CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 213072
Review 2

Drug Name/Dosage Form	Roszet™ (rosuvastatin and ezetimibe) tablets
Strength	5 mg Rosuvastatin/10 mg Ezetimibe 10 mg Rosuvastatin /10 mg Ezetimibe 20 mg Rosuvastatin /10 mg Ezetimibe 40 mg Rosuvastatin /10 mg Ezetimibe
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Althera Life Sciences LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	9/23/2020, 10/26/2020, 12/09/2020, 12/28/2020, 1/19/2021, 2/08/2021, 2/11/2021	Quality modules 3, 1.14 and 1.12

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API/ Office of New Drug Products (ONDP)
Drug Product	Ali Mohamadi	Branch VI/Division of New Drug Products III/ Office of New Drug Products
Process/Microbiology/ Facility	Khalid Khan	Branch II/Office of Pharmaceutical Manufacturing Assessment (OPMA)
Regulatory Business Process Manager	Leeza Rahimi/Hamet Toure	Branch I/Regulatory Business Process Management I
Biopharmaceutics	Fatima Sequeria	Division of Biopharmaceutics/ ONDP
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Ali Mohamadi	Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active	Adequate information in the NDA	LOA 8/2/2018
	III			Active		LOA 8/02/2018
	III			Active		LOA 8/2/2018
	III			Active		LOA 8/06/2018
	III			Active		LOA 8/3/2018
	III			Active		LOA 8/2/2018
	II			Adequate	4/01/20 (Dr. Mitra Chem Review #5)	LOA 9/16/2019
	II			Adequate	10/19/20 (Dr. Leginus)	LOA 9/17/2018

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	(b) (4)	
RLD	NDA 021366 (Rosuvastatin; Crestor) NDA 021445 (Ezetimibe; Zetia)	

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213072 is approval, which includes acceptable recommendation for the facilities listed in the application.

II. Product Overview

Roszet is a fixed dose combination tablet containing 10mg of ezetimibe and 5mg to 40mg of rosuvastatin calcium and is intended for the treatment of hyperlipidemia and (b) (4). Ezetimibe is a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and rosuvastatin calcium is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

Roszet will be available in 4 different strengths for oral administration. The tablets are imprinted with either "5" or "AL" or "II" or "77" for strength differentiation. The tablets are packaged in sealed 30ct HDPE bottles containing 1g desiccant.

- 10 mg ezetimibe/5 mg rosuvastatin as pink colored, round, biconvex tablets with embossing "5".
- 10 mg ezetimibe/10 mg rosuvastatin as pink colored, round biconvex tablets with embossing "AL".
- 10 mg ezetimibe/20 rosuvastatin as pink colored, round biconvex tablets with embossing "II" in
- 10 mg ezetimibe/40 mg rosuvastatin as pink colored, round biconvex tablets with "77".

Roszet™ should to be stored in original packaging, at USP controlled temperature at 20 to 25ºC (68 to 77 ºF) protected away from moisture.

Proposed Indication(s) including Intended Patient Population	Intended for treatment of hyperlipidemia
Duration of Treatment	Chronic
Starting dose	The recommended starting dose of ROSZET is (b) (4) for patients where 5/10 mg/day is indicated.
Maximum Daily Dose	10mg of ezetimibe and 40 mg of rosuvastatin.

III. Regulatory History

Complete Response Letter Issues: The NDA 213072 was originally submitted on July 29, 2019. A complete response letter was sent for this NDA on May 27, 2020 due to facility related deficiencies identified during inspection of (b) (4)

(b) (4) and (b) (4).

a) (b) (4) is the drug substance manufacturer for rosuvastatin calcium.
b) (b) (4) validated the chromatographic methods used for purity, assay, dissolution, and uniformity of dosage units. Since the facility inspection identified data integrity issues at (b) (4), the drug product review concluded that the data submitted in the NDA might not reflect the true values, specifically related to quality controls of finished ROSZET tablets, batch analyses results, and stability results.

The CR letter required that satisfactory resolution of the facility deficiencies, revalidation of chromatographic methods and acceptable stability data before this application may be approved. In addition, the CR letter contained comments related to manufacturing batch record.

There were no deficiencies associated with drug substance and biopharmaceutics sections of this NDA in the first cycle review. For details, please refer to the OPQ integrated quality review dated April 20, 2020 in DARRTS under NDA 213072.

End of Review Type A Meeting: During the June 29, 2020 end of review Type A meeting, the applicant received guidance from the agency on their plan to resolve CR letter issues.

Resubmission: The applicant resubmitted the application on September 29, 2020 with the following information:

a) The two non-compliant facilities, (b) (4) that performed method validation and (b) (4) that supplied rosuvastatin calcium drug substance were removed from the NDA. The applicant also removed (b) (4), a ezetimibe drug substance manufacturing facility from the application and kept (b) (4) for providing rosuvastatin calcium drug substance and (b) (4) for the supply of ezetimibe drug substance.
b) To confirm the reliability of the chromatographic methods used for release and stability, the applicant validated the analytical methods and transferred the methods to the drug product manufacturing facility. The revalidation confirmed that no changes to the method were needed. Using the revalidated methods, the applicant tested the stability samples and submitted data in the resubmission.
c) The resubmission contained 6 months of accelerated stability and 12 to 18 months of long-term stability data for 3 batches of highest and lowest strength batches manufactured with (b) (4) drug substance to support the proposed shelf life for all four strengths.
d) The applicant provided initial time point stability data for one batch of each intermediate strengths (20mg/10mg and 10mg/10mg) using (b) (4) drug substances packaged in 30ct HDPE containers (b) (4). During the

review cycle provided additional stability data for the two intermediate strength tablets.

e) In addition, the applicant provided dissolution data, batch genealogy and additional dissolution data for intermediate strengths manufactured with [redacted] drug substance.

f) To comply with CR letter comment, the applicant also provided updated batch manufacturing records with [redacted] for all strengths.

IV. Summary of Quality Assessments

The CMC information provided in the resubmission was reviewed by OPQ review team consisting of Dr. Joseph Leginus (Drug substance), Dr. Ali Mohamadi (Drug product), Dr. Fatima Sequeira (Biopharmaceutics), and Dr. Khalid Khan (manufacturing process, and facilities). The Office of Testing and Research, located at St. Louis, MO verified the analytical method used for assay and purity for rosuvastatin and ezetimibe tablets.

The overall OPQ recommendation for NDA 213072 resubmission is approval, which includes acceptable recommendation for the facilities listed in the application.

A. Quality Assessment Overview

Drug Substance

Originally, the applicant proposed to use rosuvastatin calcium from [redacted] or [redacted] and Ezetimibe drug substance from [redacted] and [redacted] for drug product manufacturing. In the resubmission, the applicant simplified the sourcing strategy and decided to use [redacted] and [redacted] sourced drug substances for drug product manufacturing.

The applicant referenced DMF [redacted] and [redacted] for CMC information related to rosuvastatin calcium (DMF [redacted]) and ezetimibe (DMF [redacted]). Dr. Joseph Leginus reviewed the CMC information available for the two drug substances. Dr. Leginus' s review concluded that the CMC information provided in [redacted] and [redacted] DMFs is adequate to support their use in the manufacture of ROSZET tablets. Please refer to drug substance review dated 12/25/20 in panorama for additional details.

Drug Product

The drug product is a film-coated [redacted] immediate release tablet. It contains 10 mg of ezetimibe [redacted] and 5 mg to 40 mg of rosuvastatin [redacted]. The 4 different strengths will be differentiated by the imprint on the tablets as indicated in the product overview section.

[redacted] The film coating contains hypromellose, titanium dioxide, [redacted] and ferric oxide [redacted]. The tablets are

packaged [redacted] in 30 ct HDPE bottles with [redacted] closure and 1g of desiccant cannister.

The Roszet tablets manufacturing process involves [redacted] tablets are film coated and packaged in 30ct HDPE bottles with 1g desiccant [redacted].

The applicant revalidated the chromatographic methods used for releasing the product and transferred them to the drug product manufacturer. Per reviewer request, the Division of Pharmaceutical Analysis (DPA) located at St. Louis, MO verified the chromatographic method used for assay and purity of the drug product. The DPA method verification report concluded that the proposed methods are acceptable for quality control purpose. The method verification report contained one comment related to an error in the equation used of the assay calculation. The applicant corrected the error and provided the updated methods on 2/8/2021.

The CMC information for drug product including drug product specification, method information, reference standard, impurities, container closure system, stability data, post-approval stability protocol and commitment, environmental assessment, and product label was reviewed by Dr. Mohamadi.

The applicant used bracketing approach to assess the stability of the product. The resubmission contained 6 months of accelerated stability data and 12 to 18 months of long-term stability data for 3 batches of highest and lowest strength batches packaged in 30ct HDPE bottles with desiccant. The applicant also provided 3months of long-term and accelerated stability data for one batch of each intermediate strengths (20mg/10mg and 10mg/10mg) packaged in 30ct HDPE bottles. All the above batches were manufactured using [redacted] drug substances. The applicant also provided stability comparison between product manufactured using current and withdrawn drug substance manufacturing facilities and concluded that the stability of the drug product manufactured from the current and withdrawn facilities was comparable. Dr. Mohamadi reviewed the stability information and granted 24 months shelf-life for the drug product packaged in 30ct HDPE bottles, when stored at 20 ° to 25°C.

The applicant sought exemption from environmental impact analysis per 21CFR 25.31(b) as the action on this NDA may not significantly affect the quality of the human environment. Dr. Mohamadi granted categorical exclusion from submitting environmental assessment. Please refer to drug product review dated 2/16/2021 for additional information.

The overall conclusion of the drug product and labeling review is that the CMC information provided in the NDA is adequate. Please refer to drug product review dated 2/10/2021 and quality labeling review 2/16/2021 in Panorama for additional details.

The bioequivalence (BE) studies conducted for this NDA used the highest (5 mg/10 mg) and lowest (40 mg/10 mg) strength Roszet tablets. The applicant sought biowaiver for the two intermediate strengths 10/10 mg and 20/10 mg based on dissolution profiles and BE studies. Dr. Bryan Ericksen, the biopharm reviewer for the original submission reviewed the dissolution method and acceptance criteria, dissolution data, and concluded that the biowaiver request can be granted.

For the resubmission, Dr. Sequeira reviewed the comparative dissolution data provided for the highest and lowest strength drug products manufactured using rosuvastatin calcium and ezetimibe drug substance from resubmission facilities ((b) (4)) as well as withdrawn facilities ((b) (4)). Dr. Sequeira concluded that the firm's dissolution data showed that the drug product manufactured from these two sources of drug substance are comparable. Dr. Sequeira's review also confirmed that the proposed dissolution method and acceptance criteria are adequate to support the NDA. Please refer to biopharm review dated 1/29/2021 in panorama for additional details.

Dr. Khalid Khan reviewed the batch formula, manufacturing process/in-process control information, updated batch record information as well as facility information provided in the original submission and in the resubmission. The overall manufacturing inspection recommendation for the facilities associated with this application in Panorama is approve. Dr. Khan has recommended a post-approval inspection for the drug product manufacturing facility, Piramal Enterprises Ltd, India (FEI#: 3005259207).

Time run: 2/17/2021 11:58:33 AM

Latest Submission Manufacturing Status for NDA-213072-Original-1

Latest Overall Manufacturing Inspection Recommendation	Inspection Requested	Inspection Completed	pOAI/OAI Alerts	Pending Profile
Approve Completion Date: 2/16/2021 NDA-213072-ORIG-1-AMEND-24	0	0	No	No

Hint: Click Facility ID link to open Facility Program
Click Facility Name to open Facility Status View: Detail
Click here to Refresh the Report

Facility ID	FEI	Facility DUNS	Facility Name	Latest Facility Status /As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason
			(b) (4)	Approve Facility (b) (4) Based on File Review	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	**Other Supply Chain:** RELEASE TESTER(PACKAGE)	Compliant as of (b) (4)	EIR endorsed VAI on (b) (4)
				Approve Facility (b) (4) Based on File Review	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	**Substance Supply Chain:** MANUFACTURER: ROSUVASTATIN PACKAGER: ROSUVASTATIN RELEASE TESTER: ROSUVASTATIN STABILITY TESTER: ROSUVASTATIN	Compliant	
110002658	3005259207	862202793	PIRAMAL ENTERPRISES LIMITED	Approve Facility 4 /1 /2020 District Recommendation	TCM TABLETS, PROMPT RELEASE	**Product Supply Chain:** MANUFACTURER: ROSUVASTATIN AND EZETIMIBE PACKAGER: ROSUVASTATIN AND EZETIMIBE STABILITY TESTER: ROSUVASTATIN AND EZETIMIBE RELEASE TESTER: ROSUVASTATIN AND EZETIMIBE	Compliant	
			(b) (4)	Approve Facility (b) (4) Based on File Review	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	**Substance Supply Chain:** MANUFACTURER: EZETIMIBE	Compliant	

Dr. Khan has concluded that overall the process and facilities information provided in the NDA is adequate. Please refer to his process/facilities review in Panorama dated 2/04/2021.

OVERALL ASSESSMENT AND SIGNATURES:

There are no outstanding deficiencies related to drug substance, drug product, process, biopharm, and facilities, the *OPQ overall recommendation for NDA 213072 is approval.*

Muthukumar Ramaswamy, Ph.D. 2/18/21

Application Technical Lead Name and Date:

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FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: November 23, 2020

To: Elise Luong, Drug Product Reviewer
Leeza Rahimi, RBPM

Through: Laura C. Pogue, Ph.D., Lab Chief Branch II, CDER/OPQ/OTR/DPAB2

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPAB2
Alicia Hoover, Ph.D., MVP Coordinator, CDER/OPT/OTR

Subject: Method Verification for NDA 213072: Assay and purity for Rosuvastatin and Ezetimibe tablets

The following methods were evaluated and are *acceptable* for quality control and regulatory purposes:

1. Assay and Chromatography purity of Rosuvastatin and Ezetimibe from Document No: PHL-PT-QC-STP-FTP-100178, version 2.0, effective date 24-Oct-2019

The following methods were evaluated and are *acceptable with modifications* for quality control and regulatory purposes:

2. Assay and Chromatography purity of Rosuvastatin and Ezetimibe from Document No: PHL-PT-QC-STP-FTP-100144, version 2.0, effective date 24-Oct-2019

Comments regarding the assay method above (PHL-PT-QC-STP-FTP-100144):

1. There is an error in the equation for the assay calculation on page 28 of 42. The original volume of stock sample dissolving was 500 mL, not 250 mL. The equation should be 500/Weight of sample not 250/Weight of sample.

Original analyst worksheets can be viewed using this ECMS link:

http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8847c2326

Summary of Analysis **NDA 213072**

1. Document No: PHL-PT-QC-STP-FTP-100178, version 2.0

Assay: % Label Claim

Rosuvastatin/ Ezetimibe (5/10 mg) tablets	% Label Claim	Specifications	Pass/Fail
Rosuvastatin	104.1	(b) (4)	Pass
Ezetimibe	99.5		Pass

Purity for Rosuvastatin/ Ezetimibe (5/10 mg) tablets:

RRT	Compounds	Average of % Impurity	Specifications	Pass/Fail
			(b) (4)	Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
	Total % Impurities		(b) (4)	Pass

2. Document No: PHL-PT-QC-STP-FTP-100144, version 2.0

Assay: % Label Claim

Rosuvastatin/ Ezetimibe (40/10 mg) tablets	% Label Claim	Specifications	Pass/Fail
Rosuvastatin	101.8	(b) (4)	Pass
Ezetimibe	101.3		Pass

Purity for Rosuvastatin/ Ezetimibe (40/10 mg) tablets:

RRT	Compounds	Average of % Impurity	Specifications	Pass/Fail
			(b) (4)	Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
	Total % Impurities		(b) (4)	Pass

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Roszet	Adequate
Established name(s)	rosuvastatin and ezetimibe	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Dosage range is 5 mg/10 mg per day through 40 mg/10 mg per day Tablets (rosuvastatin/ezetimibe): 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Swallow ROSZET tablets whole at any time of the day, with or without food. Do not crush, dissolve, or chew tablets.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>Tablet</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>
<table>
<tr><th>Strength</th><th>Contents</th><th>Description</th></tr>
<tr><td>5 mg/10 mg</td><td>rosuvastatin 5 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with "5" embossed on one side</td></tr>
<tr><td>10 mg/10 mg</td><td>rosuvastatin 10 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with "AL" embossed on one side</td></tr>
<tr><td>20 mg/10 mg</td><td>rosuvastatin 20 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with "II" embossed on one side</td></tr>
<tr><td>40 mg/10 mg</td><td>rosuvastatin 40 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with "77" embossed on one side</td></tr>
</table>
</td><td>Adequate</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance</td><td>Strength is expressed in a free base form as USP monograph for rosuvastatin tablets. The equivalency statement is included in section 11: ROSZET tablets 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg contain the equivalent of 5, 10, 20, and 40 mg rosuvastatin (provided as rosuvastatin calcium 5.2, 10.4, 20.8, and 41.7 mg) and 10 mg ezetimibe</td><td>Adequate</td></tr>
</table>

<table>
<tr>
<td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting</td>
<td>
<table>
<tr><th>Strength</th><th>Contents</th><th>Description</th></tr>
<tr><td>5 mg/10 mg</td><td>rosuvastatin 5 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with “5” embossed on one side</td></tr>
<tr><td>10 mg/10 mg</td><td>rosuvastatin 10 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with “AL” embossed on one side</td></tr>
<tr><td>20 mg/10 mg</td><td>rosuvastatin 20 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with “II” embossed on one side</td></tr>
<tr><td>40 mg/10 mg</td><td>rosuvastatin 40 mg/ezetimibe 10 mg</td><td>round pink biconvex tablets with “77” embossed on one side</td></tr>
</table>
</td>
<td>Adequate</td>
</tr>
<tr>
<td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”</td>
<td>N/A</td>
<td>Adequate</td>
</tr>
<tr>
<td>For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.</td>
<td>N/A</td>
<td>Adequate</td>
</tr>
</table>

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	rosuvastatin calcium and ezetimibe	Adequate
Dosage form(s) and route(s) of administration	Tablet	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	ROSZET tablets 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg contain the equivalent of 5, 10, 20, and 40 mg rosuvastatin (provided as rosuvastatin calcium 5.2, 10.4, 20.8, and 41.7 mg) and 10 mg ezetimibe.	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	pregelatinized starch, microcrystalline cellulose, meglumine, dibasic calcium phosphate dihydrate , crospovidone, colloidal silicon dioxide, sodium stearyl fumarate, mannitol, sodium lauryl sulfate, croscarmellose sodium, povidone, ferric oxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, polyethylene glycol, and ferric oxide.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Adequate

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	Rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor. Ezetimibe is a dietary cholesterol absorption inhibitor.	Adequate
Chemical name, structural formula, molecular weight	(3R,4S)-1-(p-Fluorophenyl)-3-[(3S)-3-(p-fluorophenyl)-3-hydroxypropyl]-4-(p-hydroxyphenyl)-2-azetidinone, 409.43 g/mol [S-[R*,S*-(E)]]-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1), 1001.14 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	Adequate
Other important chemical or physical properties (such as pKa or pH)	Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0. Ezetimibe is a white, crystalline powder, which is insoluble in water.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	5 mg/10 mg (rosuvastatin 5 mg and ezetimibe 10 mg) 10 mg/10 mg (rosuvastatin 10 mg and ezetimibe 10 mg) 20 mg/10 mg (rosuvastatin 20 mg and ezetimibe 10 mg) 40 mg/10 mg (rosuvastatin 40 mg and ezetimibe 10 mg)	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	round pink biconvex tablets with "5" embossed on one side, NDC 70661-001-30 round pink biconvex tablets with "AL" embossed on one side, NDC 70661-002-30 round pink biconvex tablets with "II" embossed on one side, NDC 70661-003-30 round pink biconvex tablets with "77" embossed on one side, NDC 70661-004-30	Adequate

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor’s Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from moisture. Once the bottle has been opened, use the capsules within 30 days. Store in the original container to protect from light.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at controlled room temperature (USP), 20 to 25 ºC (68 to 77 ºF) [see USP Controlled Room Temperature].	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic	N/A	Adequate

derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”		
Include information about child-resistant packaging	N/A	Adequate

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Piramal Enterprise Limited, Plot No. 67-70, Sector 2, Dist. Dhar, Pithampur, Madhya Pradesh 454775, India Manufactured for: Althera Pharmaceuticals LLC 89 Headquarters Plaza Morristown NJ 07960 USA	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	**Roszet** **rosuvastatin and ezetimibe tablets**	Adequate
Dosage strength	**5 mg/10 mg**	Adequate
Route of administration	N/A	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains the equivalent of 5 mg rosuvastatin (provided as rosuvastatin calcium 5.2 mg) and 10 mg ezetimibe	Adequate
Net contents (e.g. tablet count)	30 Tablets	Adequate
"Rx only" displayed on the principal display	Rx Only	Adequate
NDC number	NDC 70661-001-30	Adequate
Lot number and expiration date	GTIN: 00000000000000 S/N : 000000000000 EXP : YYYY-MM-DD LOT : 00000	Adequate
Storage condition (b) (4) [redacted]	Store at 20 to 25°C (68 to 77°F). Protect from moisture.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Adequate

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Adequate
Bar code		Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Althera Pharmaceuticals LLC, Morristown, NJ 07960 CODE : MP/DRUGS/25/10/92 Made in India Issue. 02/2021	Adequate
Medication Guide (if applicable)	**WARNING:** As with all medications, keep out of the reach of children. **RECOMMENDED DOSAGE:** See Prescribing Information.	Adequate
No text on Ferrule and Cap overseal	N/A	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Adequate
And others, if space is available	(b) (4)	Adequate

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 2/11/2021

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

Ali Mohamadi

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Date: 2/12/2021 09:36:16PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

David Claffey

Digitally signed by David Claffey
Date: 2/16/2021 09:19:23AM
GUID: 508da71e00029e20b201195abff380c2

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BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	NDA-213072-ORIG-1-RESUB-23
Product Name	Roszet (Rosuvastatin/Ezetimibe)
Applicant	Althera Life Sciences, LLC
Dosage Form/Strengths	tablets, 40/10 mg, 20/10 mg, 10/10 mg, and 5/10 mg
Route of Administration	Oral
Indication for Use	Roszet is indicated for primary (b) (4) non-familial) hyperlipidemia.
Submission Date	09/23/2020
Review Date	12/7/2020
Primary Reviewer	Fatima Sequeira, Ph.D.
Secondary Reviewer	Min Li, Ph.D.
Recommendation	**Adequate**

1. REVIEW SUMMARY:

Background:

Althera Life Sciences LLC submitted a 505(b)(2) on September 29, 2019. In the review for the original, Biopharm approved their biowaiver and deems the approved dissolution method for their drug product was appropriate.[1] The applicant has received Complete Response letter dated May 27, 2020, and Type A End of Review meeting on June 29, 2020 for their product of Roszet, Rosuvastatin/Ezetimibe tablets.[2]

Submission:

The firm is addressing issues from the Complete Response Letter issued on May 27, 2020. The firm propose to remove the API manufacturer ((b) (4)) due to inspectional issues. Note the drug product manufactured using APIs from (b) (4) and (b) (4) has been used in the clinical studies.

Reviewer's Assessment:

The approved dissolution specifications are provided below. The firm has provided dissolution data to support that the change of API manufacturing sites (from (b) (4)) for both drug substances would not impact in vitro dissolution. The provided dissolution data is

[1] https://panorama.fda.gov/task/view?ID=5da095d3008bd38a342aab1aa06f6ab1

[2] \\CDSESUB1\evsprod\nda213072\0023\m1\us\12-cover-letters\meeting-minutes-july-9th-2020.pdf

sufficient to support the dissolution similarity between the products manufactured by [redacted] (b) (4) and [redacted] (b) (4) will produce comparable drug products.

Approved dissolution method and acceptance criterion for Rosuvastatin:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criterion/criteria
II (Paddle)	50	pH 6.6 citrate buffer 37°C±0.5°C	900	30 minutes	NLT [redacted] (b) (4) %

Approved dissolution method and acceptance criterion for Ezetimibe:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Acceptance criterion/criteria
I (Basket)	75	pH 4.5 acetate buffer with 0.45% SLS; 37°C±0.5°C	900	30 minutes	NLT [redacted] (b) (4) %

Conclusion and Recommendation:

The dissolution data is adequate to support the proposed change in NDA-213072-ORIG-1-RESUB-23.

2. REVIEW:

a) List Submissions being reviewed (table):

09/23/2020	Amendment (NDA-213072-ORIG-1-RESUB-23)

The applicant provided comparative dissolution data from drug product manufactured by [redacted] and [redacted]. The firm showed that their new API vendors [redacted] is comparable between strengths, and across drug substance sources for highest and lowest strengths to [redacted]. Therefore, the [redacted] drug product should be considered comparable.

The firm provided two types of pH studies @ pH 1.2, 4.5, 6.8

- comparison of the different API sources ([redacted] vs. [redacted]) @40mg/10mg strengthen and

A. Comparative Dissolution across drug substances: F2 Values				
	40mg/10mg ([redacted] vs [redacted])		5mg/10mg ([redacted] vs [redacted])	
	Rosuvastatin	Ezetimibe	Rosuvastatin	Ezetimibe
pH 1.2	74	77	61	77
pH 4.5	Dissolution >85% in 15 min	85	Dissolution >85% in 15m	88
pH 6.8	Dissolution >85% in 15m	61	Dissolution >85% in 15m	82
pH 6.6 citrate buffer[1] (QC for Rosuvastatin)	Dissolution >85% in 15m	-	Dissolution >85% in 15m	-
pH 4.5 with SLS[2] (QC for Ezetimibe)	-	Dissolution >85% in 15m	-	Dissolution >85% in 15m

- comparisons of the dissolution of the 40mg/10 compared to 20mg/10mg, 10 mg/10 mg, and 5 mg/10 mg

B. Comparative Dissolution across strengths (for [redacted] batches): F2 values						
	40/10mg vs 20/10mg		40/10mg vs 10/10mg		40/10mg vs 5/10mg	
	Rosuvastatin	Ezetimibe	Rosuvastatin	Ezetimibe	Rosuvastatin	Ezetimibe
pH 1.2	61	58	70	57	69	58
pH 4.5	Dissolution >85% in 15m	62	Dissolution >85% in 15m	59	Dissolution >85% in 15m	61
pH 6.8	Dissolution >85% in 15m	69	Dissolution >85% in 15m	72	Dissolution >85% in 15m	61
pH 6.6[1]	Dissolution >85% in 15m	-	Dissolution >85% in 15m	-	Dissolution >85% in 15m	-
pH 4.5 with SLS[2]	-	Dissolution >85% in 15m	-	Dissolution >85% in 15m	-	Dissolution >85% in 15m

[1] pH 6.6 citrate buffer is QC media for Rosuvastatin, [2] pH 4.5 with SLS is QC media for Ezetimibe,

The applicant provided f2 values were appropriate. In cases where the drug product dissolved in less than 15 minutes no f2 was calculated. In all pH cases the results were comparable.

Additionally, detailed comparative dissolution data including batch information, individual vessels, mean, and CV% are provided. The results provided showed low variability and ability to meet the drug product specification.

In-vitro Dissolution Study details of Rosuvastatin/Ezetimibe tablets 40mg/10mg ((b) (4)) vs 40mg/10mg ((b) (4)) (Rosuvastatin content/ pH 6.6 Citrate buffer):

40mg/10mg tablet:

Rosuvastatin ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 40 mg/10 mg ((b) (4)															
Batch No.	RETD8002															
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml															
Apparatus	USP Type II (Paddle)															
RPM	50															
% Rosuvastatin Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10	(b) (4)														100	3.4
15															102	1.7
20															103	1.2
30															103	1.1
45															103	1.2
60															103	1.2
Product Name	Rosuvastatin and Ezetimibe tablets 40 mg/10 mg (b) (4)															
Batch No.	REATB8003															
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml															
Apparatus	USP Type II (Paddle)															
RPM	50															

Rosuvastatin ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 40 mg/10 mg (b) (4)
Batch No.	REATB8003
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml
Apparatus	USP Type II (Paddle)
RPM	50

% Rosuvastatin Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10	(b) (4)														95	5.8
15															99	1.5
20															100	0.8
30															100	0.6
45															101	0.6
60															101	0.6

*** REATA8003 is a pivotal clinical batch.**

Ezetimibe ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 40 mg/10 mg ((b) (4)
Batch No.	RETD8002
Media/Volume	pH 4.5 acetate with 0.45% SLS in 900ml
Apparatus	USP Type I (Basket)
RPM	75

% Ezetimibe Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10	(b) (4)														96	4.2
15															97	3.4
20															97	3.4
30															97	3.4
45															97	3.5
60															97	3.6

Ezetimibe ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 40 mg/10 mg ((b) (4))
Batch No.	REATB8003
Media/Volume	pH 4.5 acetate with 0.45% SLS in 900ml
Apparatus	USP Type I (Basket)
RPM	75

% Ezetimibe Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10														(b) (4)	97	2.1
15															98	1.8
20															97	1.8
30															98	1.8
45															98	1.7
60															98	1.9

20mg/10mg tablet:

Rosuvastatin ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 20 mg/10 mg ((b) (4)
Batch No.	REATD0001
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml
Apparatus	USP Type II (Paddle)
RPM	50

% Rosuvastatin Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10														(b) (4)	95	3.1
15															97	1.1
20															98	1.0
30															98	1.0
45															98	1.0
60															98	1.1

Ezetimibe ((b) (4))

Product Name	Rosuvastatin and Ezetimibe tablets 20 mg/10 mg (b) (4)
Batch No.	REATD0001
Media/Volume	pH 4.5 acetate with 0.45% SLS in 900ml
Apparatus	USP Type I (Basket)
RPM	75

% Ezetimibe Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10	(b) (4)														100	2.1
15															99	1.5
20															100	1.4
30															99	1.4
45															99	1.4
60															99	1.4

10mg/10mg tablet:

Rosuvastatin (b) (4):

Product Name	Rosuvastatin and Ezetimibe tablets 10 mg/10 mg (b) (4)
Batch No.	REBTC0001
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml
Apparatus	USP Type II (Paddle)
RPM	50

% Rosuvastatin Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10	(b) (4)														100	1.9
15															101	1.7
20															101	1.6
30															101	1.6
45															101	1.6
60															101	1.6

Ezetimibe (b) (4)

Product Name	Rosuvastatin and Ezetimibe tablets 10 mg/10 mg (b) (4)
Batch No.	REBTC0001
Media/Volume	pH 4.5 acetate with 0.45% SLS in 900ml
Apparatus	USP Type I (Basket)
RPM	75

% Ezetimibe Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10														(b) (4)	101	1.7
15															101	1.0
20															101	0.6
30															101	0.6
45															101	0.6
60															101	0.7

5mg/10mg tablet:

Rosuvastatin ((b) (4)):

Product Name	Rosuvastatin and Ezetimibe tablets 5 mg/10 mg ((b) (4))
Batch No.	REBTA0003
Media/Volume	pH 6.6 citrate buffer (QC Media) in 900ml
Apparatus	USP Type II (Paddle)
RPM	50

% Rosuvastatin Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10														(b) (4)	98	2.3
15															99	2.0
20															99	2.0
30															99	1.9
45															99	1.9
60															99	2.0

Ezetimibe ((b) (4))

Product Name	Rosuvastatin and Ezetimibe tablets 5 mg/ 10 mg ((b) (4))
Batch No.	REBTA0003
Media/Volume	pH 4.5 acetate with 0.45% SLS in 900ml
Apparatus	USP Type I (Basket)
RPM	75

% Ezetimibe Release																
Time in Minutes	1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Mean	% CV
10														(b) (4)	106	0.9
15															106	0.7
20															106	0.6
30															106	0.7
45															107	0.6
60															107	0.6

Fatima Sequeira

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Min Li

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/s/

MUTHUKUMAR RAMASWAMY
02/18/2021 10:29:42 AM

Recommendation: Complete Response

NDA 213072
Review 1

Drug Name/Dosage Form	Roszet™ (rosuvastatin and ezetimibe) tablets
Strength	5 mg Rosuvastatin/10 mg Ezetimibe 10 mg Rosuvastatin /10 mg Ezetimibe 20 mg Rosuvastatin /10 mg Ezetimibe 40 mg Rosuvastatin /10 mg Ezetimibe
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Althera Life Sciences LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments (NDA 213072)	Original submission (7/29/2019). Amendments: 8/14/19, 9/16/19, 9/19/19, 11/14/19, 11/27/19, 1/02/20, 1/10/20, 1/17/20, 3/17/20, and 3/23/20.	Quality modules 3, 1.14, and 1.12

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Soumya Mitra	Branch II/New Drug API/ONDP
Drug Product	Elise Luong	Branch VI/Division of New Drug Products III/ Office of New Drug Products
Process/Microbiology/ Facility	Khalid Khan	Branch II/OPMA
Regulatory Business Process Manager	Leeza Rahimi	Branch I/Regulatory Business Process Management I
Biopharmaceutics	Bryan Ericksen	Division of Biopharmaceutics/ ONDP
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Elise Luong	Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active	Adequate information in the NDA	LOA 8/2/2018
	III			Active		LOA 8/02/2018
	III			Active		LOA 8/2/2018
	III			Active		LOA 8/06/2018
	III			Active		LOA 8/3/2018
	III			Active		LOA 8/2/2018
	III			Active		LOA 8/24/2018
	III			Active		LOA 8/21/2018
	II			Adequate	6/23/19 (Dr. Kinsley Chem Review #5)	LOA 2/1/2019
	II			Adequate	4/01/20 (Dr. Mitra Chem Review #5)	LOA 9/16/2019
	II			Adequate	3/28/20 (Dr. Mitra Review#1)	LOA 3/11/2019
	II			Adequate	3/18/20 (Dr. Mitra Chem Review # 13)	LOA 9/17/2018

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND	(b) (4)	
RLD	NDA 021366 (Rosuvastatin; Crestor) NDA 021445 (Ezetimibe; Zetia)	

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213072 is complete response, which includes recommendation for the facilities listed in the application.

II. Summary of Complete Response Issues

1. [redacted] is the site that performed analytical method validation of the methods used for chromatographic purity, assay, dissolution, and uniformity of dosage units. During the Pre-approval inspection of the facility from [redacted], *major deficiencies related to product specific findings without impact to commercial product were observed*. An initial field recommendation for the facility is withhold due to (i) [redacted] The following method validation deficiencies noted included:
   a. [redacted]
   b.
   c.

   The overall manufacturing recommendation from Process/Facility reviewer for NDA [redacted] is "withhold" approval in Panorama.

2. Based on initial field recommendation, the drug product reviewer has concluded that the data submitted in the NDA might not reflect the true values. Areas affected are: Quality controls of finished ROSZET tablets, batch analyses results, and stability results.

Action Letter Language

1. During a recent inspection of the [redacted] and [redacted] manufacturing facilities for this NDA, our field investigator conveyed deficiencies to the representatives of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. Due to data integrity deficiencies identified at [redacted] (b) (4) during PAI inspection, we do not consider the method validation information provided in the NDA application as reliable.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES:

A. Revalidate the analytical method used for assay, chromatographic purity, content uniformity, and dissolution using suitable reference standards / working standards.
B. After revalidation of the analytical method, repeat runs and re-analyze the existing stability samples. Include additional long-term stability data beyond 12 months for the 40 mg/10 mg and 10 mg/10 mg strengths, and beyond 9 months for the 5 mg/10 mg strength in your complete response. In addition, provide at least six-month long-term (25°C/60%RH) and accelerated (40°C/75%RH) stability data for new lots of drug product, one batch each strength, using the re-validated method.

Additional Product Quality Comments:

In your response to information request #1 provided in amendment dated 03/17/2020, you have indicated that [redacted] (b) (4) " and the revised batch manufacturing records were provided. Please note the following comments and respond with supporting data and corresponding corrected documents:

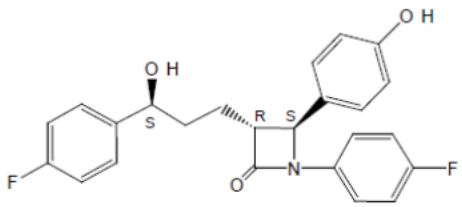
a) We noticed that executed batch manufacturing records for [redacted] (b) (4) of rosuvastatin 5 mg/ezetimibe 10 mg tablets manufactured in batches REBTA002, REBTA003 and REBTA004, and the proposed commercial batch manufacturing records for this strength did not have provision for recording the [redacted] (b) (4), contrary to your response.

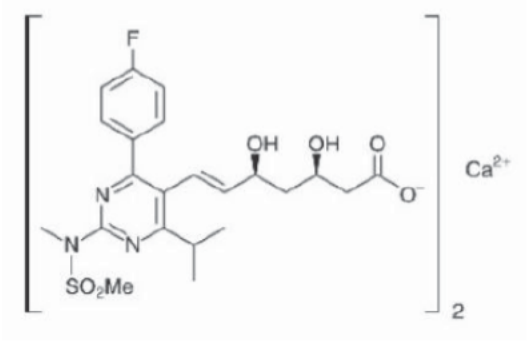
b) For 20 mg/10 mg, [redacted] (b) (4) are not supported by the actual observed data on the exhibit batches. Provide data to support these limits.

III. Summary of Quality Assessments

A. Product Overview

Roszet is a fixed dose combination drug product that contains ezetimibe and rosuvastatin calcium. Ezetimibe is a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and rosuvastatin calcium is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.





Ezetimibe, Molecular weight: 409.4 **Rosuvastatin calcium, Molecular weight 1001.14**

Roszet™ is intended for the treatment of hyperlipidemia and [(b) (4)]. Roszet will be available in 4 different strength tablets for oral administration. Tablets are differentiated by imprint.

- 10 mg ezetimibe/5 mg rosuvastatin as round pink biconvex tablets with embossing "5" in 30 ct bottles.
- 10 mg ezetimibe/10 mg rosuvastatin as round pink biconvex tablets with embossing "AL" in 30 ct [(b) (4)] bottles [(b) (4)].
- 10 mg ezetimibe/20 rosuvastatin as round pink biconvex tablets with embossing "II" in in 30 ct [(b) (4)] bottles [(b) (4)]
- 10 mg ezetimibe/40 mg rosuvastatin as round pink biconvex tablets with "77" in 30 ct [(b) (4)] bottles [(b) (4)].

Roszet™ should to be stored in original packaging (sealed HDPE bottles with desiccant) at USP controlled temperature at 25ºC (77 ºF).

Proposed Indication(s) including Intended Patient Population	Intended for treatment of hyperlipidemia
Duration of Treatment	Chronic
Starting dose	The recommended starting dose of ROSZET is [(b) (4)] for patients where 5/10 mg/day is indicated.
Maximum Daily Dose	10mg of ezetimibe and 40 mg of rosuvastatin.

B. Quality Assessment Overview

Drug Substance

Roszet contains ezetimibe and rosuvastatin calcium. CMC information for drug substances used in the manufacturing of drug product are referenced to the following Type II DMFs for rosuvastatin (DMF [(b) (4)] DMF [(b) (4)]) and ezetimibe (DMF [(b) (4)]; DMF [(b) (4)]). Dr. Soumya Mitra reviewed the drug substance CMC information. His review concluded that the drug substance information is adequate to support the approval of this NDA.

Drug Product

The drug product is a film-coated [redacted] tablet containing 10 mg of ezetimibe [redacted] and 5 to 40 mg of rosuvastatin [redacted]. The drug product will be available in 4 different strengths of fixed dose combination tablets: 5mg rosuvastatin/10mg ezetimibe, 10 mg rosuvastatin/10 mg ezetimibe, 20 mg rosuvastatin/10 mg ezetimibe, and 40 mg rosuvastatin/10 mg ezetimibe. Various strength tablets are imprinted with either "5" or "AL" or "II" or "77" for product strength differentiation.

[redacted] The film coating contains hypromellose, titanium dioxide, [redacted] and ferric oxide [redacted]. The tablets are packaged in [redacted] 30 ct [redacted] HDPE bottles with [redacted] closure and 1g of desiccant cannister.

With the exception of coating agents, all excipients used in the drug product are compendial grade. The components of coating agents meet compendial standards and are acceptable for intended use. The final product formulation was proven based on data available from BE studies.

Roszet manufacturing process involves [redacted] tablets are film coated and packaged in bottles [redacted].

CMC information on quantitative composition of drug product, excipient compatibility, batch analysis, method validation, drug product specification, container closure system, reference standard, stability data, container/closure system, label, and environmental assessment was reviewed by Dr. Luong. Based on her initial assessment of method validation information, Dr. Luong requested that pre-approval inspection be performed at [redacted], a site that performed analytical method validation. Pre-approval inspection of this facility on [redacted] uncovered data integrity issues related to analytical method validation data (Refer to Section II for a summary of complete response issues for additional details).

Therefore, the drug product reviewer has concluded that data submitted in the NDA might not reflect the true values. Areas affected by this issue include quality controls of finished ROSZET tablets, batch analyses results, and stability results. Dr. Luong has concluded that the CMC information provided in the NDA is inadequate to support the NDA. Please refer to drug product review dated 4/06/20 in panorama for additional details.

Biopharmaceutics reviewer, Dr. Bryan Ericksen reviewed the dissolution method, supporting dissolution data, dissolution acceptance criteria, and the biowaiver request. The bioequivalence (BE) studies used the highest (5 mg/10 mg) and lowest (40 mg/10 mg) strength Roszet tablets. The applicant sought biowaiver for the two intermediate strengths 10/10 mg and 20/10 mg based on dissolution profiles and BE studies. Dr. Ericksen's review concluded that biowaiver can be granted. Dr. Ericksen's recommendation for this NDA is adequate. Please refer to biopharma review dated 2/14/20 in Panorama. Due to issues pertaining to analytical method validation for dissolution testing, the biopharmaceutics recommendations for this NDA will be considered as tentative, until the applicant satisfactorily addresses the 483 deficiencies.

Dr. Khalid Khan reviewed the manufacturing process/in-process control information and facility compliance information for facilities associated with this NDA. His process review includes manufacturing process description, risk assessment for manufacturing process controls and their relationship to drug product critical quality attributes. Dr. Khan's initial review indicated that the firm was unable to (b) (4) and did not meet uniformity of dosage units acceptance criteria according to USP <905> for the 5mg strength exhibit batches. Accordingly, the applicant was requested to manufacture new batches of lower strength (b) (4) tablets to demonstrate capability to manufacture the product will meet quality standards consistently. The applicant provided batch release data for new batches, which met the quality acceptance criteria. The process reviewer has one product quality deficiency comment related to in-process controls to be conveyed in the complete response letter. Refer to Section II Additional Product Quality Comments for additional details.

Due to facility related deficiencies observed at (b) (4) , a site that performed analytical method validation) and (b) (4) , drug substance manufacturing site for supplying rosuvastatin), Dr. Khan has concluded that overall the process and facilities information provided in the NDA is inadequate. Please refer to Section II for a summary of complete response issues as well as process/facilities review in Panorama dated 4/13/20.

OVERALL ASSESSMENT AND SIGNATURES:

Since there are outstanding deficiencies related to drug product, process, and facilities, the *OPQ overall recommendation for NDA 213072 is complete response.*

Muthukumar Ramaswamy, Ph.D. 4/17/20

Application Technical Lead Name and Date:

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental Analysis (EA)

In accordance with 21 CFR 25.31(b), Althera Life Science, LLC. Claims a categorical exclusion from the requirement to prepare an Environmental Assessment as the drug will be utilized under this NDA for commercialization is not expected to exceed the threshold of 1 μg/L (i.e. 1 ppb). The annual production quantities for human use of the active moieties for this fixed ratio combination product, Rosuvastatin and Ezetimibe, are not expected to exceed (b) (4) Kg and (b) (4) Kg respectively.

Althera claims that to the best of the company's knowledge, no extraordinary circumstances exist.

Assessment: ***Adequate from a CMC perspective.***

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 03/24/2020.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D.; 04/06/2020 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ROSZET®	Reviewed by DMEPA
Established name(s)	Rosuvastatin Ezetimibe	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Immediate Release Film-coated Fixed Ratio Combination Tablets Rosuvastatin / Ezetimibe 5 mg / 10 mg 10 mg / 10 mg 20 mg / 10 mg 40 mg / 10 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A (The tablet is not scored)

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Ready to use tablet	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

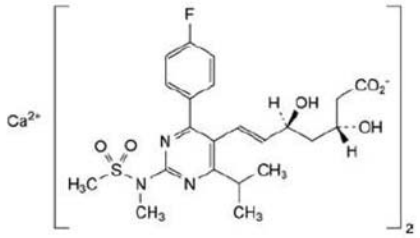
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Rosuvastatin / Ezetimibe Fixed Ratio Combination Tablets	Adequate
Strength(s) in metric system	ROSZET 5 mg / 10 mg (rosuvastatin 5 mg/ezetimibe 10 mg) ROSZET 10 mg / 10 mg (rosuvastatin 10 mg/ezetimibe 10 mg) ROSZET 20 mg / 10 mg (rosuvastatin 20 mg/ezetimibe 10 mg) ROSZET 40 mg / 10 mg (rosuvastatin 40 mg/ezetimibe 10 mg)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Rosuvastatin equivalent of 5, 10, 20, or 40 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Section 3.2.P.1	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A

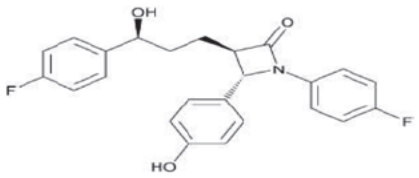
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	ROSZET® Rosuvastatin Ezetimibe	Reviewed by DMEPA
Dosage form(s) and route(s) of administration	Tablet and oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Rosuvastatin equivalent of 5, 10, 20, or 40 mg	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	pregelatinized starch, microcrystalline cellulose, meglumine, calcium (b) (4) phosphate dihydrate, crospovidone, colloidal (b) (4), sodium stearyl fumarate, mannitol, sodium lauryl sulphate, croscarmellose sodium, (b) (4), ferric oxide (b) (4), magnesium stearate	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A

(b) (4)

Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Rosuvastatin: HMG-CoA reductase inhibitor, therapeutic class C10AA07. Ezetimibe: Inhibitor of intestinal cholesterol and related phytosterol absorption, therapeutic class C10AX09	Adequate
Rosuvastatin Chemical name, structural formula, molecular weight	Bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2[methyl(methyl sulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt  Rosuvastatin Calcium 1001.14 g/mol $(C_{22}H_{27}FN_3O_6S)_2Ca$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A

Other important chemical or physical properties (such as pKa or pH)	White amorphous powder, sparingly soluble in water and methanol, slightly soluble in ethanol, a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH 7.0	Adequate
Ezetimibe Chemical name, structural formula, molecular weight	1-(4-flourophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl-2-azetidinone  409.43 g/mol $C_{24}H_{21}F_2NO_3$	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	White crystalline powder, freely to very soluble in ethanol, methanol, acetone, practically insoluble in water.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	ROSZET (Rosuvastatin / Ezetimibe) Tablets: 5 mg / 10 mg 10 mg / 10 mg 20 mg / 10 mg 40 mg / 10 mg	Adequate
Available units (e.g., bottles of 100 tablets)	See inserted table below	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See inserted table below	Adequate. The description has been provided in the NDA
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	The tablet is not scored N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Tablet Strength	Film-Coated Tablet, Color/Shape	Tablet Markings	Package Size	NDC Number
5 mg / 10 mg	Round pink biconvex	Embossing of "5"	Bottles of 30	70661-001-30
10 mg / 10 mg	Round pink biconvex	Embossing of "AL"	Bottles of 30 (b) (4)	70661-002-30 (b) (4)
20 mg / 10 mg	Round pink biconvex	Embossing of "II"	Bottles of 30 (b) (4)	70661-003-30 (b) (4)
40 mg / 10 mg	Round pink biconvex	Embossing of "77"	Bottles of 30 (b) (4)	70661-004-30 (b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Protect from moisture	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	The (b) (4) desiccants are contained inside a (b) (4) which has a distinct not-eatable appearance	Adequate

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature]. Protect from moisture	The storage condition is supported by data and is acceptable.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
[redacted] (b) (4)		

FDA Comment (10/15/19): In the subsection 16 How Supplied/Storage and Handling, there was [redacted] (b) (4) .

Response (11/14/19): We would like to clarify to the Agency, the ROSZET 5 mg/10 mg tablets [redacted] (b) (4)

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl

alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Althera Pharmaceuticals LLC 89 Headquarters Plaza, Morristown NJ 07960 USA ROSZET is a trademark of Althera U.S. Patent No. 9,763,885	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

(b) (4)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4) Rosuvastatin/Ezetimibe Tablets	Adequate
Dosage strength	Rosuvastatin / Ezetimibe 10 mg / 10 mg 20 mg / 10 mg 40 mg / 10 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Rosuvastatin equivalent of 5, 10, 20, or 40 mg	Adequate
Net contents (e.g. tablet count)	Rosuvastatin / Ezetimibe 10 mg / 10 mg (b) (4) 20 mg / 10 mg 40 mg / 10 mg	Adequate
"Rx only" displayed on the principal display	Yes	Yes
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage condition (b) (4)	Store at 20-25°C (68° to 77°F). Protect from moisture.	Adequate

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
(b) (4)		
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Althera Pharmaceuticals LLC, Morristown, NJ 07960	Adequate
Medication Guide (if applicable)	Labels have medication guide	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	The drug product is a novel fixed ratio combination (FRC) tablet of 2 active pharmaceutical ingredients (APIs). There is no USP standard of strength, quality, or purity for the said novel FRC tablet. However, each of the 2 APIs are USP grade.	Adequate
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *Adequate.*

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Note: In the applicant's 11/27/19 response to OND Information Request dated 11/26/19 about the carton labeling, the applicant indicated that the 30 count (b) (4) *count bottle configurations do not contain a carton.*

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The labels are acceptable from a CMC perspective.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 04/04/20

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., 04/06/2020

Elise Luong

Digitally signed by Elise Luong
Date: 4/06/2020 01:35:26PM
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Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 4/06/2020 03:33:18PM
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BIOPHARMACEUTICS

Product Background:

The current submission is for the approval of Roszet (Rosuvastatin/Ezetimibe) tablets, 40/10 mg, 20/10 mg, 10/10 mg, and 5/10 mg. Roszet is indicated for primary ((b) (4) non-familial) hyperlipidemia.

NDA-213072-ORIG-1

Drug Product Name / Strength: Roszet (Rosuvastatin/Ezetimibe) / 40/10 mg, 20/10 mg, 10/10 mg, and 5/10 mg

Route of Administration: Oral

Applicant Name: Althera Life Sciences, LLC

Review Summary: Adequate

A biowaiver was requested for two intermediate strengths, and supporting data are adequate. Bridging of formulations is not necessary. The Applicant used the FDA Dissolution Database method for Rosuvastatin. The dissolution method development report adequately explained the choice of parameters chosen for the in-house method for Ezetimibe. The discriminating ability of the method was adequately demonstrated. The proposed acceptance criteria of Q= (b) (4) % in 30 minutes for both Rosuvastatin and Ezetimibe are adequate.

Approved dissolution method and acceptance criterion for Rosuvastatin

USP Apparatus	Speed (RPM)	Medium/Temperature	Volume (mL)	Acceptance criterion
2 (Paddle)	50	pH 6.6 citrate buffer / 37 ± 0.5°C	900 mL	Q= (b) (4) % in 30 minutes

Approved dissolution method and acceptance criterion for Ezetimibe

USP Apparatus	Speed (RPM)	Medium/Temperature	Volume (mL)	Acceptance criterion
1 (Basket)	75	pH 4.5 acetate buffer with 0.45% SLS / 37 ± 0.5°C	900 mL	Q= (b) (4) % in 30 minutes

List Submissions being reviewed:

07/29/2019	NDA 213072/Sequence 0001/Original Submission
01/02/2020	NDA 213072/Sequence 0012/Response to Information Request

Concise Description Outstanding Issues Remaining:

None

BCS Designation

Reviewer's Assessment: Both Rosuvastatin and Ezetimibe are BCS Class 2

Solubility:

Rosuvastatin is slightly soluble in water. Ezetimibe is practically insoluble in water.

Permeability:

The Applicant did not provide permeability information on either compound. However, a literature search revealed that both Rosuvastatin and Ezetimibe are BCS Class 2 drugs with high permeability.

Dissolution:

Dissolution results in Module 3.2.P.2 indicate that Rosuvastatin dissolution was near 100% in pH 6.6 citrate buffer, and Ezetimibe dissolution was near 100% in pH 4.5 acetate buffer with 0.45% SLS.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: Adequate

The Applicant did provided a dissolution method development report in response to an information request in Sequence 0012. The FDA Dissolution Database method was used for Rosuvastatin without modification. However, the FDA dissolution database method for Ezetimibe was modified in several respects: media volume, apparatus and RPM. According to the dissolution method development report, these changes were made because (b) (4)

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

Discriminating ability of the dissolution method

Four batches were manufactured with variations in material attributes, formulation variables, and process parameters as shown in the table below:

QUALITY ASSESSMENT

Variations in Rosuvastatin portion			
Test	**Changes in material attributes**	**Changes in Formulation variables**	**Changes in Process parameters**
Discrimination Test-1	(b) (4)		
Discrimination Test-2			
Discrimination Test-3			

Variations in Ezetimibe portion			
Test	**Changes in material attributes**	**Changes in Formulation variables**	**Changes in Process parameters**
Discrimination Test	(b) (4)		

Note: (b) (4)

(b) (4)

Batch compositions for the altered batches and dissolution results are shown in the tables below.

5.2.2 Composition of Batch: AL320-10/10-F085:

Description	For reference: proposed product, Mg/tab	AL320-10/10-F085, Mg/tab
(b) (4)		

QUALITY ASSESSMENT

Dissolution of Product: Rosuvastatin and Ezetimibe 10/10mg tablets AL320-10/10-F085		
Media	pH 4.5 Acetate buffer with 0.45% SLS, 900ml	pH 6.6 citrate Buffer, 900ml
Apparatus	USP Type-1, basket	USP Type-2, Paddle
RPM	75	50
Time	30 min	30 min
Tablets	**% Ezetimibe dissolved**	**% Rosuvastatin dissolved**
1	(b) (4)	(b) (4)
2		
3		
4		
5		
6		
Average	**58.16**	**58.31**
Minimum	(b) (4)	(b) (4)
Maximum		
Ezetimibe result:	Out of Specification (NLT (b) (4) % Q in 30 min)	
Rosuvastatin result:	Out of Specification (NLT (b) (4) % Q in 30 min)	

5.2.3 Composition of Batch: AL320-10/10-F086:

Description	For reference: proposed product, Mg/tab	AL320-10/10-F086 Mg/tab
[redacted] (b) (4)		
Total Tablet weight		

Dissolution of Product: Rosuvastatin and Ezetimibe 10/10mg tablets AL320-10/10-F086		
Media	pH 4.5 Acetate buffer with 0.45% SLS, 900ml	pH 6.6 citrate Buffer, 900ml
Apparatus	USP Type-1, basket	USP Type-2, Paddle
RPM	75	50
Time	30 min	30 min
Tablets	**% Ezetimibe dissolved**	**% Rosuvastatin dissolved**
1	(b) (4)	(b) (4)
2		
3		
4		
5		
6		
Average	**31.14**	**68.12**
Minimum	(b) (4)	(b) (4)
Maximum		
Ezetimibe result:	Out of Specification (NLT (b) (4) % Q in 30 min)	
Rosuvastatin result:	Out of Specification (NLT (b) (4) % Q in 30 min)	

5.2.4 Composition of Batch: AL320-10/10-F089:

Description	For reference: proposed product, Mg/tab	AL320-10/10-F089 Mg/tab
(b) (4)		

Total Tablet weight	(b) (4)

Dissolution of Product: Rosuvastatin and Ezetimibe 10/10mg tablets AL320-10/10-F089

Media	pH 4.5 Acetate buffer with 0.45% SLS, 900ml	pH 6.6 citrate Buffer, 900ml
Apparatus	USP Type-1, basket	USP Type-2, Paddle
RPM	75	50
Time	30 min	30 min
Tablets	% Ezetimibe dissolved	% Rosuvastatin dissolved
1	(b) (4)	(b) (4)
2		
3		
4		
5		
6		
Average	79.95	42.48
Minimum	(b) (4)	(b) (4)
Maximum		
Ezetimibe result:	Out of Specification (NLT (b) (4)% Q in 30 min)	
Rosuvastatin result:	Out of Specification (NLT (b) (4)% Q in 30 min)	

In all cases, dissolution did not meet the acceptance criteria for either Ezetimbe or Rosuvastatin, (b) (4) Therefore, the discriminating ability of the method has been adequately demonstrated.

Acceptance criteria

The Applicant proposed acceptance criteria of Q= (b) (4)% in 30 minutes for both Rosuvastatin and Ezetimibe. Data in Module 5.3.1.3 show that these criteria are adequate. See the four comparative dissolution reports:

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Bridging of Formulations

Reviewer's Assessment: Adequate

Information in Module 3.2.P.5.4 shows that the 10 mg/10 mg and 20 mg/10 mg strengths were manufactured only at (b) (4), whereas the 40 mg/10 mg and 5 mg/10 mg strengths were manufactured at both (b) (4) and (b) (4). In response to an information request, the Applicant provided the following table showing batches used in clinical studies.

Batch used in clinical studies		
Study No.	**Product details**	**Batch details**
RP.18.340	Roszet 40/10mg	REATB8003
RP.18.342	Roszet 40/10mg	
RP.18.343	Roszet 5/10mg	RETA8003

According to Module 3.2.P.5.4, batch RETA8003 was manufactured at (b) (4), while batch REATB8003 was manufactured at (b) (4). Dissolution results were presented for both of these batches (See comparative dissolution reports referenced above), and both met the acceptance criterion of Q= (b) (4)% in 30 minutes. Since the exhibit batches are used for the clinical trials, no bridging of formulations is necessary.

Biowaiver Request

Reviewer's Assessment: Adequate

The Applicant conducted bioequivalence studies for the highest (40 mg/10 mg) and lowest (5 mg/10 mg) strengths. These studies will be reviewed by Office of Clinical Pharmacology. Please refer to clinical pharmacology review for additional details. A biowaiver is requested for the intermediate strengths: 20 mg/10 mg and 10 mg/10 mg. Comparative dissolution results were presented for the highest and lowest strengths but not the two intermediate strengths in Module 2.7.1. The above referenced data in Module 5.3.1.3 cannot be used for f2 comparisons because dissolution is always greater than (b) (4)% at the first time point in the quality control media. These results are sufficient to support the biowaiver request pending acceptable BE studies.

List of Deficiencies:

1. None

Primary Biopharmaceutics Reviewer Name:

Bryan Ericksen, Ph.D.

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

Haritha Mandula, Ph.D.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
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