CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	213072
Link to EDR	\\cdsesub1\evsprod\NDA213072
Submission Dates	07/29/2019, 10/29/2019, 12/17/2019, and 3/17/2020
Submission Type	Standard Review
Brand Name	ROSZET
Generic Names	Rosuvastatin calcium and ezetimibe
Dosage Form and Strength	Fixed dose combination immediate release tablets; 5/10, 10/10, 20/10, and 40/10 mg/mg rosuvastatin/ezetimibe
Route of Administration	Oral
Proposed Indication	Treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia
Applicant	Althera Life Sciences, LLC
Associated IND	136,378
OCP Review Team	*S.W. Johnny Lau, RPh, PhD*
OCP Final Signatory	*Jayabharathi Vaidyanathan, PhD (Team Leader)*

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1. EXECUTIVE SUMMARY

The applicant is developing fixed dose combination (FDC) rosuvastatin calcium and ezetimibe (ROSZET) immediate release (IR) tablets to treat hyperlipidemia. The applicant submitted NDA 213072 via the 505(b)(2) regulatory pathway for the following 4 strengths of ROSZET FDC IR tablets for once daily oral administration:

- 5 mg rosuvastatin/10 mg ezetimibe (ROSZET 5/10 mg)
- 10 mg rosuvastatin/10 mg ezetimibe (ROSZET 10/10 mg)
- 20 mg rosuvastatin/10 mg ezetimibe (ROSZET 20/10 mg)
- 40 mg rosuvastatin/10 mg ezetimibe (ROSZET 40/10 mg)

The individual innovator products (references) for rosuvastatin calcium is CRESTOR 5, 10, 20, and 40 mg IR oral tablets and for ezetimibe is ZETIA 10 mg IR oral tablet. Both CRESTOR and ZETIA have the approved indication to treat hyperlipidemia.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has reviewed NDA 213072's clinical pharmacology data submitted on July 29, 2019, October 29, 2019, December 17, 2019, and March 16, 2020.

The Office of Pharmaceutical Quality (OPQ) recommends a complete response for this application. Major deficiencies were noted during the pre-approval inspection of the manufacturing facility and it was concluded that the facility was not ready for commercial manufacturing. Therefore, OPQ has concluded that the data submitted for quality controls of the finished ROSZET tablets, batch analyses, and stability results are not acceptable. In addition, OPQ reviewer noted content uniformity concerns for the rosuvastatin 5 mg (b) (4) ROSZET tablets, and the applicant was asked to manufacture three new batches of the ROSZET 5/10 mg strengths tablets to demonstrate that the product meets the quality standards consistently. Further OPQ will have additional product quality comments related to in-process controls for the 5mg rosuvastatin (b) (4) ROSZET tablets.

Acceptability of the clinical pharmacology data will depend on satisfactory resolution of the above-mentioned deficiencies from OPQ.

The following are the key review issues with specific recommendations and comments:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	Three relative bioavailability studies provide bridges to reference the effectiveness and safety of the ROSZET FDC IR oral tablets to the Food and Drug Administration's findings of the innovators' effectiveness and safety for individual rosuvastatin calcium and ezetimibe IR oral tablets.

General dosing instructions	The proposed dosing is acceptable. See section 2.2.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing is acceptable. See section 2.2.
Labeling	See section 2.4 for labeling recommendations.
Bridge between the "to-be-marketed" and clinical trial formulations	The applicant assessed the to-be-marketed formulations of the FDC tablets in the pivotal relative bioavailability studies.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Findings of 3 Relative Bioavailability Studies

Study (b) (4)-083-18 shows that the 90% confidence interval (CI) of the rosuvastatin C_{max} geometric mean ratio (GMR), AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 40/10 mg tablet versus the coadministration of a 40 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost under fasting. The 90% CI of the unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 40/10 mg tablet versus the coadministration of a 40 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost under fasting.

Study (b) (4)-084-18 shows that the 90% CI of the rosuvastatin C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 40/10 mg tablet versus the coadministration of a 40 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost after a high fat meal. The 90% CI of the unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 40/10 mg tablet versus the coadministration of a 40 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost after a high a high fat meal.

Study (b) (4)-085-18 shows that the 90% CI of the rosuvastatin C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 5/10 mg tablet versus the coadministration of a 5 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost under fasting. The 90% CI of the unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR for a ROSZET 5/10 mg tablet versus the coadministration of a 5 mg CRESTOR tablet and a 10 mg ZETIA tablet are all within the 80 – 125% bioequivalence goalpost under fasting.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The dosage range of ROSZET is 5/10 mg/day to 40/10 mg/day. The recommended starting dose of ROSZET is (b) (4) for patients where 5/10 mg/day is indicated. For patients

switching to ROSZET from coadministration of a statin and ezetimibe, the starting dose should be based on an equivalent dose of rosuvastatin and 10 mg of ezetimibe.

(b) (4)

ROSZET should be used as an adjunct to other (b) (4) lowering treatments (b) (4) in these patients or (b) (4).

(b) (4)

ROSZET can be administered as a single dose at any time of the day, with or without food. After initiation and or upon titration of ROSZET, lipid concentrations should be analyzed within 2 or more weeks and dosage adjusted accordingly.

ROSZET is not recommended for children.

In Asian patients, consider initiation of ROSZET therapy with 5/10 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20/10 mg/day.

2.2.2 Therapeutic individualization

ROSZET is contraindicated in patients with (b) (4)

For patients with severe renal impairment (not on hemodialysis), the starting ROSZET dose is 5/10 mg and not to exceed 10/10 mg once daily.

In Asian patients, consider starting ROSZET therapy with 5/10 mg once daily.

Avoid the coadministration of the following individual drugs with ROSZET:

- Cyclosporine because of increased exposure to rosuvastatin (610%) and total ezetimibe (240%).
- Gemfibrozil because of increased risk of myopathy or rhabdomyolysis

Atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir in combination with ROSZET will increase rosuvastatin exposure. Start ROSZET at 5/10 mg once daily and limit ROSZET dose to 10/10 mg once daily.

Fibrates or lipidmodifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Use caution when coadministering these medications with ROSZET.

Rosuvastatin prolongs INR when coadministered with coumarin anticoagulants. Monitor the use of ROSZET and coumarin anticoagulants.

Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction. Thus, dosing of ROSZET should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

Summary of labeling recommendation for different sections are listed below:

- Section 2: The proposed dosing recommendations are acceptable.
- Section 7: The proposed labeling for Drug Interactions is acceptable.
- Section 8: The proposed labeling for Use in Specific Populations is acceptable.

Section 12.3: Delete the following statement under Section 12.3 Pharmacokinetics of ROSZET's proposed label because the Guidance for the Clinical Pharmacology Labeling Section recommends (b) (4)

(b) (4)

Effect of ezetimibe coadministration on R- and S- warfarin C_{max} should be ↑3% and ↑1%, respectively, instead of ↓3% and ↓1%, respectively, in the table.

Effect of rosuvastatin coadministration on warfarin should be "Change in Cmax" rather than "Change in (b) (4)" in the table.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The applicant's rosuvastatin calcium and ezetimibe tablets are FDC IR oral tablets. The individual innovator rosuvastatin calcium and ezetimibe IR oral tablets were approved on August 12, 2003 (NDA 021366) and October 25, 2002 (NDA 021445), respectively.

The applicant had a teleconference with the Division of Metabolism and Endocrinology Products (DMEP) on October 3, 2017 to discuss the clinical and quality related issues for the development of ROSZET FDC IR oral tablets (PIND 136378's minutes in DARRTS Reference ID: 4176311 dated November 2, 2017). DMEP notified the applicant that the 3 proposed relative bioavailability studies were safe to proceed (IND 136378's letter in DARRTS Reference ID: 4358140 dated December 4, 2018).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Both rosuvastatin calcium and ezetimibe are cholesterol lowering agents.

Mechanism of Action of Rosuvastatin Calcium and Ezetimibe

Rosuvastatin competitively inhibits HMG-CoA reductase, which is a rate-limiting enzyme in cholesterol biosynthesis in the liver, whereas ezetimibe is a cholesterol absorption inhibitor in the gastrointestinal tract.

Summary of General Clinical Pharmacology and Pharmacokinetics

Pharmacokinetic Parameter	Rosuvastatin	Ezetimibe	Ezetimibe Glucuronide
C_{max}	-	3.4 – 5.5 ng/mL	45 – 71 ng/mL
T_{max}	3 – 5 hours	4 – 12 hours	1 – 2 hours
Dose proportionality	C_{max} and AUC increased in approximate proportion to dose	5 – 20 mg	-
Absolute bioavailability	20%	Undeterminable	-
Food	Not affect rosuvastatin AUC	High-fat or non-fat meals had no effect on the extent of ezetimibe absorption. Ezetimibe C_{max} increased 38% under high-fat meals.	-
Volume of distribution at steady state (mean)	134 liters	-	-
Plasma protein binding	88% mostly to albumin	> 90%	> 90%
Metabolism	About 10% to N-desmethyl rosuvastatin via CYP 2C9	10 – 20% ezetimibe in plasma	80 – 90% in plasma
Excretion	Rosuvastatin and its metabolites are excreted in feces (90%)	69% dose in feces	9% dose in urine
Elimination half-life	19 hours	22 hours	22 hours

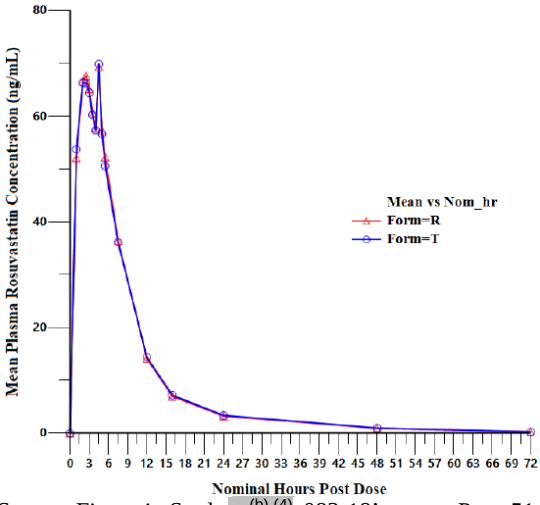
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The applicant conducted 3 relative bioavailability study to support NDA 213072, namely Studies (b) (4)-083-18, (b) (4)-084-18, and (b) (4)-085-18. These studies serve as pivotal bridging studies to reference the efficacy and safety of the reference products, CRESTOR and ZETIA.

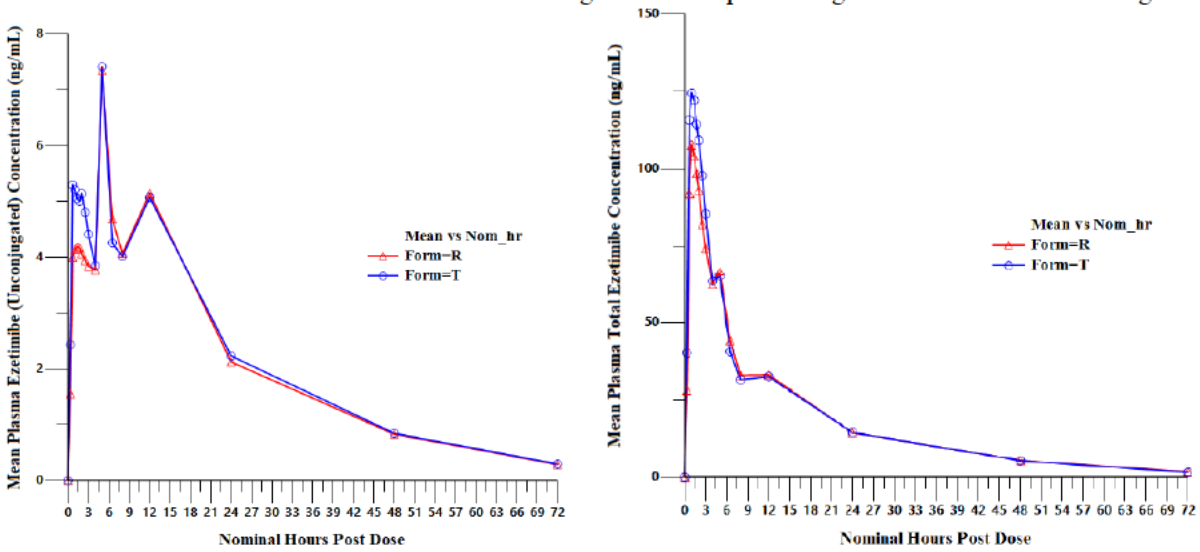
Study (b) (4) **-083-18** is a study of the to-be-marketed ROSZET 40/10 mg FDC tablet (biobatch size is 30% of the proposed commercial batch size) versus coadministration of corresponding strengths of individual CRESTOR plus ZETIA tablets (both are US products). The design was an open label, randomized 2-treatment, 2-period, 2-sequence, crossover, single dose study. A 14-day washout separated the 2 single-dose oral administrations. Sixty-one healthy volunteers completed both treatments of single dose of the to-be-marketed ROSZET 40/10 mg FDC tablet and single doses of coadministration of 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under **fasting**. Serial plasma samples were collected predose and 72 hours postdose to determine the rosuvastatin, unconjugated ezetimibe, and total ezetimibe concentrations via validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assays.

Figure 1. Mean plasma rosuvastatin concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet (T) versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets (R) under fasting.



Source: Figure in Study (b) (4) -083-18's report Page 51 of 85

Figure 2 (left). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets under fasting.
Figure 3 (right). Mean plasma total ezetimibe concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets under fasting.



Source: Figures in Study (b) (4)-083-18's report Pages 52 and 53 of 85

Table 1. Statistical comparisons of rosuvastatin, unconjugated ezetimibe, and total ezetimibe PK upon the ROSZET 40/10 mg FDC tablet administration versus the coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets under fasting.

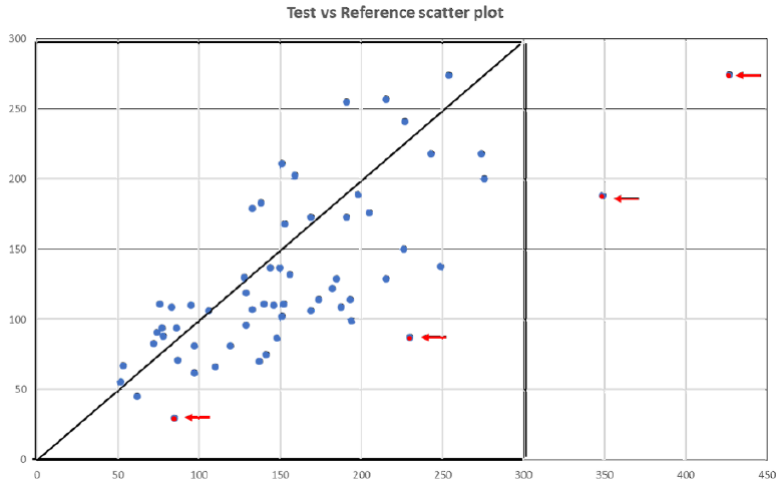
Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Coadministration	FDC Tablet/ Coadministration
Rosuvastatin	C_{max} (ng/mL)	68.768	70.462	97.60 (91.56, 1.04.03)
	AUC_{0-t} (ng*hr/mL)	598.947	599.5857	99.89 (94.57, 105.51)
	$AUC_{0-\infty}$ (ng*hr/mL)	604.3998	606.5423	99.65 (94.47, 105.11)
Unconjugated Ezetimibe	C_{max} (ng/mL)	8.3922	7.9226	105.93 (97.89, 114.62)
	AUC_{0-t} (ng*hr/mL)	139.6338	137.7857	101.34 (95.97, 107.01)
	$AUC_{0-\infty}$ (ng*hr/mL)	148.2384	146.3142	101.32 (94.76, 108.33)
Total Ezetimibe	C_{max} (ng/mL)	144.3903	119.9918	120.33 (112.57, 128.63)
	AUC_{0-t} (ng*hr/mL)	1170.8763	1126.9451	103.90 (99.02, 109.01)
	$AUC_{0-\infty}$ (ng*hr/mL)	1246.2267	1197.867	104.04 (98.89, 109.45)

Source: Modified from the tables in Study (b) (4)-083-18's report Page 56 of 85

The 90% confidence interval (CI) of rosuvastatin C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the rosuvastatin component of ROSZET 40/10 mg FDC tablet is bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the unconjugated ezetimibe component of ROSZET 40/10 mg FDC tablet is bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of total ezetimibe AUC_{0-t} GMR and $AUC_{0-\infty}$ GMR of ROSZET 40/10 mg FDC tablet to the individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet are within the 80 – 125% bioequivalence goalposts under fasting. However, the 90% CI of total ezetimibe C_{max} GMR for ROSZET 40/10 mg FDC tablet to the individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet is 112.57 – 128.63% and does not meet the 80 – 125% bioequivalence goalpost. The total ezetimibe C_{max} GMR for ROSZET 40/10 mg FDC tablet shows a 20% increase to that of the individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet. Thus, the total ezetimibe component of ROSZET 40/10 mg FDC tablet is **not** bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting. The applicant explained that this difference in ezetimibe C_{max} GMR of ROSZET 40/10 mg to the individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet was due to the following:

Applicant's Justification	Reviewer's Comment
The applicant identified 4 potential outliers who had higher total ezetimibe C_{max} as shown in the scatter plot marked in red). These outliers explain about 5% of the difference between the FDC tablet and coadministration of individual tablets. 	The lower 2 "outliers" do not seem to be outliers but within the usual variability of total ezetimibe C_{max} instead. The upper 2 "outliers" seem to be outliers for total ezetimibe C_{max}. However, the usual practice is to include all data for bioequivalence analysis unless appropriate outlier analyses have been conducted.
The assayed ezetimibe content of the reference product and the ROSZET 40/10 mg tablet is 98.3 and 101.2%, respectively. The applicant claims this observation explains 3% of the difference in total ezetimibe C_{max}.	The ezetimibe content in the reference and ROSZET 40/10 mg tablet is within the acceptable finished product specifications.
Applicant showed results from a replicate design study under fasting that the ROSZET 10/10 mg tablet is bioequivalent to the reference products.	This study used the European reference products.

This reviewer recommends accepting the applicant's claim that the ROSZET 40/10 mg FDC tablet is bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting because:

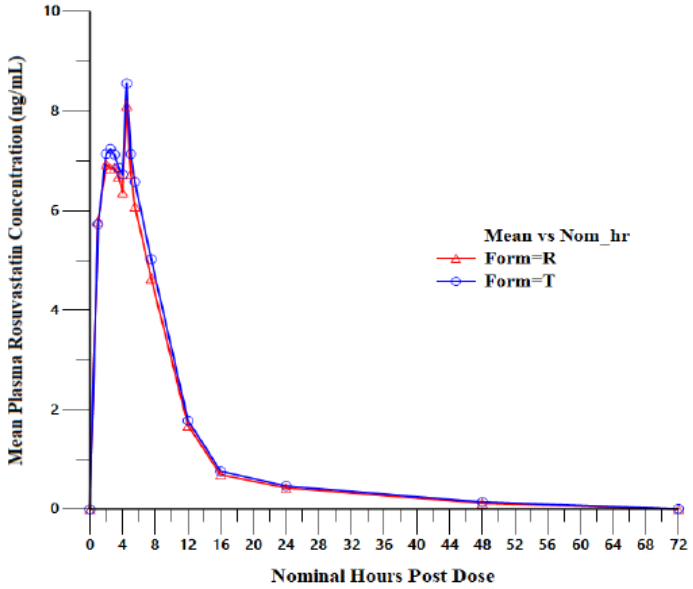
- The prespecified primary PK parameters for Study (b) (4)-083-18 are rosuvastatin C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ as well as unconjugated ezetimibe C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (IND

136378's Clinical Pharmacology review by Dr. Tao Liu in DARRTS Reference ID: 4352195 dated November 20, 2018). All these parameters met the 80 – 125% bioequivalence goalposts for the ROSZET 40/10 mg FDC tablet versus individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting.

- The unconjugated ezetimibe PK parameters were used as primary PK parameters in relative bioavailability studies conducted for previously approved FDC products containing ezetimibe.
    - The primary PK parameters for the approved simvastatin and ezetimibe FDC tablets (NDA 021687) are simvastatin C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ as well as unconjugated ezetimibe C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-687_Vytorin_BioPharmr.pdf.
    - The primary PK parameters for the approved atorvastatin and ezetimibe FDC tablets (NDA 0200153) are atorvastatin C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ as well as unconjugated ezetimibe C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/200153Orig1s000ClinPharmR.pdf.
    - The primary PK parameters for the approved bempedoic acid and ezetimibe FDC tablets (NDA 211617) are bempedoic acid and its metabolite C_{max} and AUC_{inf} as well as unconjugated ezetimibe and ezetimibe glucuronide C_{max}, AUC_{last} and AUC_{inf}. In the relative bioavailability study, the C_{max} of both unconjugated ezetimibe and ezetimibe glucuronide was about 13 – 20% lower in the FDC tablet versus those of individual tablets. These differences were concluded to be not of clinical relevance because the overall extent of ezetimibe and ezetimibe glucuronide exposure (as measured as AUC) was similar https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211617s000lbl.pdf.
- The secondary PK parameters are total ezetimibe C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ which serve as supportive data. As both total ezetimibe AUC_{0-t} and $AUC_{0-\infty}$ met the bioequivalence criteria, the total ezetimibe C_{max} difference for the proposed FDC tablet may not be of clinical relevance.

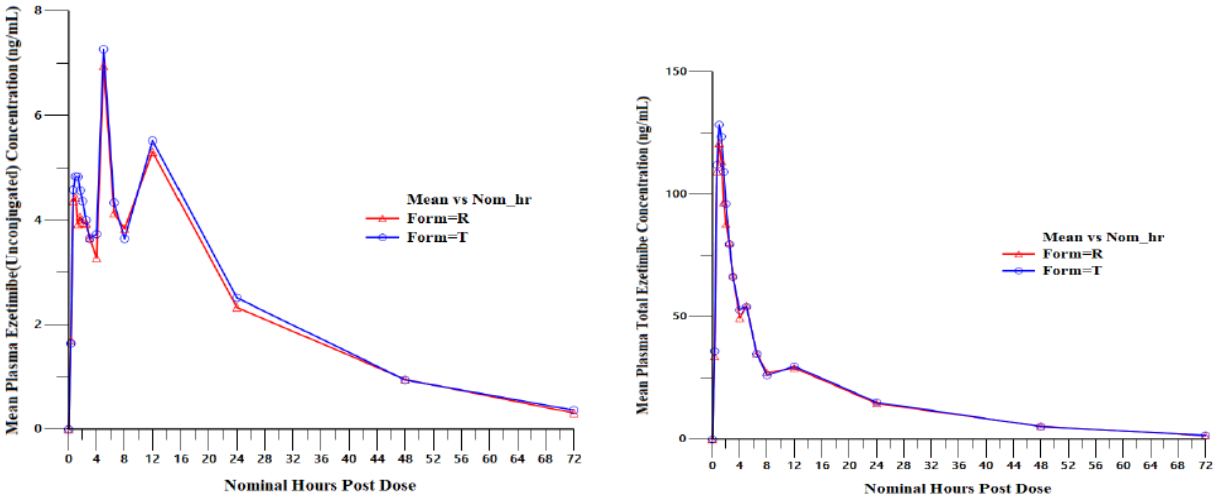
Study (b) (4) **-085-18** is a study of the to-be-marketed ROSZET 5/10 mg FDC tablet (biobatch size is 30% of the proposed commercial batch size) versus coadministration of corresponding strengths of individual CRESTOR plus ZETIA tablets (both are US products). The design was an open label, randomized 2-treatment, 2-period, 2-sequence, crossover, single dose study. A 14-day washout separated the 2 single-dose oral administrations. Sixty-four healthy volunteers completed both treatments of single dose of the to-be-marketed ROSZET 5/10 mg FDC tablet and single doses of coadministration of 5 mg CRESTOR tablet plus 10 mg ZETIA tablet under **fasting**. Serial plasma samples were collected predose and 72 hours postdose to determine the rosuvastatin, unconjugated ezetimibe, and total ezetimibe concentrations via validated LC-MS/MS assays.

Figure 4. Mean plasma rosuvastatin concentration-time profiles upon dosing of the ROSZET 5/10 mg FDC tablet (T) versus coadministration of individual 5 mg CRESTOR plus 10 mg ZETIA tablets (R) under fasting.



Source: Figure in Study (b) (4)-085-18's report Page 52 of 85

Figure 5 (left). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the ROSZET 5/10 mg FDC tablet versus coadministration of individual 5 mg CRESTOR plus 10 mg ZETIA tablets under fasting.
Figure 6 (right). Mean plasma total ezetimibe concentration-time profiles upon dosing of the ROSZET 5/10 mg FDC tablet versus coadministration of individual 5 mg CRESTOR plus 10 mg ZETIA tablets under fasting.



Source: Figures in Study (b) (4)-085-18's report Pages 53 and 54 of 85

Table 2. Statistical comparisons of rosuvastatin, unconjugated ezetimibe, and total ezetimibe PK upon the ROSZET 5/10 mg FDC tablet administration versus the coadministration of individual 5 mg CRESTOR plus 10 mg ZETIA tablets under fasting.

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Coadministration	FDC Tablet/ Coadministration
Rosuvastatin	C_{max} (ng/mL)	8.3407	7.9592	104.79 (98.24, 111.78)
	AUC_{0-t} (ng*hr/mL)	72.3571	66.8046	108.31 (102.32, 114.65)
	$AUC_{0-\infty}$ (ng*hr/mL)	75.8454	69.6212	108.94 (103.07, 115.14)
Unconjugated Ezetimibe	C_{max} (ng/mL)	7.8760	7.4821	105.27 (96.38, 114.97)
	AUC_{0-t} (ng*hr/mL)	150.0159	141.1016	106.32 (101.00, 111.91)
	$AUC_{0-\infty}$ (ng*hr/mL)	161.4829	151.0037	106.94 (101.11, 113.10)
Total Ezetimibe	C_{max} (ng/mL)	134.7210	124.6790	108.05 (100.83, 115.79)
	AUC_{0-t} (ng*hr/mL)	1109.7925	1074.4103	103.29 (98.26, 108.58)
	$AUC_{0-\infty}$ (ng*hr/mL)	1193.2103	1142.0656	104.48 (99.42, 109.79)

Source: Modified from the tables in Study (b) (4)-085-18's report Pages 56 and 57 of 85

The 90% CI of rosuvastatin C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the rosuvastatin component of ROSZET 5/10 mg FDC tablet is bioequivalent to the coadministration of individual 5 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the unconjugated ezetimibe component of ROSZET 5/10 mg FDC tablet is bioequivalent to the coadministration of individual 5 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of total ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR are within the 80 and 125 bioequivalence goalposts for ROSZET 5/10 mg FDC tablet versus coadministration of individual 5 mg CRESTOR tablet plus 10 mg ZETIA tablet under fasting.

For NDA 231072, OSIS declined to inspect the clinical site (Memorandum in DARRTS Reference ID: 4494721 dated September 20, 2019). However, OSIS inspected the bioanalytical site on (b) (4) to (b) (4) but did not issue the Form 483.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is consistent with the dosing regimens for the reference products, CRESTOR and ZETIA.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The effect of intrinsic factors on ROSZET has not been studied. However, the effect of intrinsic factors on the exposures of the individual components of ROSZET has been studied. Relevant information from the CRESTOR and ZETIA product labels was incorporated into the ROSZET product label as the following:

- ROSZET is contraindicated in patients with [redacted] (b) (4) .

- For patients with severe renal impairment (not on hemodialysis), the starting ROSZET dose is 5/10 mg and not to exceed 10/10 mg once daily.

- In Asian patients, consider starting ROSZET therapy with 5/10 mg once daily.

Patients with Hepatic Impairment

The CRESTOR and ZETIA product labels have the following information on PK studies in patients with hepatic impairment:

- In patients with chronic alcohol liver disease, plasma rosuvastatin concentrations were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60 and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100 and 21%, respectively, compared with patients with normal liver function.

- After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased about 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased about 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC values for total ezetimibe and ezetimibe were increased about 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe is not recommended in these patients.

Patients with Renal Impairment

The CRESTOR and ZETIA product labels have the following information on PK studies in patients with renal impairment:

- Mild to moderate renal impairment (CLcr $\geq$30 mL/min/1.73 m^2) had no influence on plasma rosuvastatin concentrations. However, plasma rosuvastatin concentrations increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects CLcr >80 mL/min/1.73 m^2).

- After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl $\leq$30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased about 1.5-fold, compared to healthy subjects (n=9).

Racial or Ethnic Groups

The CRESTOR product label has the following information on the effect of race on rosuvastatin:

- Pharmacokinetic studies, including one US study, have demonstrated an about 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

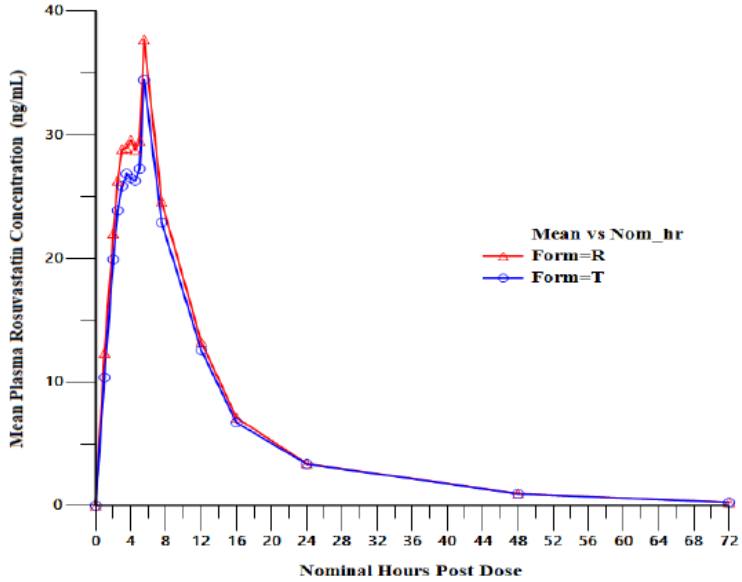
Food-drug Interaction

NDA 213072 does not contain data from food effect study for the ROSZET FDC tablets. Instead, the applicant conducted a relative bioavailability study of ROSZET FDC tablets versus coadministration of corresponding strengths of individual CRESTOR plus ZETIA tablets under fed conditions.

Study (b) (4) **-084-18** is a study of the to-be-marketed ROSZET 40/10 mg FDC tablet (biobatch size is 30% of the proposed commercial batch size) versus coadministration of corresponding strengths of individual CRESTOR plus ZETIA tablets (both are US products). The design was an open label, randomized 2-treatment, 2-period, 2-sequence, crossover, single dose study. A 14-day washout separated the 2 single-dose oral administrations. Fifty-eight healthy volunteers completed both treatments of single dose of the to-be-marketed ROSZET 40/10 mg FDC tablet and single doses of coadministration of 40 mg CRESTOR tablet plus 10 mg ZETIA tablet after receiving a high calorie (about 800 – 1000 calorie) and high fat (about 50% of total caloric content of the meal) breakfast on an overnight fast of at least 10 hours. Serial plasma samples were collected predose and 72 hours postdose to determine the rosuvastatin, unconjugated ezetimibe, and total ezetimibe concentrations via validated LC-MS/MS assays.

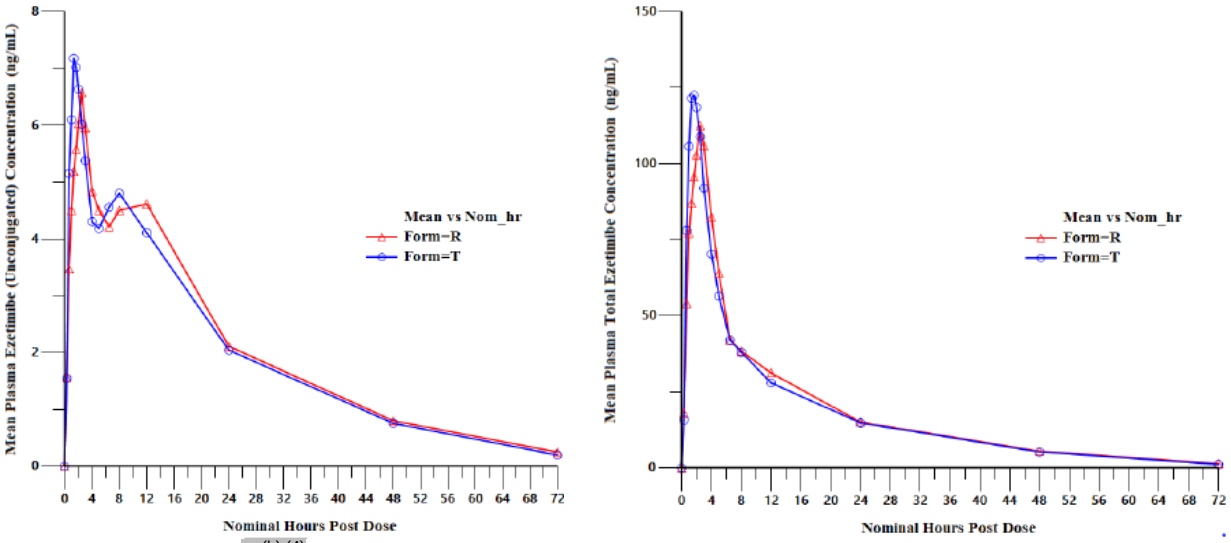
The test meal provided about 150, 250, and 500 – 600 calories from protein, carbohydrate, and fat, respectively. The high calorie and high fat test meal (breakfast) used in STUDY (b) (4) -084-18 is consistent with the recommendation by the Food Effect Guidance (https://www.fda.gov/media/121313/download).

Figure 7. Mean plasma rosuvastatin concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet (T) versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets (R) after receiving a high calorie and high fat breakfast.



Source: Figure in Study (b) (4)-084-18's report Page 55 of 89

Figure 8 (left). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets after receiving a high calorie and high fat breakfast. Figure 9 (right). Mean plasma total ezetimibe concentration-time profiles upon dosing of the ROSZET 40/10 mg FDC tablet versus coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets after receiving a high calorie and high fat breakfast.



Source: Figures in Study (b) (4)-084-18's report Pages 56 and 57 of 89

Table 3. Statistical comparisons of rosuvastatin, unconjugated ezetimibe, and total ezetimibe PK upon the ROSZET 40/10 mg FDC tablet administration versus the coadministration of individual 40 mg CRESTOR plus 10 mg ZETIA tablets after receiving a high calorie and high fat breakfast.

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Coadministration	FDC Tablet/ Coadministration
Rosuvastatin	C_{max} (ng/mL)	33.4962	36.7560	91.13 (84.40, 98.40)
	AUC_{0-t} (ng*hr/mL)	363.9669	378.6409	96.12 (90.70, 101.87)
	$AUC_{0-\infty}$ (ng*hr/mL)	368.7176	384.3824	95.92 (90.55, 101.62)
Unconjugated Ezetimibe	C_{max} (ng/mL)	9.4145	8.7577	107.50 (98.33, 117.52)
	AUC_{0-t} (ng*hr/mL)	125.0732	124.9076	100.13 (94.62 , 105.97)
	$AUC_{0-\infty}$ (ng*hr/mL)	132.1198	131.6890	100.33 (94.83, 106.14)
Total Ezetimibe	C_{max} (ng/mL)	160.2453	148.6317	107.81 (99.72, 116.57)
	AUC_{0-t} (ng*hr/mL)	1134.4868	1159.8387	97.81 (93.20, 102.66)
	$AUC_{0-\infty}$ (ng*hr/mL)	1213.5829	1221.8376	99.32 (94.41, 104.50)

Source: Modified from the tables in Study (b) (4)-084-18's report Pages 59 and 60 of 89

The 90% CI of rosuvastatin C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the rosuvastatin component of ROSZET 40/10 mg FDC tablet is bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet after receiving a high calorie and high fat breakfast because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of unconjugated ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR show that the ezetimibe component of ROSZET 40/10 mg FDC tablet is bioequivalent to the coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet after receiving a high calorie and high fat breakfast because the 90% CIs are within the 80 – 125% bioequivalence goalposts.

The 90% CI of total ezetimibe C_{max} GMR, AUC_{0-t} GMR, and $AUC_{0-\infty}$ GMR are within the 80 and 125 bioequivalence goalposts for ROSZET 40/10 mg FDC tablet versus coadministration of individual 40 mg CRESTOR tablet plus 10 mg ZETIA tablet after receiving a high calorie and high fat breakfast.

Study (b) (4)-084-18 serves as a bridge for ROSZET tablets to CRESTOR and ZETIA tablets dosing recommendations with respect to food.

The following is the product label language on food for the innovator products:

- Administration of CRESTOR with food did not affect the rosuvastatin AUC. CRESTOR can be taken with or without food, at any time of day.
- Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10 mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals. ZETIA can be administered with or without food.

Thus, ROSZET can be administered as a single dose at any time of the day, with or without food.

Drug-drug Interactions

The applicant did not conduct drug interaction study to support NDA 213072, however drug interaction studies were conducted with the individual components of ROSZET. Relevant information from the CRESTOR and ZETIA product labels was incorporated into the ROSZET product label as the following:

Avoid the coadministration of the following individual drugs with ROSZET:

- Cyclosporine because of increased exposure to rosuvastatin (b) (4) and total ezetimibe (240%).
- Gemfibrozil because of increased risk of myopathy or rhabdomyolysis.

Restriction of ROSZET dose or use caution for coadministration with other drugs:

- Atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir in combination with ROSZET will increase rosuvastatin exposure. Start ROSZET at 5/10 mg once daily and limit ROSZET dose to 10/10 mg once daily.
- (b) (4)
- Rosuvastatin prolongs INR when coadministered with coumarin anticoagulants. Monitor the use of ROSZET and coumarin anticoagulants.

(b) (4)

Interaction with Other Drugs

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 and efflux transporter breast cancer resistance protein. Concomitant administration of ROSZET with medications that are inhibitors of these transporter proteins (such as cyclosporine, certain HIV protease inhibitors) may result in increased concentrations of rosuvastatin component's plasma concentrations.

Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of 12 healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that

ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

For details of drug interactions with rosuvastatin and ezetimibe, see the product labels of CRESTOR and ZETIA.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Table 4. Bioanalytical method validation for rosuvastatin.

Analytical Validation Report	Annexure-1, Method validation report No.: MV-P-101/12, Status: Final, V: 1.00
This analytical method was used in the following studies:	Protocol No.: (b) (4) 083/084/085-18 and Study No.: RP.18.0340, 342, 343
Short description of the method	Description: A LC-MS/MS method for the estimation of Rosuvastatin in human K2EDTA plasma using Rosuvastatin D3 as an Internal Standard (ISTD) was developed and validated. The procedure involves liquid-liquid extraction method. The analyte and ISTD were eluted from a Zorbax, Eclipse XDB-C18, 100 x 4.6 mm, 3.5 µ at 30°C with a mobile phase consisting of 0.1% formic acid solution: Acetonitrile (40:60) (v/v) at a flow rate of 0.700 mL/min. Mass spectrometric detector was used to measure the analyte and ISTD using multiple reaction monitoring [Rosuvastatin (analyte): 482.20→258.10 (m/z) and Rosuvastatin D3 (ISTD): 485.20→261.20 (m/z)]. Each analysis required no longer than 3.5 min. Quantitation was achieved by measurement of the peak area ratio of the drug to the ISTD.
Biological matrix	Human plasma (K_2EDTA - Anticoagulant)
Analyte	Rosuvastatin
Internal standard (IS)	Rosuvastatin D3
Calibration concentrations (ng/mL)	STD-1: 0.100 ng/mL, STD-2: 0.200 ng/mL, STD-3: 0.748 ng/mL, STD-4: 2.303 ng/mL, STD-5: 6.580 ng/mL, STD-6: 18.799 ng/mL, STD-7: 37.597 ng/mL, STD-8: 75.195 ng/mL and STD-9: 100.260 ng/mL
Linearity	0.100 to 100.260 ng/mL
Lower limit of quantification (ng/mL)	0.100 ng/mL
QC concentrations (ng/mL)	LOQ QC: 0.103 ng/mL, LQC: 0.293 ng/mL, LMQC: 2.549 ng/mL, MQC: 37.824 ng/mL, HQC: 75.648 ng/mL
Within-run accuracy LOQ QC, LQC, LMQC, MQC and HQC	LOQ QC = -10.68% to 0.00% LQC, LMQC, MQC, HQC = -0.34% to 3.73%
Within-run precision LOQ QC, LQC, LMQC, MQC and HQC	LOQ QC = 2.17% to 6.80% LQC, LMQC, MQC, HQC = 0.80% to 2.74%
Between-run accuracy LOQ QC, LQC, LMQC, MQC and HQC	LOQ QC = -5.83% LQC, LMQC, MQC, HQC = 1.02% to 2.25%
Between-run precision LOQ QC, LQC, LMQC, MQC and HQC	LOQ QC = 6.19% LQC, LMQC, MQC, HQC = 1.53% to 2.36%
Matrix Factor (MF) (all QC) IS normalized MF (all QC) C.V.% of IS normalized MF (all QC)	Low QC 90.74% 99.46% NA High QC 96.88% 99.78% NA
Dilution integrity	1/2 and 1/4 times of Rosuvastatin at a concentration of 151.297 ng/mL
Haemolysis Effect Accuracy (% bias)	-3.41% for LQC and 1.62% for HQC
Lipemic Effect Accuracy (% bias)	-4.10% for LQC and 1.61% for HQC

Source: Table 7 of "summary-biopharm-1.pdf"

In general, the bioanalytical method validation for rosuvastatin appears acceptable.

Table 5. Bioanalytical method validation for unconjugated ezetimibe. The applicant uses "free ezetimibe" interchangeably with "unconjugated ezetimibe" throughout the study reports.

Analytical Validation Report	Annexure-1, Method validation report No.: MV-P-MV-048/17Status: Final, V: 1.00	
This analytical method was used in the following studies:	Protocol No.: (b) (4)083/084/085-18 and Study No.: RP.18.0340, 342, 343	
Short description of the method	Description: A LC-MS/MS method for the estimation of Free Ezetimibe and Free Ezetimibe with co-administered drug in human K2EDTA plasma using Ezetimibe D4 as an internal standard (ISTD) was developed and validated by Liquid liquid extraction method. The analyte and ISTD were separated on a Zorbax, Eclipse, XDB– C18, 50 x 4.6 mm, 3.5 µm at 30°C with a mobile phase consisting of Methanol:20mM Ammonium acetate with 0.1% glacial acetic acid (70:30) at a flow rate of 0.600 mL/min. Mass spectrometric detector was used to measure the analyte and ISTD using multiple reaction monitoring [Ezetimibe (analyte): 408.10→271.00 (m/z) and Ezetimibe D4 (ISTD: 412.10→275.10 (m/z)]. Each analysis required no longer than 4.00 min. Quantitation was achieved by measurement of the peak area ratio of the analyte to the ISTD.	
Biological matrix	Human plasma (K_2EDTA - Anticoagulant)	
Analyte	Free Ezetimibe	
Internal standard (IS)	Ezetimibe D4	
Calibration concentrations (ng/mL)	STD 1: 0.050 ng/mL, STD 2: 0.100 ng/mL, STD 3: 0.252 ng/mL, STD 4: 1.259 ng/mL, STD 5: 2.517 ng/mL, STD 6: 5.035 ng/mL, STD 7: 10.069 ng/mL, STD 8: 15.029 ng/mL and STD 9: 20.039 ng/mL	
Linearity	0.050 to 20.039 ng/mL	
Lower limit of quantification (ng/mL)	0.050 ng/mL	
QC concentrations (ng/mL)	LOQQC: 0.050 ng/mL, LQC: 0.143 ng/mL, MQC: 7.644 ng/mL, HQC: 15.288 ng/mL and DIQC: 76.438 ng/mL	
Within-run accuracy (Including outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = -8.00% to 3012.00% LQC = -2.10% to 57.34% MQC, HQC, DIQC = 0.30% to 9.05%	
Within-run accuracy (Excluding outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = -8.00% to -6.00% LQC = -3.50% to 0.00% MQC, HQC, DIQC = 0.30% to 9.05%	
Between-run accuracy (Including outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = 1000.00% LQC = 18.18% MQC, HQC, DIQC = 0.95% to 6.91%	
Between-run accuracy (Excluding outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = -6.00% LQC = -2.10% MQC, HQC, DIQC = 0.95% to 6.91%	
Within-run precision (Including outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = 8.51% to 237.53% LQC = 1.40% to 95.11% MQC, HQC, DIQC = 0.60% to 1.68%	
Within-run precision (Excluding outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = 8.51% to 13.04% LQC = 1.40% to 3.62% MQC, HQC, DIQC = 0.60% to 1.68%	
Between-run precision (Including outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = 388.00% LQC = 72.78% MQC, HQC, DIQC = 1.14% to 1.98%	
Between-run precision (Excluding outlier) LOQ QC, LQC, MQC, HQC and DIQC	LOQ QC = 10.64% LQC = 2.86% MQC, HQC, DIQC = 1.14% to 1.98%	
Matrix Factor (MF) (all QC) IS normalized MF (all QC) C.V.% of IS normalized MF (all QC)	Low QC 0.98% 1.01% 0.99%	High QC 0.79% 1.01% 0.99%
(Including outlier) Hemolysis Effect Accuracy	14.69% for LQC and 4.06% for HQC	
(Excluding outlier) Hemolysis Effect Accuracy	4.20% for LQC and 4.06% for HQC	
Lipemic Effect Accuracy	-0.70% for LQC and 5.89% for HQC	
Dilution integrity	5 times than HQC concentration of Free Ezetimibe at a concentration of 76.438 ng/mL	

Source: Table 8 of "summary-biopharm-1.pdf"

Table 6. Bioanalytical method validation for total ezetimibe.

Analytical Validation Report	Annexure-1, Method validation report No.: MV-P-MV-015/16, Status: Final, V: 1.00
This analytical method was used in the following studies:	Protocol No.: (b) (4) -083/084/085-18 and Study No.: RP.18.0340, 342, 343

Short description of the method	Description: A LC-MS/MS method for the estimation of Total Ezetimibe in human K2EDTA plasma using Ezetimibe D4 as an internal standard (ISTD) was developed and validated. The procedure liquid liquid extraction method. The analyte and ISTD were separated on a Zorbax, Eclipse XDB-C18, 100 x 4.6 mm, 3.5 µm column at 30°C with a mobile phase consisting of Methanol:20mM Ammonium acetate with 0.1% glacial acetic acid (w/v) (70:30) (v/v) at a flow rate of 1.000 mL/min. Mass spectrometric detector was used to measure the analyte and ISTD using multiple reaction monitoring [Ezetimibe (analyte): 408.10→271.00 (m/z) and Ezetimibe D4 (ISTD: 412.10→275.10 (m/z)]. Each analysis required no longer than 4.00 min. Quantitation was achieved by measurement of the peak area ratio of the analyte to the ISTD.	
Biological matrix	Human plasma (K_2EDTA - Anticoagulant)	
Analyte	Total Ezetimibe	
Internal standard (IS)	Ezetimibe D4	
Calibration concentrations (ng/mL)	STD-1: 1.014 ng/mL, STD-2: 2.028 ng/mL, STD-3: 4.056 ng/mL, STD-4: 10.140 ng/mL, STD-5: 40.559 ng/mL, STD-6: 101.398 ng/mL, STD-7: 202.796 ng/mL, STD-8: 300.438 ng/mL and STD-9: 400.584 ng/mL	
Linearity	1.014 to 400.584 ng/mL	
Lower limit of quantification (ng/mL)	1.014 ng/mL	
QC concentrations (ng/mL)	LOQQC: 1.014 ng/mL, LQC: 3.028 ng/mL, LMQC: 30.896 ng/mL, MQC: 154.477 ng/mL, HQC: 308.956 ng/mL and DIQC: 1544.778 ng/mL	
Within-run accuracy LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = -10.65% to 6.11% LQC, LMQC, MQC, HQC, DIQC = -11.79% to 1.72%	
Within-run accuracy in presence of Rosuvastatin LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = -0.49% LQC, MQC, HQC, DIQC = -9.63% to -4.28%	
Within-run precision LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = 1.55% to 11.52% LQC, LMQC, MQC, HQC, DIQC = 0.59% to 7.64%	
Within-run precision in presence of Rosuvastatin LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = 3.87% LQC, MQC, HQC, DIQC = 1.10% to 4.03%	
Between-run accuracy LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = -1.18% LQC, LMQC, MQC, HQC, DIQC = -5.51% to -1.02%	
Between-run precision LOQ QC, LQC, LMQC, MQC, HQC and DIQC	LOQ QC = 9.68% LQC, LMQC, MQC, HQC, DIQC = 1.49% to 5.23%	
Matrix Factor (MF) (all QC) IS normalized MF (all QC) C.V.% of IS normalized MF (all QC)	Low QC 0.95% 1.00% 1.00%	High QC 0.94% 1.01% 0.99%
Dilution integrity	5 times than HQC concentration of Total ezetimibe at a concentration of 1544.778 ng/mL	
Haemolysis Effect Accuracy (% bias)	-1.06% for LQC and -0.09% for HQC	
Lipemic Effect Accuracy (% bias)	1.49% for LQC and -0.38% for HQC	

Source: Table 9 of "summary-biopharm-1.pdf"

In general, the bioanalytical method validation for total ezetimibe appears acceptable.

In Table 5, the unconjugated ezetimibe's QC Intra-run accuracy ranged -8.00% to 3012.00% for LOQ QC, which is unusual. Thus, DMEP sent the applicant an Information Request for these observations.

Initially, the applicant responded on December 17, 2019 to the Information Request. According to the applicant, FDA's auditors (Hasan A. lrier, Ph.D. and Paul Li-Hong Yeh, Ph.D) conducted an FDA audit of the bioanalytical facility from (b) (4) to (b) (4). During the review, typographical errors were identified in method validation report MV-048/17. The FDA inspectors instructed the applicant to correct the response provided to the FDA earlier. No 483's were issued after the audit by the FDA inspectors. On March 16, 2020, the applicant submitted the amended response to the Information Request as the following:

RESPONSE TO THE QUERY RECEIVED FROM US-FDA AGENCY FOR STUDY: (b) (4)-083-18, (b) (4)-084-18, and (b) (4)-085-18

1. What QC observation(s) did you exclude for all 3 analytes in the 3 studies?

Response:

Summary of runs in which QCs were excluded in method validation and study sample analysis is tabulated below (Request to kindly refer to Attachment 01 for the details of the runs):

ANALYSIS	ANALYTE	Number of Runs in which QCs were excluded	REASON FOR EXCLUSION*
Method Validation	Free Ezetimibe	05	Outlier - Not within the acceptance limits
	Total Ezetimibe	03	Outlier - Not within the acceptance limits
	Rosuvastatin	01	Outlier - Not within the acceptance limits
Study			
1. (b) (4)-083-18/RP.18.0340	Total Ezetimibe	01	Global %CV and Global %Bias is not within acceptance limits
	Free Ezetimibe	NIL	Not Applicable
	Rosuvastatin	NIL	Not Applicable
2. (b) (4)-084-18/ RP.18.0342	Total Ezetimibe	NIL	Not Applicable
	Free Ezetimibe		
	Rosuvastatin		
3. (b) (4)-085-18/ RP.18.0343	Total Ezetimibe	NIL	Not Applicable
	Free Ezetimibe		
	Rosuvastatin		

*The runs indicated in the above table were excluded as per our in-house SOPs:

a. The values were excluded on basis of SOP, (b) (4)-SOP-021 *('Study Sample Analysis', Attachment-02, page no 16 of 19, Sec. 5.17.3)* which indicates that the global precision should be ≤15% at each QC level and % bias (accuracy) should be ±15% at each QC level. Further it also details that the concentration of any QC sample leading to 'out of acceptance limit' for global accuracy and precision of that QC level should be excluded from the calculation with proper justification (eg: Outlier test). However, both the included and excluded details are presented in the in Bioanalytical report prepared for the study.

b. The statistical basis for exclusion is as per our in-house SOP, (b) (4)-SOP-027, *('Calculation, Acceptance, Reporting of Results and Transfer of Data for Pharmacokinetic Analysis' (Attachment-03), page no.5 of 7, Section 5.1.7 "Reporting of Bioanalytical Results:", Sub-section -"Table - Quality Control samples data"*) which indicates to exclude QCs from the statistical calculations on the grounds like statistical outlier.

In addition, we would like to inform that, there were no Quality Control samples excluded in Study no. RP.18.0340, for Free Ezetimibe and Rosuvastatin and in Study no.RP.18.0342 & RP.18.0343, for all the three analytes.

One QC observation (LQC in run 5, analysed on 30-Apr-2019) in Study no. RP.18.0340 ((b) (4)-083-18) for the analyte Total Ezetimibe was excluded from the global QC calculation.

The details of QC observations that were excluded from the Method Validation of Free Ezetimibe (MV-048/17), Total Ezetimibe (MV-015/16) , Rosuvastatin (MV-101/12) and the study RP.18.0340- (Total Ezetimibe) are provided in Attachment-01.

2. Why did you exclude those QC observation(s) for all 3 analytes in the 3 studies?

Response:

In study no. RP.18.0340, for the analyte, Total Ezetimibe, only one QC observation (LQC) in run 5, which was analysed on 30-Apr-2019, was excluded from the global QC calculation.

According to the in-house SOP, (b) (4)-SOP-021- *"Study Sample Analysis", Attachment-02, page no 16 of 19, Sec. 5.17.3,* the global precision should be ≤15% at each QC level and % bias (accuracy) should be ±15% at each QC level. Further it also details that the concentration of any QC sample leading to 'out of acceptance limit' for global accuracy and precision of that QC level should be excluded from the calculation with proper justification (e.g.: Outlier test). The statistical basis for exclusion is as per our in-house SOP, (b) (4)-SOP-027, *('Calculation, Acceptance, Reporting of Results and Transfer of Data for Pharmacokinetic Analysis' (Attachment-03), page no.5 of 7, Section 5.1.7 "Reporting of Bioanalytical Results:", Sub-section -"Table - Quality Control samples data"*) which indicates to exclude QCs from the statistical calculations on the grounds like statistical outlier.

In relevance to the above stated in-house SOP criteria, the LQC, was subjected to an outlier test, due to the erratic value, and excluded from the global calculation of % CV as well as % Bias, for Total Ezetimibe, in the study RP.18.0340.

3. If you exclude those QC observation(s), did you exclude the whole bioanalytical batch's results including those unknown samples of that bioanalytical batch with QC samples?

Response:

We clarify that the whole bioanalytical batch's results including those unknown samples were not excluded.

RESPONSE TO THE QUERY RECEIVED FROM US-FDA AGENCY FOR STUDY: [(b) (4)]083-18, [(b) (4)]084-18, and [(b) (4)]085-18

The batch (Study sample, Run ID 05, 30 -Apr -2019; Ref Attachment 1) was accepted based on our SOP [(b) (4)]*SOP-021- "Study Sample Analysis", attachment-02, page no 16 of 19,Sec. 5.17.3)* which indicates that "For entire run acceptance requires that at least 67% of QC samples (four out of six or 2/3 of QCs), including 50% at each concentration level meet the criteria of ±15%".

At the end of the sample analysis, one QC sample *(Study Number RP.18.0340, Analyte: Total Ezetimibe)* was rejected as per SOP ([(b) (4)]*SOP-021- "Study Sample Analysis", attachment-02 page no 16 of 19, Sec. 5.17.3)* which indicates the concentration of any QC sample leading to 'out of acceptance limit' for global accuracy and precision of that QC level should be excluded from the calculation with proper justification (e.g.: Outlier test).

Thus, based on the above two SOPs which are in line with the guidelines, not the whole batch, but the LQC sample *(Study sample, Run ID 05, 30- Apr- 2019)* in the study was rejected.

4. How does your practice of excluding those QC observation(s) relate to the Bioanalytical Guidance at:https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf ?

Response:
This is to bring to your kind notice that our procedure is in line with the FDA guidance document 'Bioanalytical Method Validation Guidance for Industry', Section C, Validated Methods: Expectations of In-Study Analysis and Reporting (page.12) which states that "QC results (including outliers) from analytical runs that meet the acceptance criteria should be included in the estimation of accuracy and precision during the study's sample analysis"

The above statement is also reflected in the SOPs that were followed during the method validation procedures and study sample analysis is also in line with the guidelines:

a. [(b) (4)]SOP-021- *"Study Sample Analysis", Attachment-02, page no 16 of 19, Sec. 5.17.3*
b. [(b) (4)]SOP-027, *"Calculation, Acceptance, Reporting of Results and Transfer of Data for Pharmacokinetic Analysis" page no.5 of 7, Section 5.1.7 "Reporting of Bioanalytical Results:", Sub-section -"Table - Quality Control samples data", Attachment-03)*

In general, this reviewer found that the applicant's response to the December 5, 2019 Information Request is consistent with the Bioanalytical Method Validation Guidance (https://www.fda.gov/media/70858/download).

5. REFERNCES

- White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. J Clin Pharmacol 2002;42:963-70.
- Kosoglou et al. Ezetimibe: A review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 2005;44: 467-94.

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/s/

SZE W LAU
04/20/2020 04:05:06 PM

JAYABHARATHI VAIDYANATHAN
04/20/2020 04:43:56 PM