. This appears to be a strategy to minimize the need to test for mutagenic impurities specifically on release. (b) (4) is the highest detected mutagenic impurity in development history for this drug substance. All other potential mutagenic impurities were well below this level. By setting the threshold toxicological concern to (b) (4) %, it supports not needing to test for mutagenic impurities that have been demonstrated to be much lower than (b) (4) the level of the TTC. There is precedence for the Agency adopting this strategy, and based on the ICH S9 guidance, the applicant is taking advantage of this to limit the need for release testing. In practice, application data supports this approach. This analytical methods in this section were reviewed by this reviewer and found to be suitable for the purpose intended, and validated as such. Originally, the applicant had attempted to request (b) (4) Based on feedback from the drug product reviewer, which may have the effect of prolonging the review period for this application being reviewed at an accelerated schedule due to perceived patient need, the Agency asked them to withdraw this request and they did.

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

Applicant's Response:

<u>Reviewer's Assessment</u>: This is covered in the topic above.

2.3.S.5 Reference Standards or Materials

12. Are the drug substance reference standards satisfactory?

Applicant's Response:

- The (b) (4) reference standard is described (it is used for both drug substance and drug product)
  - Current source is (b) (4) (Manufactured by (b) (4) (b) (4))
  - Additional to specification data, the following was reported
    - NMR spectrum
    - residue on ignition (b) (4)
    - assigned purity as (b) (4)
    - assigned purity as (b) (4)

Reviewer's Assessment: The reference standard was adequately characterized for use in the analytical methods associated with this application.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

Applicant's Response:
The drug substance is stored in (b) (4), (b) (4)
Stability studies demonstrated the suitability of these materials. The bags are well established in the pharmaceutical industry for packaging of drug substance. Primary packaging complies with 21 CFR 177.1520.

Reviewer's Assessment: These materials adequately meet regulations for use in storing drug substance.

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

Applicant's Response:
A total of five batches of material have been place on stability. Three of these batches are "primary stability studies" performed on pilot level material, using the same process as the commercial process. The two "supportive stability" batches are on batches produced earlier in development, with some differences in the manufacturing conditions including different (b) (4) The batch sizes for the primary stability batches are roughly (b) (4) commercial scale (b) (4) kg. Stability data on the primary batches have been reported to (b) (4) Testing includes description, assay, organic impurities, mutagenic impurities, water content, (b) (4) particle size distribution and microbiological quality.

Primary Stability Batches (Only key changes discussed)
- **C605/1 (manufactured Jul 2014 AZ, (b) (4) Scale (b) (4) kg)**

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(b) (4)

[redacted]

Post-Approval Commitment

(b) (4)

[redacted]

(b) (4)

Reviewer's Assessment: Due to the accelerated nature of this application, shorter than typical stability studies have been completed. The drug substance appears to be adequately stable under long term and accelerated storage conditions of (b) **respectively. The material tolerated** (b) (4) **as well, and does not appear to be sensitive to light in bulk form. Supportive stability studies that were performed on the drug substance produced under slightly different conditions indicate** (b) (4) (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
The drug substance reviewer recommends approval from the perspective of the drug substance for this NDA.

- **The applicant should be notified in the approval letter that the comparability protocol is excepted as proposed with the exception that reporting at CBE (30) is required instead of CBE(0).**

Signed: Charles F. Jewell Jr. 9/23/2015

Secondary Review Comments and Concurrence:
I concur.
Signed: Kasturi Srinivasachar, Acting Branch Chief DNDAPI; 9/23/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Tagrisso (osimertinib tablets) is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. The indication is being approved under

accelerated process based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The recommended dose is one 80mg tablet taken once a day with or without food until disease progression or unacceptable toxicity. Tablets are to be swallowed whole with water. Patients who have difficulty swallowing solids can be dosed using an aqueous dispersion administered orally or by nasogastric tube. The dispersion is prepared by adding one tablet to 4 tablespoons (approximately 50 mL) non-carbonated water in a cup and stirring continuously until the tablet is completely dispersed. Tablets are not to be crushed, heated or ultrasonicated during preparation. The cup is to be rinsed with 4-8 ounces of water and administered immediately. (b) (4)

2.3.P.1 Description and Composition of the Drug Product

Tagrisso is film-coated tablets containing 40mg or 80mg osimertinib (AZD9291) freebase (equivalent to 47.7 or 95.4 mg of mesylate salt, respectively). Tablets are made from (b) (4) The 40mg tablet is 9mm round, biconvex, beige and debossed with 'AZ' over '40' on one side and plain on the reverse. The 80mg tablet is 7.25x14.5mm oval, biconvex, beige and debossed with 'AZ 80' on one side and plain on the reverse. The commercial presentation is a 30-count, 75cc white HDPE bottle with induction innerseal, (b) (4) screw cap, (b) (4)

Unit Composition

	mg/tablet			
Component. Grade	***40mg***	***80mg***	***%***	***Function***
CORE[e]				
AZD9291 mesylate[a], in house	047.7	095.4	(b) (4)	Active
Mannitol, NF	(b) (4)			
Microcrystalline Cellulose, NF				
LS-HPC, NF				
Sodium Stearyl Fumarate, NF				
Nominal Weight, Core				
COATING[b,c]				
Polyvinyl Alcohol, USP				
Titanium Dioxide, USP				
(b) (4), NF				
Talc, USP				
Yellow Ferric Oxide, NF				
Red Ferric Oxide, NF				
Black Ferric Oxide, NF				
(b) (4)				
Nominal Weight, Coating				
Nominal Weight, Tablet	261.709	518.396		

LS-HPC = low-substituted hydroxypropyl cellulose

(b) (4)

riety composite, e.g., (b) (4)

c Target amount corresponding to appx (b) (4)

d (b) (4)

The typical commercial batch size is appx (b) (4) and (b) (4) for 40mg and 80mg tablet strengths, respectively (b) (4) and (b) (4) tablets). The formula is applicable for batch size up to (b) (4) based on maximum amount for (b) (4) (b) (4)

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Reviewer's Assessment:

This is a 505(b)(1) application.
Tablets are (b) (4)

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

3.2.P.2.1.1 Components

The proposed drug product is an immediate release, film-coated tablet made from a (b) (4)

Drug Product - Quality Target Product Profile (QTPP)
Appearance, Identity, Assay, Degradants, UDU, Dissolution – included in the release specification
Microbiological Quality, Disintegration, Hardness: developmental IPCs
(b) (4)

Drug Substance - Key Physicochemical Characteristics
Appearance: white to brown powder
Molecular Weight: (b) (4) gm/mol as mesylate salt
Melting Point: Appx 248ºC (b) (4)
(b) (4)
(b) (4)
pKa: 4.4 (b) (4) 9.5 (b) (4)
Polymorphism: (b) (4)
Particle Size: (b) (4)
PhysicoMechanical Attributes: (b) (4)
Stability: (b) (4)

Solubility: pH-dependent freebase solubility profile (b) (4)

Medium	*pH*[a]	*mg/mL*[c]
(b) (4)		

(b) (4)

3.2.P.2.1.2 Excipient Compatibility

Excipients were selected as follows:

(b) (4)

3.2.P.2.6 Compatibility

Tablets are formulated to be dispersible. When dosing of whole tablets is not possible, tablets may be administered as an aqueous dispersion. The impact of dispersion preparation on physiochemical properties of the final dosage form were assessed using 40mg batch (b) (4) and 80mg batch (b) (4).

(b) (4)

Study for Use of Tablet Dispersion

In early development studies, (b) (4)

(b) (4)

[redacted]

Dissolution Testing of Dispersion

Mean dissolution at pH 1.3, 4.5 and 6.8 for samples taken within 20 minutes of start of preparation for n=6 dispersions prepared under ambient conditions were compared to intact tablets. Conclude no significant differences in dissolution profiles within tablet dispersions and intact tablets. Dissolution using pH 1.3 media meets the proposed dissolution criterion (see NDA section 3.2.P.5.1) and dissolution was (b) (4) [redacted]

N=6 Mean %Dissolution results for dispersed vs. intact tablets

Time ***40mg tablet*** ***80mg tablet***

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Proposed handling instructions

Preparation of dispersions for oral administration

For patients who have difficulty swallowing tablets, AZD9291 film-coated tablets may be dispersed in two fluid ounces or 50 mL of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in water, without crushing, (b) (4) until dispersed and the resultant dispersion swallowed immediately. (b) (4) of water should then be used (b) (4) left in the glass. This should be, (b) (4) swallowed. No other liquids should be used. (b) (4)

Preparation of dispersions for administration using nasogastric tubes

AZD9291 film-coated tablets may be dispersed in (b) (4) mL of non-carbonated drinking water. No other liquids should be used.

The tablet should be dropped in water, without crushing, (b) (4) until dispersed and the resultant dispersion transferred immediately to an (b) (4). An additional (b) (4) of water should then be used to (b) (4) left in the glass (b) (4) No other liquids should be used. (b) (4)

Amendment S-009

Question 6: Given the lack of discriminating ability of your proposed dissolution method, consider the use of disintegration (DT) in lieu of dissolution testing. For this purpose, submit data showing the increased discriminating ability of disintegration testing towards the CMAs and CPPs identified for your product.

Response 6

No CMAs have been identified for tablets and the proposed dissolution method was shown to have some discriminating power with respect to the (b) (4)

The formulation development studies showed (b) (4)

Amendment S-033

Question 8: For the compatibility studies in NDA section 3.2.P.2.6, provide a description of the preparation of the proposed aqueous dispersion which details the pH, temperature, mixing time, mixing by (b) (4) (b) (4).

Question 29:

(d) (b) (4) (b) (4)

Response 8

(b) (4)

[redacted]

Reviewer's Assessment:

32P21: Tablet QTPPs are typical for this dosage form. Drug substance is low solubility an [redacted] (b) (4) Excipients were selected for [redacted] (b) (4)

32P24: Commercial presentation and bulk packaging are described in NDA

section 3.2.P.7. There are no qualification issues for the proposed container closure system. NDA shows that as long as tablets are reasonable dry, they are stable and perform as expected.

32P26: Compatibility studies for aqueous dispersion address only water and administration by oral or NG routes.

S-009/Response 6: Not including DT as a specification is (b) (4) Include this information in the package insert.

S-033/Responses 8 & 29d: Accept the conclusion that continuous (b) (4) stirring results in a dispersion that can be prepared at 15-30°C/ typical drinking water pH range; (b) (4). Package insert indicates the use of non-carbonated water which would have a lower pH and ionic strength due to carbonic acid.

S-033/Response 9: Accept the conclusion that dispersion is not significantly affected by tablet core hardness.

2.3.P.4 Control of Excipients

18. Is the quality of all excipients adequately controlled with satisfactory specifications?

No excipient is of animal or human origin.

Tablet Core: Mannitol NF; Microcrystalline Cellulose NF; Low Substituted Hydroxypropylcellulose NF; and Sodium Stearyl Fumarate, NF. Lots are accepted based on supplier CoA.

Film-Coating: (b) (4) Components may be obtained as a proprietary coating mixture, e.g., (b) (4) (product code (b) (4) manufactured by (b) (4) LoA for (b) (4) type II DMF (b) (4) is provided. Composition is as follows

(b) (4)
- Polyvinyl Alcohol (b) (4)
- Titanium Dioxide (b) (4)
- Macrogols (b) (4)
- Talc, (b) (4)
- Iron Oxide Yellow (b) (4)
- Iron Oxide Red (b) (4)
- Iron Oxide Black (b) (4)

Specification, Film-Coating

Description	(b) (4)
Identification (IR)	(b) (4)

Amendment S-033

Question 10: Provide a copy of the supplier's certificate of analysis for each lot of each excipient used to manufacture of the NDA registration batches of 40 mg and 80 mg tablets.

Response 10

Provided is tabulated list of excipient batches used to manufacture the primary stability study batches WAAB, VAAD, VAAE, VAAF, 14-001472AZ and 14-001473AZ. The initial commercial batches are CAAB, CAAC, AAAB, AAAC, AAAD. CoAs are provided for the listed excipient batches.

DP Batch#	*A*	*B*	*C*	*D*	*E*
WAAB	972	2051246	71331C	E310G	DT621649
VAAD	931	2051246	71331C	E310G	DT621649
VAAE	972	2051246	71331C	E310G	DT621649
VAAF	972	2051246	71331C	E310G	DT621649
14-001472AZ	931	2051246	71331C	E310G	DT606134
14-001473AZ	931	2051246	71331C	E310G	DT606134
CAAB	1021	3071300	71437C	E522G	DT630628
CAAC	1021	3071300	71437C	E522G	DT630628
AAAB	1021	3071300	71437C	E522G	DT630628
AAAC	1021	3071300	71437C	E522G	DT630628
AAAD	1021	3071300	71437C	E522G	DT630628

(b) (4)

[redacted]

Reviewer's Assessment:

Excipient and (b) (4) material grades are acceptable and acceptance specification is supplier CoA. Noted that core excipients, (b) (4) excipients and (b) (4) are USP/NF grade, but tablets are made in (b) (4) [redacted]

S-033/Response 10: Excipient specifications are based on supplier CoAs which address (b) (4) specification is acceptable, but AstraZeneca may create (b) (4) [redacted] Excipient formulation and material grades are listed.

2.3.P.5 Control of Drug Product

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future

commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

20. Are all the analytical procedures appropriately described and validated for their intended use?

3.2.P.5.1 Specification

Test	***Method***	***Criterion***
Description	visual	40 mg: round, biconvex, beige f/c tablets debossed 'AZ' over '40'/plain 80 mg: oval, biconvex, beige f/c tablets debossed 'AZ 80'/plain
Identity[a]	HPLC-UV	Consistent with t_R and UV spectra of RS
Assay	HPLC	(b) (4) % label claim
Degradants	HPLC	(b) (4) NMT (b) (4) % (b) (4) NMT (b) (4) % Total NMT (b) (4)
Dissolution	UV	Q (b) (4) % at 30 minutes, apparatus 2 (USP/EP/JP)
UDU[a]	HPLC	US JP/EP

a release testing only

Amendment S-033

Question 11: Specify when and how samples for release and stability testing are selected.

Response 11

Release samples are taken (b) (4)

Question 19: Specify whether multiple batches of bulk tablets will be combined to obtain a batch of packaged tablets. If yes, then the following additional information is needed:

(a) A description of how batches of bulk tablets are to be traced in the packaging process and reported on the certificate of analysis for packaged tablets.

(b) A description of how this procedure is to be addressed in the post approval stability studies.

(c) A release specification for batches of bulk tablets and packaged tablets which addresses identity, purity, assay, drug release and physicochemical attributes.

Response 19

(b) (4)

Question 20: Establish a specification for the release of bulk tablets from the manufacturing site (b) (4) and their acceptance at the packaging site (b) (4) and for the release of finished product from the (b) (4)

Response 20

All release testing is performed at AstraZeneca AB (Södertälje, Sweden) and the (b) (4)

An Inspection Plan is established for each bulk drug product received at AstraZeneca Pharmaceuticals LP (Newark, DE). The Inspection Plan will include a (b) (4)

Finished product release will include an additional documentation review by Quality Assurance.

Amendment S-041

Comment 2: The proposed release specification should be revised to specify that samples for release and stability testing will be taken from tablets in their finished package. Since you propose to (b) (4)

Response 2

AstraZeneca remains confident in the proposal that (b) (4) straZeneca has revised the proposed release specification to specify that samples for release and stability testing will be taken from tablets in their finished package (NDA section 3.2.P.5.1 has been revised).

NDA section 3.2.P.5.1: The following statement has been added, "The specification for AZD9291 40 and 80 mg film-coated tablets is presented below. Testing will be performed on tablets taken from the primary pack."

3.2.P.5.2 Method Descriptions

In each method description includes the following:

* Identification of the "Principle" of the method (e.g., HPLC or UV analysis)
* A procedure with exemplified (b) (4)
* Method Performance Verification (MPV) criteria chosen to assure method performance after limited adjustments (exemplified conditions).

Revisions to the method are controlled under (b) (4)

METHOD DESCRIPTIONS

(b) (4)

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3.2.P.5.5 Characterization of Impurities

Organic Impurities/Degradation Products

Comprehensive studies have been performed for impurities and degradants from AZD9291 mesylate (see NDA section 3.2.S.3.2). An assessment of impurity profiles in (b) (4) (see NDA section 3.2.P.5.4) and stability study results (see NDA section 3.2.P.8.3) were performed to identify degradants in tablets. No impurities except those observed in drug substance were observed and no tablet specific degradants were observed.

Metal Impurities

Metal impurities are controlled in drug substance. Excipients and process used for tablets present a very low likelihood of introducing metal impurities of toxicological concern.

Solvents

Controlled per ICH Q3C(R5). (b) (4)

3.2.P.5.6 Justification of Specification

Acceptance criteria are based on USP expectations, development history, batch analysis data and stability data. 40mg and 80mg tablets are manufactured from a (b) (4) thus the specifications differ only in tablet appearance. (b) (4) 1,2.

ASSAY ((b) (4) % LC)

Criterion is consistent with USP precedent and the proposed HPLC method was shown to be specific. Batch analysis data is summarized as follows:

	40mg	***80 mg***
Batch Count	(b) (4)	
Mean		
Range		
3 SD		
Mean+3SD		

CONTENT UNIFORMITY (USP)

Test is based on content uniformity with (b) (4) using an HPLC method that is specific for AZD9291 in tablets.

	40mg	***80mg***
Number of batches	(b) (4)	
Range of individual		
Range of AV (accept (b) (4) %)		

DEGRADATION PRODUCTS

HPLC method was shown to be stability indicating and specific with (b) (4) Per ICH Q6A, synthesis impurities which are not degradants and are named on drug substance specification are not included as specified degradation products for tablets.

(b) (4)

[redacted]

DISSOLUTION (Q= (b) (4) % at 30 minutes)

The proposed ug product is an immediate release tablet. In-vivo findings indicates that product quality will be assured by a dissolution method that demonstrates complete release and rate of dissolution is not significant. The proposed criterion addresses product variability and product performance on stability.

TESTS NOT INCLUDED in the SPECIFICATION

Microbiological Quality

Not considered necessary for the following reasons:

* Microbial challenge tests confirm that AZD9291 mesylate does not support microbial growth.
* (b) (4)
* Microbiological testing is routinely performed for (b) (4)
* Microbial control has been demonstrated at time of manufacture for all tablet batches listed in Table 1.

(b) (4)

(b) (4)

Metal Impurities

Tablets are made under GMP and metal impurities are controlled in drug substance. Excipients and manufacturing process are unlikely to introduce metal impurities of toxicological concern.

(b) (4)

Reviewer's Assessment:

3.2.P.5.1

Tests: Acceptable to establish identity, purity and assay for the finished drug product. Drug substance has (b) (4) Absence of DT in the specification is accepted in NDA section 3.2.P.2.6.

S-033/Response 13h: Drug substance reference standard test value (b) (4)

S-033/Response 11: (b) (4)

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(b) (4)

21. Is the proposed control strategy for the drug product manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale (refer to question #33 of the process section)?

Applicant's Response:

Reviewer's Assessment: Refer to responses to questions 20.

2.3.P.6 Reference Standards or Materials

22. Are the proposed drug product reference standards acceptable?

The proposed control strategies are as follows

(b) (4)

[redacted]

Reviewer's Assessment:

Control Strategy for tablets is acceptable based on information provided in NDA sections 3.2.P.3, 3.2.P.5 and 3.2.P.8

2.3.P.7 Container Closure System

23. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen, moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?

(b) (4)

[redacted]

(b) (4)

[redacted]

Reviewer's Assessment:

NDA section 3.2.P.3.1 indicates:

* AstraZeneca (Sodertalje, Sweden) for manufacture and testing
* AstraZeneca (Newark, DE) for (b) (4)

The NDA proposes (b) (4) See comments and conclusion in NDA section 3.2.P.8.

Materials of construction and descriptions are acceptable for the proposed use and dosage form. Request that the acceptance specifications be revised to include an Identity for material of construction.

Supplier DMFs are not reviewed in that sufficient CMC information is provided in the NDA.

S-033/Response 18a,b: Accepted

2.3.P.8 Stability

24. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?

25. Are the post-approval stability protocols and other stability commitments for the drug product adequate?

3.2.P.8.1 Stability Summary and Conclusion

PRIMARY STUDIES

3x40mg and 3x80mg batches manufactured using the commercial manufacturing process at (b) (4) production scale in the commercial package were placed on stability per ICH Q1A at ICH LT, ICH INT, ICH ACC and stressed (thermal, photolytic, humidity) conditions. One batch of each tablet strength in bulk packs was also included. Bulk package and primary packages are described in NDA section 3.2.P.7.

Drug substance batches used to manufacture the tablets (tables 1 and 2) were manufactured using a process representative of the commercial process and are considered to be representative of the current and future drug substance quality.

Proposed commercial pack and bulk pack are used in the studies. Study duration will be (b) (4) but only 6M is provided. Data are used to set an initial shelf life for 40mg and 80mg tablets. (b) (4)

Batches Tested

Table 1: 40mg tablet stability batches

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(b) (4)

STABILITY CONCLUSION (Amendments S-011 and S-033)

Primary Package

Based on the data in the primary and supportive studies for 40mg and 80mg tablets and the data in Amendment S-033/Response 21 (ICH LT/9M, ICH INT/9M, ICH ACC/6M tablets in primary container), conclude that an initial shelf life of (b) (4) is supported for commercial tablets packaged in an HDPE bottle containing (b) (4) with a product label storage condition of 'Store at 25°C (77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]'.

Shelf life will be reviewed periodically and updated as appropriate when more data becomes available.

Bulk Package

Based on the data in amendment S-033/Response 21 (ICH LT/9M and ICH ACC/6M), conclude that an initial shelf life of (b) (4) is supported for tablets (40mg and 80mg) when stored in the (b) (4) with a product label storage condition of "Store at 25°C (77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]'.

The shelf life will be reviewed periodically and updated as appropriate when more data becomes available

Amendment S-011

Reference the pre-NDA meeting on 09 Dec 2014, where FDA acknowledged the agreement to receiving 6M stability data plus supportive data from 12M DP stability data from clinical batches and 24M DS stability data from clinical batches. During the meeting, FDA expressed strong preference to receive 9M DP stability data within 30 days of the final component of the NDA submission.

Amendment S-033

Question 22: Regarding the stability information in NDA sections 3.2.P.8.1 and 3.2.P.8.3:

(a) For tables 1 and 2 in NDA section 3.2.P.8.1, identify the site and date for packaging into bottles for each listed batch.

(b) The stress studies show (b) (4) and the formation of new degradation products under light stress, therefore the label storage statement should be revised to include a "protect from light (b) (4) statement.

Response 22a

The requested information is tabulated below.

DP Batch	***Strength***	
WAAB	40mg	(b) (4)
14-001472AZ	40mg	
14-001473AZ	40mg	
VAAD	80mg	
VAAE	80mg	
VAAF	80mg	

Response 22b

Light Protection

AstraZeneca disagrees. The photolytic study shows little or no increase in individual unspecified or total degradants and no new degradants were observed in the study. Provided is a data summary (from NDA section 3.2.P.8.3).

(b) (4)

(b) (4)

.

Question 23: The submitted stability studies are not adequate to support the proposed shelf-life in that they do not address (b) (4)

(b) (4)

for the manufacture and control of drug substance and drug product. Until acceptable studies have been completed and submitted, we recommend the following:

a. (b) (4)

b. The initial shelf-life for tablets in bottles should be revised to 12 months.

Response 23

As discussed in S-033/Responses 21 (above) and 22 (NDA section 3.2.P.8.2), AstraZeneca believes that the submitted stability data (b) (4)

Batch Suitability

Tablet batches in the primary studies were made at (b) (4) scale using a manufacturing process that is representative of commercial batches. The packaging system is that to be used for marketing. This meets the requirement of ICH Q1A(R2).

Interpretation of Stability Data

The currently available tablet stability data shows (b) (4) (S-033/Response 22b), but the data for stress conditions shows little or no change for any attribute tested. The absence of notable changes to the CQAs (description, assay, degradants, dissolution) under stress conditions show that tablets are inherently stable. This indicates that the level of protection afforded by the bulk and primary packages are unlikely to be required.

(b) (4)

Overall Conclusion

Based on the considerations above, AstraZeneca is of the opinion that overall shelf life of (b) (4) is appropriately supported, but recognizes the FDA concern around the (b) (4) This aligns with the currently available long term stability data in the (b) (4) during which little or no change was seen in any of the attributes tested.

Question 24: (b) (4)

Response 24

AstraZeneca acknowledges that the submission of additional stability data during the NDA review period would result in an extension of the review clock. To avoid this AstraZeneca can confirm that they do not intend to provide any further stability data during the NDA review period.

As discussed in S-033/Response 23, tablet batches used in the stability studies fully satisfy the batch selection requirements of ICH Q1A(R2). AstraZeneca continues to believe that (b) (4)

Question 30: [redacted]

Response 30

[redacted]

Amendment S-041

Comment 4: Pending approval of the NDA, we have concluded that based on the stability data and information submitted to the NDA, the data supports the following timeframes:

a) [redacted]

b) A shelf life of 12 months with storage of finished product at USP controlled room temperature when packaged in the proposed HDPE bottle with [redacted]

The stability data and information submitted to the NDA does not include a study of [redacted] proposed in the NDA; and the specifications for release and acceptance [redacted]

Response 4

AstraZeneca accepts the Agency's position. NDA section 3.2.P.8.1 has been revised to indicate:

[redacted]

3.2.P.8.2 Post-Approval Stability Protocol and Commitment

The primary stability studies will continue per the protocol presented in NDA section 3.2.P.8.1.

The shelf life assigned is limited by the amount of stability data currently available, thus will be reviewed periodically and updated as appropriate based on a combination of data from the primary stability batches and those from commercial stability studies.

Commercial Stability Program

[redacted]

Annual Maintenance Stability Studies

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3.2.P.8.1

Batches: The listed batches are adequate for the intended purpose in that they use acceptable drug substance, manufacturing process and packaging.

Protocol: Sample times, conditions and testing for the primary, stress and supportive studies are acceptable. The HPLC methods for assay and degradants are not the NDA methods, but are adequate for the intended purpose and there is no method change during the study. The HPLC methods used are more sensitive, but have a problem with resolution.

Data Summary: The study results and discussion reflect the tabulated data in NDA section 3.2.P.8.3. The summary and discussion presumes that commercial and clinical tablet are equivalent, thus does to differentiate. NDA section 3.2.P.8.3 show these batches have different degradant profiles, but no unpredictable changes or new degradants.. There is no tabulated study data for long term storage of bulk tablets and the primary studies are (b) (4) then packaged into bottles and placed on long term stability.

Conclusion Primary Container: Concur with the NDA conclusion in amendment S-002 that commercial tablets in the primary package for (b) (4) is supported by the submitted study data.

(b) (4)

k

g

y

S-011 and S-033-Response 21 - Revised Conclusions: (b) (4)

S-011: The comment is acknowledged.

S-033/Response 22a: Accepted in that the requested information is provided. Noted that the NDA proposed packaging site (b) (4)

S-033/Response 22b: Accept the applicant's conclusion regarding light and moisture protection. (b) (4) Noted that the primary package is a 30-count bottle with (b) (4) which indicates that the applicant anticipated the problem.

S-033/Response 23: Noted that the stability conclusion (NDA section 3.2.P.8.1) in amendment S-002 is for (b) (4)

(b) (4)

[redacted]

(b) (4)

S-041/Response 5: The applicant's proposal to submit the protocol within 6 weeks after NDA approval is acceptable, but the NDA cannot be amended after approval. In a 10/21/15 Tcon, AstraZeneca stated that the protocol would be submitted as an amendment to IND 117879.

3.2.P.8.3

Primary Studies: No significant difference in trends or degradant profiles between 40mg and 80mg tablets in either package. All tests meet specification. (b) (4)

No new degradants and no significant degradation are reported over time/conditions, (b) (4)

Stress Studies: (b) (4)

No new degradants and no significant degradation are reported.

Phase 1 Tablets: (b) (4)

All batches meet specification across time/condition.

Clinical Batches: Degradants show no change as in the primary studies (b) (4)

All batches meet current specification across time/condition.

Summary: Data shows no increase in observed degradants over time/condition and specification is met across time/condition. Degradant profile is dependent (b) (4) (b) (4)

R.2 Comparability Protocols

26. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Reviewer's Assessment: None

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
The NDA is recommended for approval in that the CMC information regarding drug product is complete and acceptable.
The applicant is being allowed to release and market (b) (4) tablet batches not made by the NDA process for the purpose of launching this breakthrough designated product.
The applicant has agreed to submit an amendment to IND 117879 containing additional stability information, a protocol for a stability study which addresses the contiguous manufacturing process and additional stability information.

Signed: William M. Adams, CMC-DP reviewer 22 Oct 2015

Secondary Review Comments and Concurrence: I concur with the primary reviewer's conclusion regarding approvability and the allowance to release the (b) (4) tablet batches not made by the NDA process for the purpose of launching this breakthrough designated product. Please refer to the minutes of the teleconference held 21-Oct-15 regarding clarification of agreements around this issue (not yet filed)

Signed Olen Stephens, CMC DP acting branch chief 22-Oct-15

ASSESSMENT OF THE PROCESS

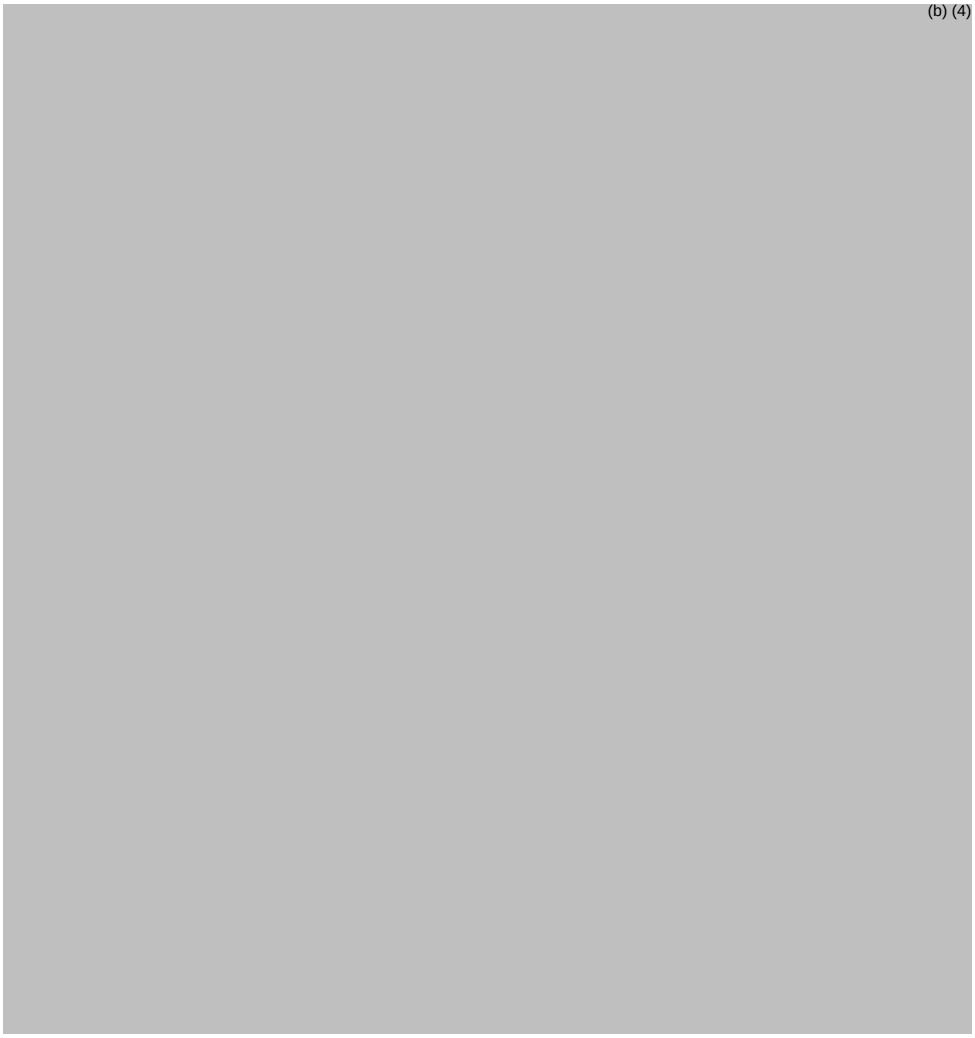
2.3.P DRUG PRODUCT

2.3.P.2.3 Manufacturing Process Development

27. Does the information described in the pharmaceutical development section support the proposed drug product manufacturing process?

Applicant's Response:

(b) (4) flow diagram of the manufacturing process of AZD 9291 film-coated tablets is presented below:



The applicant provided the following sections for process development which will be assessed later in the review:

- Quality attributes potentially impacted by the manufacturing process.
- Failure modes identified through development and from risk assessments.
- Development work and clinical manufacturing experience used to evaluate and define the control strategy
- Control strategy for each unit operation.

Finally the overall control strategy applied to ensure the quality of AZD9291 film-coated tablets is presented.

Reviewer's Assessment:

The applicant uses (b) (4) to manufacture the drug product. The overall flow chart was provided and is shown above. The following drug

product information may need to be considered in process assessment:

- Drug substance: (b) (4) . The solubility data are listed as below:

Table 1 AZD9291 mesylate solubility in various media (37°C, 24 hours)

Medium	Solution pH [a]	Solubility, as AZD9291 (mg/mL) [b, c]	Descriptive term
pH 1.2 HCl/KCl	1.24	>3	Slightly soluble
pH 4.5 acetate buffer	4.60	>11	Sparingly soluble
pH 6.8 phosphate buffer	6.73	>5	Slightly soluble
pH 7.0 phosphate buffer	7.00	0.60	Very slightly soluble
pH 7.25 phosphate buffer	7.25	0.26	Very slightly soluble
pH 7.5 phosphate buffer	7.49	0.07	Practically insoluble
FaSSIF (pH 6.5)	6.47	>5	Slightly soluble
Water	NT	3.1	Slightly soluble
Ethanol (99.5%)	NT	0.9	Very slightly soluble
Diluent [d]	NT	111	Freely soluble
DMSO	NT	18.9	Sparingly soluble
(b) (4)			

As shown above, the drug substance is highly soluble in stomach and upper GI, according to BCS definition. (b) (4)

- (b) (4)

The dissolution method used throughout development, at release and throughout the shelf life of the product, is (b) (4) See evaluation below for process development details.

28. What process parameters and material attributes were identified as critical and how do they impact the drug product CQAs?

Applicant's Response:

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(b) (4)

2.3.P.3 Manufacture

P.3.2 Batch Formula

31. Does the provided batch formula reflect the proposed composition and that of the registration batches?

Applicant's Response:

Table 1 Batch formula for AZD9291 40 mg film-coated tablets

Components	Quantity per unit (mg)	Quantity per (b) (4) kg batch (kg)
Tablet core		
AZD9291 mesylate [a]	47.7	(b) (4)
Mannitol		(b) (4)
Microcrystalline cellulose		
Low-substituted hydroxypropyl cellulose		
Sodium stearyl fumarate		
Tablet coating (nominal weight) [b, c]		
Polyvinyl alcohol		(b) (4)
Titanium dioxide		
(b) (4) 3350		
Talc		
Yellow ferric oxide		
Red ferric oxide		
Black ferric oxide		
(b) (4)		
		(b) (4)

[a] The tablet coating ingredients listed may be included as a propriety composite.

(b) (4)

Table 2 Batch formula for AZD9291 80 mg film-coated tablets

Components	Quantity per unit (mg)	Quantity per (b) (4) kg batch (kg)
Tablet core		
AZD9291 mesylate [a]	95.4	(b) (4)
Mannitol		(b) (4)
Microcrystalline cellulose		
Low-substituted hydroxpropyl cellulose		
Sodium stearyl fumarate		
Tablet coating (nominal weight) [b, c]		
Polyvinyl alcohol		(b) (4)
Titanium dioxide		
(b) (4) 3350		
Talc		
Yellow ferric oxide		
Red ferric oxide		
Black ferric oxide		
(b) (4)		
		(b) (4)

[a] The tablet coating ingredients listed may be included as a propriety composite

(b) (4)

Reviewer's Assessment:

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

(b) (4)

[redacted]

P.3.4 Controls of Critical Steps and Intermediates

33. Is the proposed control strategy for the drug product manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale (refer to question 21 of the drug product section)?

Applicant's Response:

In-process Control

(b) (4)

[redacted]

In the 10/15/2015 amendment, the applicant provided the following updated critical elements of the control strategy for AZD9291 film-coated tablets:

Unit operation	Quality attribute	Manufacturing process controls	In-process controls

(b) (4)

(b) (4)

(b) (4)

[redacted]

34. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Applicant's Response:

As part of the development strategy a microbial limit test method was developed for AZD9291 film-coated tablets, however it is not considered necessary to perform the test on the product at the time of manufacture. The justification for this approach includes consideration of all aspects of ICH Q6A Decision Tree number 8 (Microbiological Attributes of Non-Sterile Drug Products) and is discussed in 'P.5.6 Justification of Specification for Drug Product'.

Reviewer's Assessment:

See microbiology review below for details. Microbiological control is not a concern from process perspective.

R.2 Comparability Protocols

35. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Applicant's Response: N/A

Reviewer's Assessment:

No comparability protocol was provided for drug product manufacturing process.

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

The NDA is recommended for approval by the manufacturing process reviewer. There are no pending review issues and no risk mitigation actions required at this time.

- Ying Zhang 10/20/2015

Secondary Review Comments and Concurrence:

I concur with the evaluation and conclusions of the primary reviewer.

Bogdan Kurtyka, 10/20/2015

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

36. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		API manufacturing and QC testing CSN Profile	NME API manufacturer	PAI waived because of site history and low risk processes	Acceptable based on manufacturing history Post-Approval coverage recommended

Information Request sent August 21, 2015 from FDA question #1 regarding facility: You propose to use clinical lots formulated with lots of API campaign 3 or 4 for commercial launch of your drug product. Confirm the drug substance and drug product batches intended to be used for launch, provide their dates and location of manufacture and packaging, and the manufacturing processes used. Include manufacturing sites for these batches in the 356h form. Use of these batches will require a facilities evaluation and potentially inspection of their manufacturing sites before approval of the NDA.

Applicant's Response:

Drug substance intended to be used for initial commercial distribution of AZD9291 film-coated tablets in derived from establishment campaign 4, only. (b) (4) which is already included in 356h) in December 2014/January 2015, the proposed commercial specification and batch data was provided in 3.2.S.4.4 Batch Analysis for Drug Substance of NDA 208065. The manufacturing process used to produce establishment campaign 4 drug substance varied from the process described in "3.2.S.2.2 Description of Manufacturing Process and Process Controls for Drug Substance" of NDA 208065 in 3 minor aspects as described in "3.2.S.2.6 Manufacturing Process Development" and also in the information supplement "Reviewer Guide to Support Sponsor's Request for the Use of Establishment Batch (Development) Drug Substance in the Initial Drug Product Commercial Supply" provided in NDA 208065. These minor differences did not involve any critical parameter and have been assessed as having no significant impact on drug substance quality.

Reviewer's Assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	Drug substance and QC testing	12	6	10	**28**

(b) (4) is the proposed commercial drug substance manufacturer. This facility was last inspected (b) (4) as preapproval inspection for a (b) (4) drug

substance and found to be VAI with three observations related to the application inspected. The inspection prior to this last inspection was (b) (4) covered (b) (4) profile (drug substance of (b) (4)) and found to be VAI. The inspection conducted (b) (4) was classified as NAI and covered (b) (4) profile. This site has been inspected at least (b) (4) for PAI and Surveillance inspection in the last (b) (4) years with no significant compliance history. Production load has been consistent over the last 5 years. There is no significant manufacturing risked associated with the synthesis of AZD9291 at this facility. No PAI inspection was requested. However, (b) (5)

AZD9291 mesylate is the drug substance for this NDA. While this drug substance is a New Molecular Entity, the facility risk for AZD9291 mesylate API manufacture is low. AZD9291 mesylate is a solid (b) (4) The drug substance is produced by a process using (b) (4) The overall control strategy appears appropriate and the manufacturing operations are supported by development studies.

(b) (4) have been identified by the applicant as suitable starting materials. The applicant also provided a list of vendors (b) (4) Supplier's qualification and acceptance criteria were established and appeared adequate.

Assessment of IR Response: **Adequate**-The applicant requested to use clinical lots formulated with lots of API campaign 4 for commercial launch drug product. An IR was sent and confirmed that the campaign 4 drug substance batches intended to be used for launch was manufactured at the (b) (4) as listed on 356h. All batches met the proposed commercial specification, including debossing design. There is no additional risk for distributing the clinical lots manufactured at the same proposed API site as long the product met all proposed commercial specification.

Based on the inspection history and associated Risk Assessment, the facility is adequate for API production of AZD9291 mesylate.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

37. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Astrazeneca Pharmaceutical LP	2517100	Drug product primary/ secondary/packaging/ labeling/release Profile TCM	NME	low risk	Acceptable
Astrazeneca AB	3003342394	Drug product, QC/Release/Stability testing. Profile TCM/CTL	NME	low risk	Acceptable
(b) (4)		Stability Testing	NME	low risk	Acceptable

Applicant's Response:

Reviewer's Assessment:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment

Astrazeneca Pharmaceutical LP	2517100	TCM	Drug product primary/secondary packaging/labeling/release	10	6	10	**26**
Astrazeneca AB	3003342394	TCM	Drug product, QC/Release/Stability testing	7	6	10	**23**
(b) (4)		CTX	Stability testing	23	5	0	**28**

Astrazeneca AB (FEI 3003342394) is responsible for drug product manufacturing, quality control testing, drug product release, and stability testing. This firm was last inspected in March, 2014 and received a seven item FDA Form 483. They adequately addressed these observations and the inspection was classified as VAI. The inspection covered CHG, CTL, SVL, TCM, and TTR profiles. The two inspections prior to the previous inspection were both NAI. Production load has been consistent over the last five years.

Astrazeneca Pharmaceutical LP (FEI 2517100) is responsible for primary packaging, secondary packaging, labeling, and releasing of the drug product. This firm was last inspected in August, 2014 and received one item FDA Form 483 for (b) (4). This inspection was classified as VAI. The inspection prior to the last inspection was conducted in November, 2011 and classified as NAI. The inspection conducted in July, 2011 was classified as VAI with one item FDA form 483.

While this drug product is a New Molecular Entity, the facility risk for the AZD9291 drug product is low. No PAI inspection was requested. However, (b) (5)

(b) (4) is the stability testing facility. This firm was inspected in (b) (4) and no FDA Form 483 was issued. The inspection was classified as NAI. The inspection covered CTL profile. This was first FDA inspection at this facility.

AZD9291 tablets are beige film-coated tablets containing 40 and 80 mg of AZD9291. AZD9291 film-coated tablets are manufactured from a (b) (4)

(b) (4)

Please refer to the Information Requested by the drug product reviewer for additional information regarding the proposed sampling plan for tablet content uniformity.

Based on the inspection history and associated Risk Assessment, the facilities are adequate for manufacturing/testing of the drug product AZD9291 mesylate.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional history, there are no significant, outstanding manufacturing risks that prevent approval of this application.

Based on firm's inspectional history and the associated Risk Assessment, the manufacturing facilities as listed above for NDA 208065 are found to be acceptable. Post-approval inspectional coverage is recommended for drug substance and drug product manufacturers.

Thuy T. Nguyen
Consumer Safety Officer, OPQ/OPF/DIA/BI

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D.
Branch Chief, OPQ/OPF/DIA/BI

ATL Note: Refer to the facilities recommendation rendered in Panorama (copied at the end of this document) for review dates.

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics review of this NDA focused on (1) the proposed dissolution method and acceptance criteria, and (2) the bridging of the proposed commercial film-coated tablets to various osimertinib formulations used in the AURA (Expansion and Extension) and the AURA 2 Studies.

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes.

Dissolution method:

a. What are the proposed dissolution method parameters?

The proposed dissolution method for osimertinib 80 mg and 40 mg tablets is summarized in Table 38-1 below.

Table 38-1. Proposed Dissolution Method for Osimertinib 40 mg and 80 mg tablets

Apparatus	(b) (4)
Paddle speed	
Medium	
Temperature	
Quantification	

b. Why were these dissolution method parameters selected? Does the dissolution method have discriminating capability?

Per the Applicant, this dissolution method was selected based on (b) (4)

The Applicant claims that the (b) (4)

Figure 38-1.
Dissolution of 40 mg tablets (b) (4) at different pressures

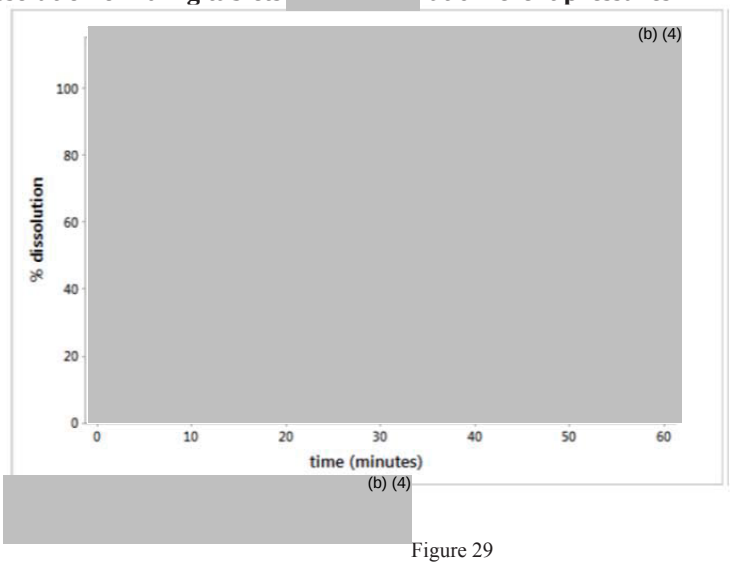


Figure 29

Table 38-2.
Tablet (b) (4) data for 40 mg tablets from clinical manufacturers

(b) (4)

(b) (4)

(b) (4)

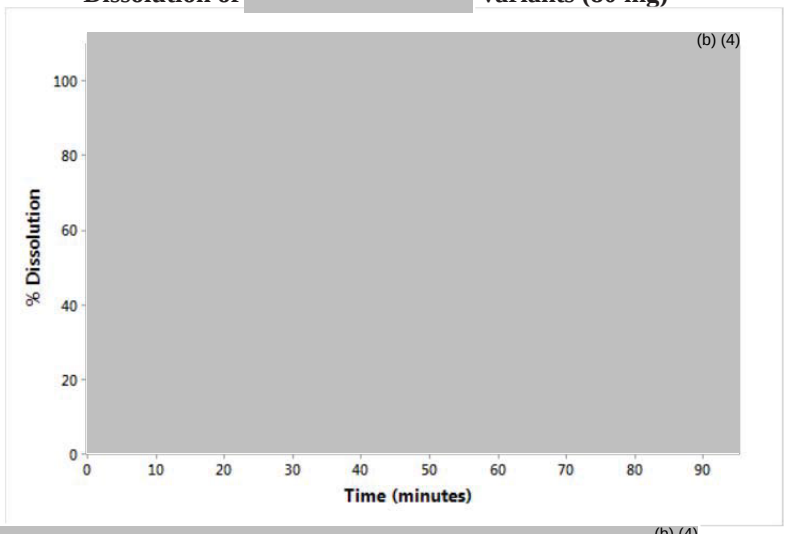
Figure 38-2.
Dissolution profiles of 40 mg coated tablets and 80 mg tablet cores (b) (4)

Source: Adapted from NDA 208-065, P.2.2 Drug Product, Figures 11 and 12; n=6

Additionally, the proposed dissolution method (b) (4) (b) (4)

Figure 38-7 compares the mean osimertinib dissolution profiles of the 3 batches of 40 mg tablets and the 12 batches of 80 mg tablets used in the pivotal Phase 2 Studies. (b) (4)

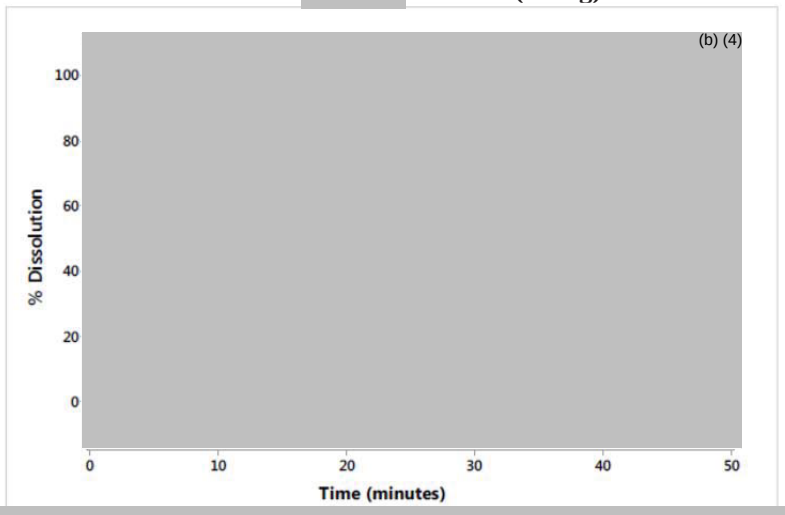
Figure 38-3.
Dissolution of (b) (4) variants (80 mg)



(b) (4)

Source: NDA 208-065. P.2.2 Drug Product, Figure 31

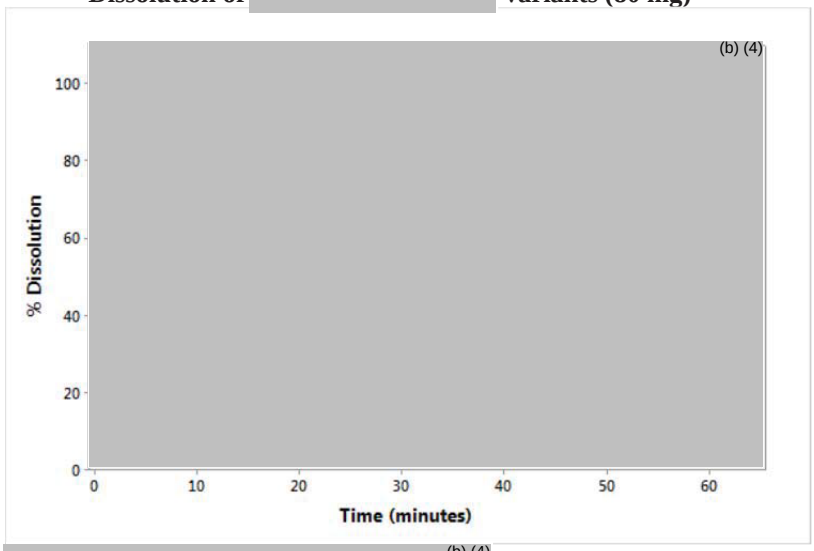
Figure 38-4.
Dissolution of (b) (4) variants (40 mg)



(b) (4)

Source: NDA 208-065, P.2.2 Drug Product, Figure 23

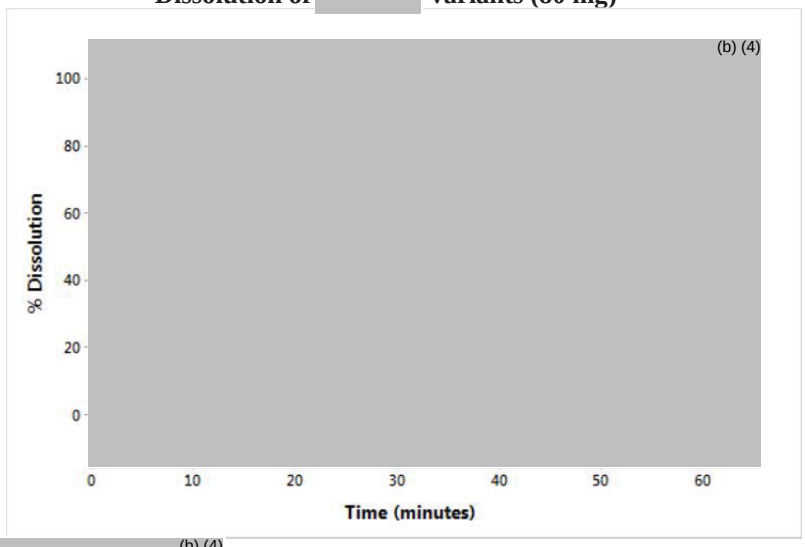
Figure 38-5.
Dissolution of (b) (4) variants (80 mg)



(b) (4)

Source: NDA 208-065, P.2.3 Manufacturing Process Development, Figure 13

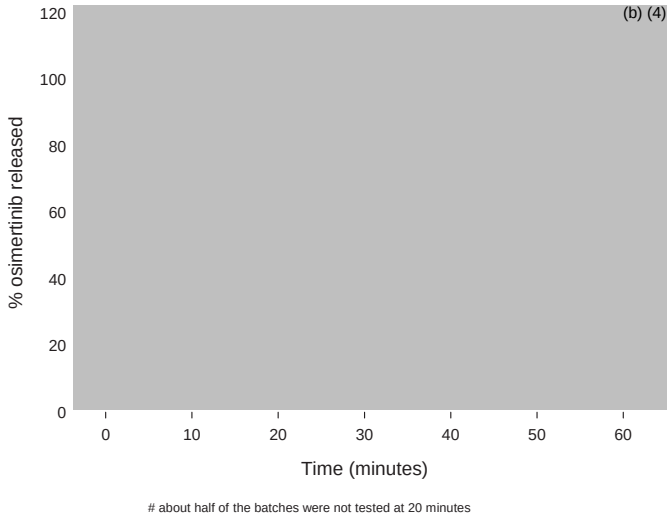
Figure 38-6.
Dissolution of (b) (4) variants (80 mg)



(b) (4)

Source: NDA 208-065, P.2.2 Drug Product, Figure 9

Figure 38-7.
Dissolution of 40 mg and 80 mg tablets used in Phase 2 Studies
AURA Extension and AURA2



c. Is disintegration a suitable alternative to dissolution for drug release testing?

The Applicant proposes not to use disintegration in lieu of dissolution testing as a routine QC test since there was no observed correlation between dissolution and disintegration rates of osimertinib tablets. (b) (4)

Reviewer's Assessment (Dissolution Method):
The proposed dissolution method exhibits discriminating capability as it was able to detect differences in (b) (4) tablet hardness of different clinical batches of 40 mg tablets. The apparent limited influence of manufacturing and formulation variables on the dissolution profiles of osimertinib tablets could be explained at least in part by the high solubility of the drug substance over a wide pH range. The sponsor's development studies did not reveal method parameters that were more sensitive and as biorelevant as those proposed.

The proposed dissolution method is adequate to assure batch-to-batch variability via monitoring complete dissolution of osimertinib tablets at the time of manufacturing release and during stability testing.

Dissolution acceptance criterion:

d. What is the proposed dissolution acceptance criterion? Why was it selected?

The proposed dissolution acceptance criterion is shown below.

Q = (b) (4) % at 30 minutes.

The Applicant set the dissolution acceptance criteria (b) (4)

Additionally, an earlier Specification time point ((b) (4) e.g., 30 minutes) would minimize variability and the probability of unnecessarily failing clinically acceptable batches.

The Applicant also states that dissolution is not the rate-limiting factor for oral absorption of osimertinib (a highly soluble compound) as evidenced by the *in vivo* equivalence of the oral capsule and the Phase 1 tablet to the oral *solution* in healthy subjects (Study 5). Since the proposed drug product is an immediate release oral dosage form, product quality can be assured by using a biorelevant dissolution method that can confirm complete drug release.

Reviewer's Assessment (Dissolution Acceptance Criterion):

In Phase 2 Studies AURA (Extension phase) and AURA2, non-small cell lung carcinoma (NSCLC) patients received osimertinib 80 mg once daily; approximately 2% of these patients had a dose reduction to 40 mg once daily due to adverse events. The reviewer's process capability analysis considered the dissolution data at the time of manufacturing release of 15 batches of 40 mg and 80 mg *plain* film-coated tablets used in the AURA Extension and AURA2 clinical trials. Table 38-3 and Figure 38-8 show that (1) if (b) (4) minutes is chosen as the specification time point for Q= (b) (4) % of these pivotal clinical lots will fail Stage 1 dissolution testing, compared to (b) (4) % if 30 minutes is chosen instead. Note that the Applicant did not determine dissolution at the (b) (4) minute time point (b) (4) (b) (4)

Table 38-3.
USP Stage 1 Dissolution Failure Rates of Phase 2 AURA (Extension) and AURA2 clinical lots 40 mg and 80 mg osimertinib tablets at various specification time points

	By Batch	By Individual Units
Time point	(b) (4)	
7.5 min		
15 min		
20 min[a]		
30 min		
45 min		
60 min[b]		

(b) (4)

Figure 38-8.
Dissolution of Phase 2 AURA Extension and AURA2 clinical lots (40 mg & 80 mg plain tablets) (b) (4) vs 30 min timepoints

In the Reviewer's secondary process capability analysis, available dissolution data from primary stability and supportive stability of clinical lots were considered. Figure 38-9 depicts the (b) (4) and 30-minute dissolution measured from pivotal clinical batches during long-term storage; (b) (4)

(b) (4)

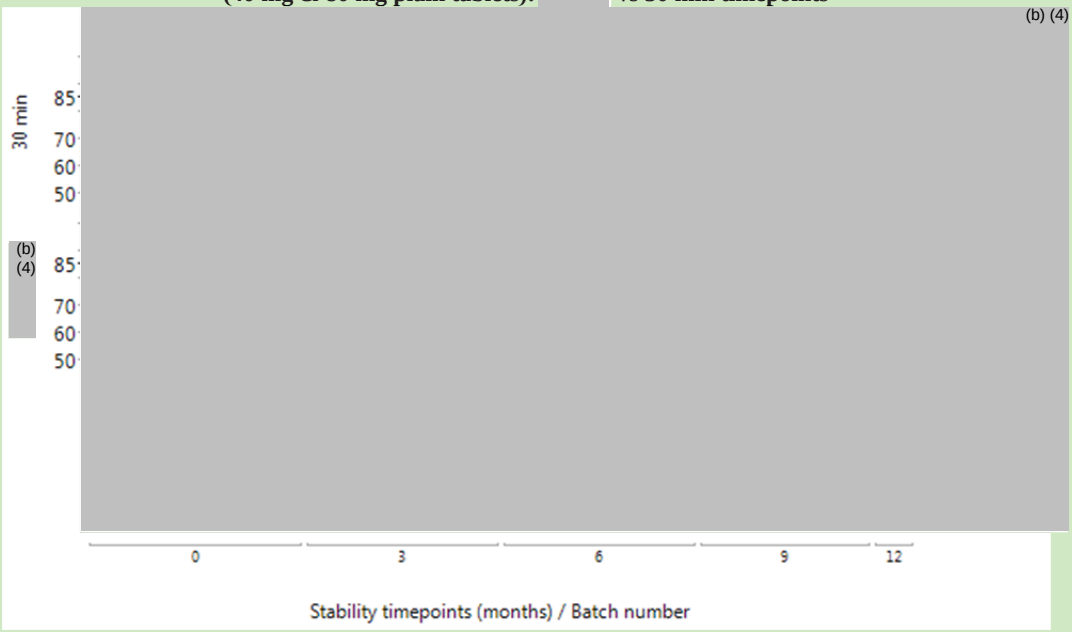
Of note, the Applicant reported that all batches at the time of release and stability testing complied with the assay/potency specification (b) (4) % of label claim) and there has been no evidence of time-dependent trends.

Table 38-4.
USP Stage 1 Dissolution Failure Rates (%) of clinical batches under long-term storage

	40 mg	80 mg
Stability Timepoint (Month; number of batches tested [a])	(b) (4)	
DissolutionTimepoint		
7.5 min		
15 min		
20 min		
30 min		
45 min		
60 min		

(b) (4)

Figure 38-10.
Dissolution of Phase 2 AURA Extension and AURA2 clinical lots placed on long-term stability (40 mg & 80 mg plain tablets): (b) (4) vs 30 min timepoints



39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

a. What formulations were used during the clinical development program?

Table 39-1 summarizes the osimertinib oral dosage forms, strengths, and batch numbers used in clinical studies. During clinical development, osimertinib (AZD9291) oral

capsules (20 and 40 mg), Phase 1 film-coated tablets, and Phase 2 *plain* film-coated tablets were evaluated in clinical trials. The film-coated tablets used in pivotal Phase 2 Studies D1560C00001 (AURA Extension) and D1560C00002 (AURA2) were initially manufactured in (b) (4) and later in the Södertälje (proposed commercial) manufacturing site. The proposed commercial *debossed* film-coated tablets are compositionally the same as the pivotal Phase 2 trial *plain* film coated tablets.

Table 39-1.
Summary of drug product batches used in the various clinical trials

Study number	AZD9291 capsules		AZD9291 Phase 1 tablets		AZD9291 film-coated tablets	
	Strength	Batch number	Strength	Batch number	Strength	Batch number
D5160C00001 (Escalation)	20 and 40 mg	All batches presented in Table 3 in '3.2.P.5.4 Batch Analyses for Drug Product'	NA	NA	NA	NA
D1560C00001 (Expansion)	NA	NA	80 mg	13-002282AZ 14-000012AZ	NA	NA
D1560C00001 (Extension)	NA	NA	NA	NA	40 mg	14-000602AZ, WAAB, 14-001472AZ
					80 mg	14-000015AZ, 14-000364AZ, 14-000745AZ, VAAB, VAAC, VAAD, 14-001471AZ, VAAE, VAAF, VAAG, VAAK, VAAM
D1560C00002	NA	NA	NA	NA	40 mg	14-000602AZ, WAAB, 14-001472AZ
					80 mg	14-000015AZ, 14-000745AZ, VAAC, VAAD, 14-001471AZ, VAAE, VAAF, VAAG, VAAK, VAAM
D1560C00005	20 mg	13-001233AZ 13-002502AZ	20 mg	13-002281AZ	NA	NA
D1560C00010	NA	NA	NA	NA	80 mg	VAAC

NA Not applicable.
Proposed commercial tablets: same as the film-coated tablets used in pivotal Phase 2 Studies D1560C00001 (AURA Extension) and D1560C00002 (AURA2) but will be debossed. Sodertalje was introduced as a manufacturing site in Phase 2. Source: Applicant's response to Quality Information Request (SDN-19 dated 10 July 2015, Table 2)

b. Are the proposed commercial tablets bridged appropriately to the tablets used in the pivotal Phase 2 trials?

(b) (4)

c. What in vitro and/or in vivo data are available to bridge the Phase 1 formulations to the pivotal Phase 2 tablets?

The 80 mg tablet used in the Expansion phase (US only tablet cohort) of Phase 1 AURA is qualitatively the same but quantitatively slightly different from that used in the pivotal Phase 2 Extension cohort of AURA (i.e., (b) (4)

The comparative *in vitro* dissolution profiles and *in vivo* PK parameters of the AURA Expansion tablet and the AURA Extension tablet are shown in Figure 39-2 and Table 39-2, respectively. In terms of mean cumulative amount dissolved, both Phase 1 (AURA Expansion) tablet and Phase 2 (AURA Extension) tablet are very rapidly dissolving (i.e., on average, (b) (4) % dissolves in (b) (4) minutes); f_2 analysis was not warranted. Furthermore, following multiple dose administration of 80 mg once daily to patients, the mean AUC_T and $C_{max,ss}$ of osimertinib were not higher for the Expansion tablet although the extent of drug release at (b) (4) were generally slightly higher as compared to the Extension tablet.

The comparative *in vitro* dissolution findings for the Phase 1 tablets and the Phase 2 tablets (as shown in Figure 39-2) are consistent with the observation during the Applicant's development studies that (b) (4) (Figure 38-3) does not result in a significant impact on the ability of the variant tablet to release > (b) (4) % of label amount within (b) (4) minutes.

Figure 39-2.
Dissolution profiles of 80 mg osimertinib tablet batches used in Phase 1 (AURA Expansion) versus Phase 2 (AURA Extension)
Left panel: by Study Phase and by batch
Right panel: by Study Phase (average of all batches)

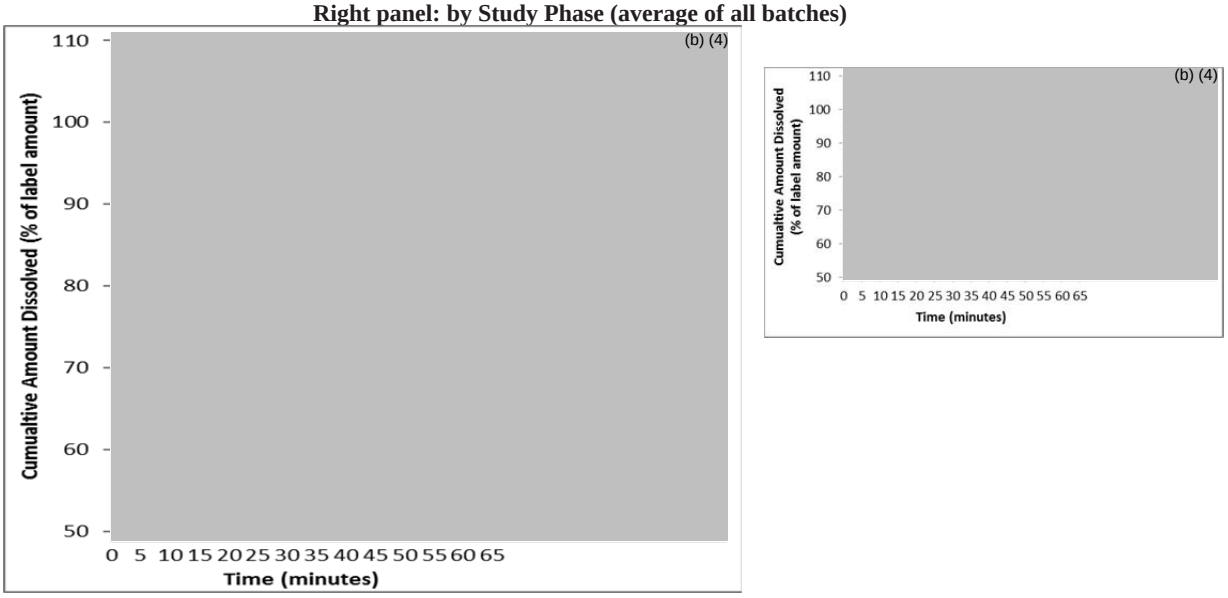
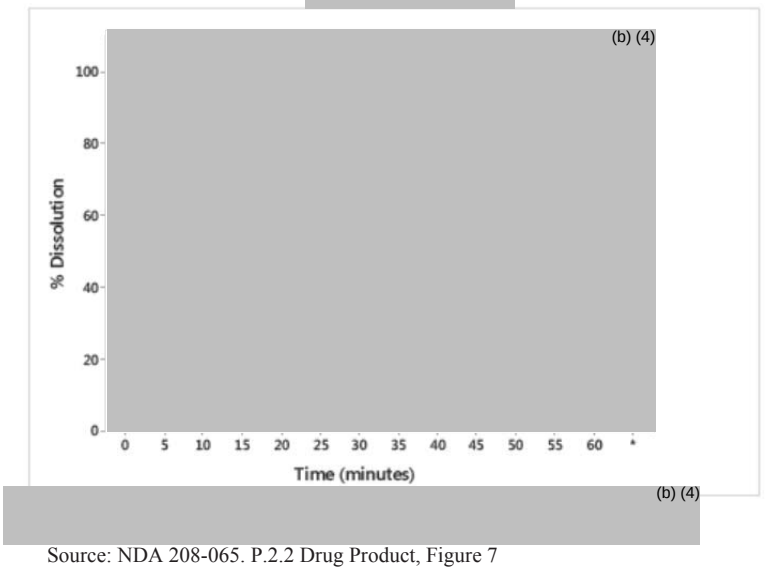


Table 39-2.
Osimertinib PK parameters following multiple dose administration of 80 mg once daily: AURA Expansion versus AURA Extension

	Expansion (n=11 patients)	Extension (n=186 patients)
AUC_T (h*nmol/L)	11095 ± 5013	13158 ± 6443
Cmax,ss (nmol/L)	579 ± 266	691 ± 333
Cmin,ss (nmol/L)	385 ± 176	429 ± 230

Figure 39-3.
Dissolution of 80 mg tablets with (b) (4)



Source: NDA 208-065. P.2.2 Drug Product, Figure 7

(b) (4)

d. Is oral or nasogastric administration of an aqueous dispersion of the tablet an acceptable alternative method of dosing patients who are unable to swallow the whole tablet?

Yes. Judging from the findings of the relative BA study (Study 5), the oral bioavailability of osimertinib is not expected to be negatively impacted when administered as an aqueous dispersion of the tablet either orally or via a nasogastric tube, because the oral bioavailability of the intact oral tablet is comparable to that of the oral solution.

According to the sponsor, some lung cancer patients who had developed difficulty swallowing tablets have received osimertinib as a pre-dispersed tablet in the clinical studies conducted. Additionally, the chemical stability of such an aqueous dispersion was reported to be acceptable over (b) (4), and the transfer of dispersed tablets through nasogastric tubes was shown to be suitable for administration using appropriate commercially available tubes. The sponsor also provided evidence that with (b) (4) the dispersion of the tablet (b) (4) in water would be complete within (b) (4)

Reviewer's Assessment:
Both 40 mg and 80 mg strengths of the proposed commercial osimertinib *debossed* film coated tablets have comparable *in vitro* dissolution characteristics [and thus are not expected to behave differently (in terms of efficacy)] to the *non-debossed* film-coated tablets evaluated in the pivotal Phase 2 clinical Studies AURA Extension and AURA2.

Based on the comparable plasma osimertinib exposures between patients who received the Phase 1 tablets in AURA Expansion and those who received the Phase 2 film-coated tablet in AURA Extension and AURA2, as well as the very rapid dissolution of both Phase 1 and Phase 2 osimertinib (80 mg) tablets (b) (4) prior to initiation of the Phase 2 trials did not impact the *in vivo* performance of osimertinib tablets.

There is adequate bridging between the clinical research and the proposed commercial formulations of osimertinib tablets.

Oral or nasogastric administration of an aqueous dispersion of the oral tablets is an acceptable alternative mode of administration for patients unable to swallow intact tablets. The labeling should include a statement recommending administration of the aqueous dispersion of the tablet (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
The Division of Biopharmaceutics has evaluated NDA 208065 and recommends APPROVAL. The Applicant's proposed dissolution method and acceptance criterion (Q = (b) (4)% in 30 min) are acceptable.

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer,
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Gerlie Gieser's assessment and approval recommendation for NDA 208065.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/OPQ

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

To justify waiver of microbial control of AZD9291 mesylate, the applicant provided the following information in Module 3.2.S.4.5:

- The manufacturing process for AZD9291 mesylate provides little or no microbial risk.
- It has been established AZD9291 mesylate does not support microbial growth (b) (4)
- More than 22 development and commercial scale batches of AZD9291 mesylate have been tested for total aerobic microbial count and total combined yeast and mold count and all the batches tested have shown (b) (4) cfu per gram) which confirms the microbial quality of AZD9291 mesylate.
- A microbial mold challenge test study has also been conducted and demonstrated that AZD9291 does not support microbial growth.
- Microbial control is being monitored during the primary stability studies at the long term storage conditions of (b) (4) RH and (b) (4) RH and will be tested annually until the end of the study.

As part of the development strategy a microbial limit test method was developed for AZD9291 film coated tablets, 40 and 80 mg. A microbiological specification is not considered necessary for the following reasons:

- The tablet manufacture includes (b) (4) (b) (4)

The manufacture uses a (b) (4) and therefore presents little microbial risk.

- (b) (4)
- Microbial control has been demonstrated at time of manufacture for all AZD9291 film-coated tablet batches listed in the following table. The results comply with pharmacopeial limits, see below.
- Microbial control is being monitored during the primary stability studies for tablets stored at the long-term conditions (b) (4) in HDPE bottles. The total aerobic microbial count, total combined yeast and mold count and the absence of E. coli was determined at the (b) (4) time point and all data complied with pharmacopeial limits. Microbial control will be monitored annually until the end of these studies.

Batches used to support the specification

40 mg	80 mg	
14-000602AZ	14-001471AZ	VAAM
14-001472AZ	14-000364AZ	VAAN
14-001473AZ	14-000015AZ	VAAP
14-002783AZ	14-000745AZ	VAAR
14-002934AZ	VAAB	VAAS
WAAB	VAAC	VAAT
ZAAB	VAAD	VAAV
	VAAE	VAAW
	VAAF	VAAX
	VAAG	VAAZ
	VAAH	VABA
	VAAK	VABB
	VAAL	VABD

Microbial content of AZD9291 film-coated tablets

Result	AZD9291 film-coated tablets (40 mg and 80 mg)
Total Aerobic Microbial Count	(b) (4) cfu/g)
Total Combined Yeast and Mould Count	cfu/g)
Escherichia coli	Complies with Ph Eur (Absent)
(b) (4)	(b) (4)
Range of (b) (4) content of tablets[a] (%w/w)	(b) (4)

Reviewer's Assessment: ACCEPTABLE

For drug product, the applicant did not include the microbial control in the release specifications. They included microbial control (TAMC, TYMC and absence of *E. Coli*.) in the primary stability studies under long-term conditions, and stated such control will be monitored annually until the end of these studies (statement provided on Page 15 in Module 3.2.P.5.6).

According to the applicant's statement, it appears that they propose to waive all microbial limits testing. The following points were considered during evaluation of such proposal:

- The applicant provided up to (b) (4) microbial control results for (b) (4) different drug substance batches, stored under different conditions ((b) (4) and all data comply with USP <1111>.
- The formulation of drug product shows the core tablet contains the drug substance, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. The following microbial control is in place for the raw materials:

Component	(b) (4)
Drug Substance (AZD9291)	
Mannitol	
MCC	
Low-substituted Hydroxypropyl Cellulose	
Sodium Stearyl Fumarate	

(b) (4)

(b) (4)

- In Module 3.2.P.8.1, the applicant stated they use (b) (4) for microbiological quality control for drug product. No method verification was provided for the microbial limit method.
- The applicant stated they conducted microbial challenge test for both drug substance and drug product; however, such test was not described in the submission.
- (b) (4)
- The microbial results of the 33 batches of drug product, as shown above, comply with the USP <1111> for non-aqueous dosage form for oral administration.
- The microbial results were provided for 3 batches of 40 mg strength, packaged in the HDPE bottles (b) (4)

(b) (4)

- The microbial results were provided for 3 batches of 80 mg strength, packaged in the HDPE bottles (b) (4)
- The microbial results were provided for 2 batches of drug product in (b) (4)
- (b) (4) of drug product did not show significant increase in stability study.

Information Request:
You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
   (b) (4)
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at the critical control points.
4. You stated "A microbial mold challenge test study has also been conducted and demonstrated that AZD9291 does not support microbial growth." Please describe this test and provide your test results.
5. You should minimally perform microbial limits testing at the initial stability time point. Provide an updated stability schedule to reflect this testing.

Response in 9/8/2015 amendment:

1. (b) (4) The data showed that the microorganism levels comply with USP <1111>, and they will not support microorganism growth due to (b) (4) The applicant proposed not to include microbial control for these excipients according to ICH Q6A decision tree.
The applicant stated (b) (4) No antimicrobial effect

on the input test organism was observed. (b) (4) To minimize the risk, the applicant proposed a maximum holding time of (b) (4), and such time is included in the batch record.

2. The microbiologically critical control point is the holding time of (b) (4) which has been determined to be (b) (4), as described above. Such information is confirmed to be included in the batch record.

3. The only critical control point with regard to microbiological control has been identified (b) (4). (b) (4) hold time (b) (4) would result in the application of local deviation procedures.

4. The mould challenge test is performed by inoculating a drug substance sample with a range of common mould spores at a concentration of 5x104 (Aspergillus brasiliensis, Mucor plumbeus, Penicillium chrysogenum). Once inoculated with moulds the samples are stored in both dry (negative) and humid (test) conditions at 20°C to 25°C. Positive controls are also prepared using nutrient media and incubated at 20°C to 25°C. The negative and test samples are then examined at 1, 2, 4, 8, 16 and 24 week time points for any mould growth. Positive controls are disposed of once growth is confirmed. AZD9291 mesylate drug substance has been subjected to this mould challenge test. Following 24 weeks storage no mould proliferation was observed. The absence of any proliferation demonstrates that AZD9291 mesylate does not support mould (fungal) growth.

5. The applicant agreed to include microbial limit tests in the initial stability time points of both commercial and annual maintenance stability programs. The stability protocol and stability commitment have been updated.

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: Not provided.

Reviewer's Assessment: ACCEPTABLE

The drug product will be packaged in HDPE bottles with (b) (4) will be included in the package. The applicant confirmed that the HDPE bottle complies with USP <671>. Based on the stability data, such package provides adequate barrier for moisture permeation and microbial ingress.
No container/closure design space or change control program was described.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: Not applicable.

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The NDA is recommended for approval by the microbiology reviewer. There are no pending review issues and no risk mitigation actions required at this time.

- **Ying Zhang 10/13/2015**

Secondary Review Comments and Concurrence:

I concur with the evaluation and conclusions of the primary reviewer.

Bogdan Kurtyka, 10/20/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?
45. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment: AstraZeneca requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (e). To the best of the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

The exemption of granted under 21 CFR 25.31(e)

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Olen Stephens, Ph.D 19-Oct-15

Application Technical Lead

Secondary Review Comments and Concurrence: NA

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert (Amendment S-025)

(a) "Highlights" Section (21CFR 201.57(a))

These highlights do not include all the information needed to use TAGRISSO safely and effectively. See full prescribing information for TAGRISSO.

TAGRISSO (osimertinib) tablet, for oral use
Initial U.S. Approval: 201X

---------- INDICATIONS AND USAGE ----------
TAGRISSO is indicated for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. (1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. (b) (4) Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

------- DOSAGE AND ADMINISTRATION -------
Confirm the presence of T790M mutation in tumor specimens prior to initiation of treatment with TAGRISSO.

80 mg orally once daily, with or without food. (2.2)

----- **DOSAGE FORMS AND STRENGTHS** ----
Tablets: 80 mg, 40 mg (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Tagrisso (osimertinib) tablets for oral use	Adequate
Dosage form, route of administration	Tablets: 80 mg, 40 mg	Adequate
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 80 mg, 40 mg	Adequate

Conclusion: The highlights section is adequate per recent labeling meetings with clinical

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

80 mg tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse.
40 mg tablets: beige, round and biconvex tablet marked with "AZ 40" on one side and plain on the reverse.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	80 mg tablets, 40 mg tablets	Adequate
Strengths: in metric system	mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	80 mg tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse. 40 mg tablets: beige, round and biconvex tablet marked with "AZ 40" on one side and plain on the reverse.	Adequate

Conclusion: Section 3 of the most recent version of the label is adequate.

#11: Description (21CFR 201.57(c)(12))

(b) (4) (osimertinib (b) (4) is a (b) (4) kinase inhibitor for oral administration. The molecular formula is $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$ and the molecular weight is 596 g/mol. The chemical name for osimertinib is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide (b) (4) Osimertinib has the following structural formula (as osimertinib mesylate).

[add molecular structure]

TAGRISSO tablets contain 40 or 80 mg of osimertinib, equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively. Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxpropyl cellulose and sodium stearyl fumarate. The tablet coating consists of, polyvinyl alcohol, titanium dioxide, ~~macrogol~~ (b) (4) 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Tagrisso (osimertinib (b) (4) tablets	(b) (4)
Dosage form and route of administration	Tablets 40 mg and 80 mg for oral administration	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	TAGRISSO tablets contain 40 or 80 mg of osimertinib, equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxpropyl cellulose and sodium stearyl fumarate. The tablet coating consists of, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.	Inadequate, the USP name for Macrogol 3350 (b) (4)
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	A (b) (4) kinase inhibitor	Adequate
Chemical name, structural formula, molecular weight	N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl] amino} phenyl)prop-2-enamide mesylate salt. Osimertinib has the following structural formula (as osimertinib (b) (4) The molecular formula is $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$ and the molecular weight is 596.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	

Conclusion: The opening line of section 11 refers to Tagrisso as "osimertinib (b) (4)

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

80 mg Tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse and are available in bottles of 30 (NDC 03101-(b) (4)
40 mg Tablets: beige, round and biconvex table marked with "AZ 40" on one side and plain on the reverse and are available in bottles of 30 (NDC 03101-(b) (4)

Store TAGRISSO at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	tablets, 40 mg and 80 mg	Adequate
Available units (e.g., bottles of 100 tablets)	30-count	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	80 mg Tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse (NDC 03101-(b) (4) 40 mg Tablets: beige, round and biconvex table marked with "AZ 40" on one side and plain on the reverse (NDC 03101-(b) (4).	Adequate
Special handling (e.g., protect from light, do not freeze)	None needed	Adequate
Storage conditions	Store TAGRISSO at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

(b) (4)
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	(b) (4) AstraZeneca Pharmaceuticals LP Wilmington, DE 19850 (b) (4)	Adequate

Conclusion: The final edit to Section 11 has been communicated to the clinical review team. The label is adequate otherwise from a CMC perspective.

2. Container and Carton Labeling

1) Immediate Container Label (Amendment S-002)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Updated labels with this information have not been provided by the applicant yet. C/C comments will be sent in conjunction with DMEPA	In-progress
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	40 mg and 80 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label	Adequate
Net contents* (21 CFR 201.51(a))	30 Tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	"See (b) (4)	Adequate
Lot number per 21 CFR 201.18	Space reserved for information	Adequate
Expiration date per 21 CFR 201.17	Space reserved for information	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" provided	Adequate
Storage (not required)	Store between at room temperature 68°F -77°F) (20°C to 25°C)	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	80 mg: NDC 03101 (b) (4) 40 mg: NDC 03101	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	AstraZeneca AB, SE-151 Sodertalje, Sweden	Adequate
Others		

Conclusion: Final container closure label review is in-progress in conjunction with DMEPA.

2) Carton Labeling: None

Conclusion: Labeling comments and edits were communicated through the clinical team.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence: I concur with the primary reviewer's edits to the label.
Olen Stephens, PhD
Acting Branch Chief
OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII

II. List of Deficiencies To Be Communicated: None

III. Attachments

A. Lifecycle Knowledge Management

			Non-High Risk Drugs			
PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	INITIAL RISK RANKING	RISK MITIGATION APPROACH	FINAL RISK EVALUATION	LIFECYCLE CONSIDERATIONS/ COMMENTS
Assay, Stability	(b) (4)		Low		Low	(b) (4)
Physical stability (solid state)			Low		Low	
Content uniformity			Medium		Medium	
Microbial limits			Low		Low	
Dissolution – (b) (4) (b) (4)			Low		Low	

(b) (4)