CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

CLINICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	4/28/2020
From	Jayabharathi Vaidyanathan, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 213072
Applicant	Althera Pharmaceuticals Industries Limited
Date of Submission	7/29/2019
PDUFA Goal Date	5/29/2020
Proprietary Name / Established (USAN) names	Roszet/rosuvastatin and ezetimibe tablets
Dosage forms / Strength	Fixed dose immediate release tablets, 40/10 mg, 20/10mg, 10/10 mg and 5/10 mg rosuvastatin/ezetimibe
Proposed Indication(s)	Treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia
Recommended:	Complete Response

1. Introduction

On July 29, 2019, the applicant (Althera Pharmaceuticals Industries Limited) submitted NDA 213072 via the 505(b)(2) pathway for Roszet (rosuvastatin and ezetimibe) fixed-dose combination (FDC) tablets indicated for the treatment of primary (b) (4) non-familial hyperlipidemia and homozygous familial hypercholesterolemia (HoFH). Rosuvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor and ezetimibe is an inhibitor of intestinal cholesterol absorption. To support their 505(b)(2) NDA application, the applicant is relying on FDA's finding of safety and effectiveness for approved listed drugs, Crestor and Zetia and have conducted three clinical relative bioavailability studies using rosuvastatin/ezetimibe FDC tablets compared to the co-administration of the individual reference products. Biowaiver is being requested for the strengths that were not evaluated in the clinical studies. The proposed tablet strengths include 40/10 mg, 20/10mg, 10/10 mg and 5/10 mg rosuvastatin/ezetimibe tablets.

The NDA will receive a Complete Response due to significant deficiencies identified in the manufacturing facilities inspection. These deficiencies impact the quality control specifications of the finished drug product and the data was deemed inadequate (Refer to Section 3: Quality).

2. Background

On August 3, 2017, the applicant submitted a Type B (Pre-IND 136378) meeting request to seek guidance on their development plan for their FDC product (rosuvastatin/ezetimibe). A meeting was granted and on October 3, 2017 the applicant had a teleconference with the Agency to discuss the 505 (b)(2) regulatory filing pathway, proposed bridging strategy, and stability program related issues for the development of the Roszet FDC immediate release tablets (see COR-MEET-03 (Meeting Minutes) dated 11/2/2017 in DARRTS).

The applicant was recommended to develop rosuvastatin/ezetimibe 5 mg/10 mg FDC tablet strength in addition to the proposed strengths (40/10 mg, 20/10 mg and 10/10 mg rosuvastatin/ezetimibe tablets) and submit formal biowaiver requests for strengths that were not planned to be evaluated in the proposed clinical study. The applicant accepted the Agency's recommendation to develop the 5/10 mg strength FDC tablets. Further, the applicant was recommended to submit drug utilization data regarding the combination of rosuvastatin (by dose) with ezetimibe in the NDA along with literature data to support safety and efficacy of the combination. The applicant submitted the IND on 10/19/2018 with the clinical protocols and conducted the relative bioavailability studies submitted in this NDA.

3. Quality (CMC/Device)

The recommendation from the Office of Pharmaceutical Quality (OPQ) is a Complete Response, which includes recommendation for the facilities listed in this application (see Dr. Ramaswamy's Integrated Quality Assessment dated 4/20/2020 in DARRTS).

Drug Substance:

The drug substance information was found to be adequate to support the approval of the NDA.

Drug Product:

A pre-approval inspection was requested for the (b) (4), a site that performed analytical method validation for the chemistry, manufacturing and controls (CMC) information. Pre-approval inspection of this facility on (b) (4) uncovered data integrity issues related to analytical method validation data. Areas affected by this issue include quality controls of the finished Roszet tablets, batch analyses result and stability results. The chemistry reviewer notes that the analytical method validation deficiencies indicate a possibility that the true data sets of the degradation products (b) (4) impurity in the stability batches of the Roszet tablets could exceed the 0.5% qualification threshold. Consequently, no product shelf-life can be granted at this point. Therefore, the drug product reviewer concluded that the data submitted in the NDA is inadequate. The applicant will need to re-perform the analytical method validation and provide adequate stability studies data. Further, the manufacturing process review indicated that the applicant was unable to (b) (4) in the 5/10 mg rosuvastatin/ezetimibe tablets and it did not meet uniformity of dosage acceptance criteria according to USP. Thus, the applicant was requested to manufacture new batches of lower strength (b) (4) tablets to demonstrate capability to manufacture the product that will meet quality standards consistently.

Biopharmaceutics:
The applicant has requested biowaiver for the two intermediate strengths 10/10 mg and 20/10 mg based on dissolution profiles. Due to the issues pertaining to the analytical method

validation for dissolution testing, the biopharmaceutics recommendations will be considered as tentative, until the applicant satisfactorily addresses the inspection related deficiencies.

Overall, the applicant has not provided adequate information to ensure the quality of the fixed combination drug product. I concur with the CMC reviewers, that adequate resolution of the above deficiencies will be needed prior to approval.

4. Nonclinical Pharmacology/Toxicology

As per Pharmacology/Toxicology reviewers, the nonclinical studies submitted with this NDA and previous FDA findings of the safety and efficacy for Crestor and Zetia are adequate to support approval of Roszet. Nonclinical studies were conducted to qualify an impurity that was identified during forced degradation studies of the rosuvastatin/ezetimibe FDC tablets. The (b) (4) was a major degradant impurity that exceeded the qualification threshold of 0.5% per ICH Q3B(R2). The applicant conducted a 90-day comparative rodent oral repeat-dose toxicity study and two in vitro genotoxicity studies in accordance with the ICH Q3B(R2) qualification criteria.

The 90-day study evaluated the toxicity of ezetimibe containing the impurity against ezetimibe alone. Ezetimibe or (b) (4) impurity at the high dose ((b) (4) mg/kg/day, (b) (4) fold greater than the human therapeutic dose (10 mg/day), based on AUC) did not cause any treatment-related adverse effects. The two genotoxicity studies conducted were an in vitro bacterial reverse mutation assay (Ames assay) and an in vitro mammalian chromosomal aberration assay in human lymphocytes, which evaluated the mutagenic and clastogenic potential of (b) (4). (b) (4) was not genotoxic in the two in vitro assays at any dose irrespective of the status of metabolic activation.

Overall, the nonclinical review concluded that there are no nonclinical concerns for the FDC tablets. I concur with reviewer's assessment that there are no nonclinical pharmacology/toxicology issues that would preclude approval (see REV-NONCLINICAL-21 (Primary Review) dated 5/4/2020 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

The applicant's submission included the results of three relative bioavailability studies. These studies establish a scientific bridge for the proposed FDC tablets to reference the efficacy and safety findings of the individual reference products (US approved Crestor and US approved Zetia).

Two studies (Study (b) (4)-083-18 and Study (b) (4)-085-18) assessed the relative bioavailability of rosuvastatin and ezetimibe from the Roszet 40/10 mg tablets and 5/10 mg compared to the coadministration of either a 40 mg Crestor tablet and a 10 mg Zetia tablets or

coadministration of a 5 mg Crestor and a 10 mg Zetia tablets, respectively under fasting conditions.

Both these studies demonstrated that the rosuvastatin and ezetimibe component from the FDC tablets met the bioequivalence criteria compared to the coadministration of the individual reference products. Table 1 shows the statistical comparisons of primary PK parameters rosuvastatin and unconjugated ezetimibe PK upon the Roszet 40/10 mg FDC as compared to the coadministration of individual 40 mg Crestor and 10 mg Zetia tablets under fasting.

Table 1: Study (b) (4)-083-18 results

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

Table 2 shows the statistical comparisons of primary PK parameters rosuvastatin and unconjugated ezetimibe PK upon the Roszet 5/10 mg FDC as compared to the coadministration of individual 5 mg Crestor and 10 mg Zetia tablets under fasting.

Table 2: Study (b) (4)-085-18 results:

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

Study (b) (4)-084-18 assessed the relative bioavailability of rosuvastatin and ezetimibe from the Roszet 40/10 mg tablets compared to the coadministration of a 40 mg Crestor tablet and a 10 mg Zetia tablets following a high calorie and high fat meal. As shown in Table 3, the 90% CI for the geometric mean ratios for rosuvastatin PK parameters met the bioequivalence goal posts. Similarly, the 90% CI for the geometric mean ratios of unconjugated ezetimibe PK

parameters met the bioequivalence goal posts. Similar to the administration of the individual reference products, the Roszet FDC tablet can be administered with or without regard to food.

Table 3: Study (b) (4)-084-18 results:

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

Overall, the clinical pharmacology review concluded that the results of the studies established bioequivalence between the proposed FDC tablets and the individual reference products, Crestor and Zetia. The recommendations from clinical pharmacology is tentative pending satisfactory resolution of the OPQ deficiencies. Refer to clinical pharmacology review (see REV-CLINPHARM-21 (Primary Review) dated 4/20/2020 in DARRTS). I concur with the review conclusions.

6. Clinical Efficacy & Safety

There are no new clinical efficacy or safety data essential for the risk/benefit assessment of rosuvastatin/ezetimibe fixed dose combination tablets. The proposed dose and dosing regimen for Roszet combination product is consistent with doses approved for rosuvastatin and ezetimibe. The submitted data from the three bioavailability studies did not have any serious adverse events. Although ezetimibe is approved broadly for coadministration with statins, approval studies did not explicitly test the safety and efficacy of ezetimibe and rosuvastatin combination therapy. Therefore, the applicant also provided published literature to substantiate the safety and efficacy of coadministration of the two drugs. Study results demonstrated that both rosuvastatin and ezetimibe contribute to LDL-C reduction, and published literature also supports the safety of coadministration.

Overall, the observed events were consistent with the known safety profiles of rosuvastatin and ezetimibe. The Applicant also provided data from a drug utilization query that supports that rosuvastatin and ezetimibe are prescribed together in clinical practice. The clinical reviewer concludes that Roszet is approvable based on a favorable benefit/risk framework (See REV-CLINICAL-21 (Primary Review) dated 5/5/2020 in DARRTS). I concur with the reviewer's conclusions.

7. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

8. Pediatrics

The applicant submitted NDA 213072 without an Agreed iPSP or a pediatric assessment. The Division consulted the Division of Pediatric and Maternal Health (DPMH) to opine on a path forward regarding the development of a pediatric assessment plan for the FDC product. The applicant plans to (b) (4) This proposed product contains a novel combination which is considered to be a new active ingredient under the Pediatric Research Equity Act (PREA). Therefore, the applicant is required to submit a pediatric assessment with the adult NDA or an Agreed initial Pediatric Study Plan (iPSP) describing how it plans to evaluate dosing, safety, and efficacy of this product in the pediatric population, including any plans to request partial waivers and/or deferral of PREA study requirements for a specific pediatric age group.

FDA approved Crestor for the following use in pediatric patients:

- Treatment of HeFH in patients 10 to 17 years of age in 2009 with expansion of the indication down to 8 years of age and older in 2014
- Treatment of HoFH in patients 7 years of age and older FDA granted Crestor pediatric exclusivity for the HeFH indication that will expire June 2022
- FDA also granted Crestor pediatric orphan exclusivity for HoFH. This orphan exclusivity expires May 2023

FDA approved Zetia (ezetimibe 10 mg) in 2008 to allow

- Co- administration with approved pediatric doses of a statin in pediatric patients 10 to 17 years of age with HeFH

To date, ezetimibe has not been approved either as monotherapy or for co-administration with statins for the treatment of pediatric patients with HoFH. Therefore, there is no approved pediatric use information for Zetia for the treatment of HoFH.

In consultation with Pediatric Review Committee (PeRC), the Division agrees that if the applicant resubmits the NDA addressing the CMC deficiencies and continues to seek approval only in adults, applicant will be issued PREA PMRs with adult approval. The PREA PMR's will be issued with a final study report submission date that corresponds to the rosuvastatin exclusivity expiration dates. The two PMRs will include assessment of Roszet (b) (4) for the treatment of HoFH in pediatric patients (b) (4) to 17 years of age. (b) (4)

(b) (4) (see CONSULT REV-DPMH-02 (Pediatric Review) dated 05/01/2020 in DARRTS).

9. Other Relevant Regulatory Issues

OSIS inspection

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portions of studies (b) (4)-083-18, (b) (4)-084-18, and (b) (4)-085-18 during (b) (4) and no objectional conditions or practices were founds during the inspection and the final inspection classification was No Action Indicated (NAI). OSIS concluded that the data from the audited studies are reliable to support a regulatory decision (see REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) in DARRTS dated 04/17/2020).

Financial Disclosure

FDA 3454 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trial.

Proprietary name

Division of Medication Error Prevention and Analysis (DMEPA) has reviewed and concluded that the proposed proprietary name, Roszet is conditionally acceptable (see REV-SURVEPI-10 (Proprietary Name Review) in DARRTS dated 11/01/2019).

10. Labeling

Since the application will be receiving a Complete Response, labeling will not be discussed in this review cycle.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

The information provided in this application does not ensure drug product quality. There is no unmet need as this is a convenience dosage form, an FDC of two components (rosuvastatin and ezetimibe) which are both approved as individual products.

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/

JAYABHARATHI VAIDYANATHAN
05/13/2020 04:48:23 PM

JOHN M SHARRETTS
05/14/2020 10:49:08 AM
I concur.

Medical Officer 505(b)(2) NDA Review
Division of Diabetes, Lipid Disorders, and Obesity

NDA – 213072

Name of Drug – Roszet (rosuvastatin/ezetimibe) tablets

Applicant – Althera Life Sciences, LLC

Date of Submission – July 29, 2019

PDUFA Goal Date – May 29, 2020

Medical Reviewer – Laura Higginbotham, MD, MPH

BACKGROUND

Regulatory

The Applicant submitted this New Drug Application (NDA) in support of the following proposed indications:

(b) (4) ***Primary*** (b) (4) ***Hyperlipidemia***
ROSZET is indicated for the reduction of (b) (4) *low-density lipoprotein cholesterol (LDL-C),* (b) (4)
in patients with primary non-familial hyperlipidemia (b) (4)

(b) (4)

(b) (4) ***Homozygous Familial Hypercholesterolemia (HoFH)***
ROSZET is indicated for the reduction of (b) (4) *LDL-C in adult patients with homozygous familial hypercholesterolemia, as an adjunct to other* (b) (4) *-lowering treatments* (b) (4) *or alone* (b) (4) .

(b) (4)

Roszet is a fixed combination drug product (FCDP) that contains rosuvastatin and ezetimibe. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in cholesterol production, and also leads to increased expression of hepatic LDL receptors with enhanced peripheral clearance of LDL-C. Ezetimibe is an inhibitor of intestinal cholesterol absorption. The bempedoic acid/ezetimibe FCDP is administered orally once daily as 40 mg/10 mg, 20 mg/10 mg, 10 mg/10 mg, or 5 mg/10 mg tablets.

The NDA application relies on FDA's previous findings of safety and effectiveness for Crestor (NDA 021366, original approval date 08/12/2003) and Zetia (NDA 021445, original approval date 10/25/2002). Crestor (rosuvastatin) is approved for the treatment of hyperlipidemia and mixed dyslipidemia, pediatric familial hypercholesterolemia, hypertriglyceridemia, primary dysbetalipoproteinemia, adult HoFH, atherosclerotic progression slowing, and primary prevention of cardiovascular (CV) disease. Zetia (ezetimibe) is approved for the treatment of patients with primary hyperlipidemia as monotherapy or in combination with statins or fenofibrates, HoFH, and homozygous sitosterolemia. Although Zetia is approved for use in combination with the entire statin drug class, data on rosuvastatin coadministration is not explicitly presented in ezetimibe labeling. Both rosuvastatin and ezetimibe are marketed worldwide with robust postmarketing data to support their safe and efficacious use.

During a pre-IND meeting in October 2017, the Division advised the company to develop FCDP dosage strengths that correspond to all available doses of rosuvastatin, to submit a biowaiver request for strengths not evaluated in clinical studies, and to submit drug utilization data on the combined use of rosuvastatin and ezetimibe in clinical practice. The rosuvastatin/ezetimibe FCDP IND was opened in October 2018.

The Applicant did not request a pre-NDA meeting. NDA 213072 was filed on September 11, 2019. A 74-day filing letter was sent to the Applicant and included the following review issues and comments: 1) request for justification of failure of one study to pass the bioequivalence (BE) criteria, 2) notification that inclusion of primary hyperlipidemia as an indication will be a review issue, and 3) reminder that the NDA is subject to the requirements of the Pediatric Research Equity Act (PREA) which requires submission of a Pediatric Study Plan (PSP).

Drug in Study

The chemical name of the rosuvastatin calcium drug substance is 6-heptenoic acid,7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-, calcium salt (2:1), with a molecular formula of $(C_{22}H_{27}FN_3O_6S)_2 \bullet Ca$ and a molecular weight of 1001.14. The chemical name of the ezetimibe drug substance is 1-(4-fluorophenyl)-3(R)-[3-(4-flurophenyl)-3(S) hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, with a molecular formula of $C_{24}H_{21}F_2NO_3$ and a molecular weight of 409.4.

The drug product, Roszet (rosuvastatin/ezetimibe), is manufactured as (b) (4) tablets at strengths of 40 mg/10 mg, 20 mg/10 mg, 10 mg/10 mg, and 5 mg/10 mg. Excipients include meglumine, microcrystalline cellulose, (b) (4) crospovidone, (b) (4) phosphate dihydrate, pregelatinized starch, colloidal silicone dioxide, sodium stearyl fumarate, mannitol, sodium lauryl sulphate, povidone, ferric oxide, (b) (4), croscarmellose sodium, magnesium stearate, and (b) (4).

Supportive Evidence Submitted to NDA 213072

- Clinical pharmacology studies (083-18, 084-18, 085-18)
- Literature studies (ACTE, GRAVITY, EXPLORER)
- Drug utilization query

The clinical pharmacology studies were reviewed in detail by Dr. Lau from the Office of Clinical Pharmacology. Refer to this review for additional details.

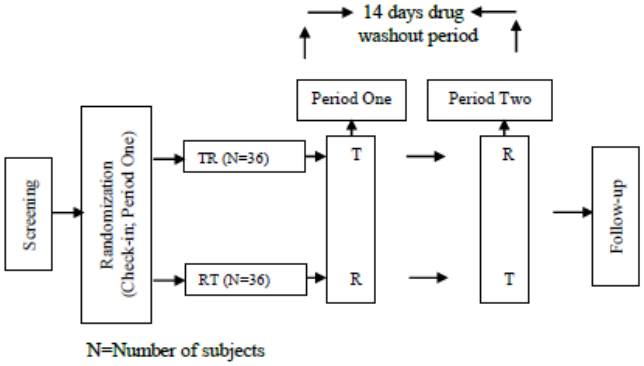
STUDY SUMMARIES

No trials evaluating clinical safety and efficacy were conducted.

083-18 (40/10 Fasting)

Study 083 was a single-center (India), open-label, randomized, single dose, two-period, crossover study to evaluate the pharmacokinetics (PK) of the 40 mg/10 mg FCDP compared to PK observed with coadministration of the reference listed drugs (RLDs). The study was conducted under fasting conditions. Enrolled subjects were randomized to a treatment sequence (test → reference vs. reference → test) and observed for 72 hours after receipt of each single dose.

Figure 1. Design of BE Studies 083, 084, and 085.



Source: Applicant; Clinical Study Report, 083-18, p. 29

Seventy-two (72) healthy male volunteers enrolled, and 61 subjects (85%) completed the study. Seven patients (10%) were lost to follow-up, 3 patients (4%) were discontinued due to positive alcohol or urine drug screen, and 1 patient (1%) withdrew consent.

BE results provided by the Applicant are included in tables below (**Tables 1-3**).

Table 1. Pharmacokinetic Parameters for Test Product and Rosuvastatin Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	68.7680	70.4624	97.60	(91.56 , 104.03)	21.32	99.99
Ln(AUC_{0-t})(ng.hr/mL)	598.9471	599.5857	99.89	(94.57 , 105.51)	18.23	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	604.3998	606.5423	99.65	(94.47 , 105.11)	17.77	100.00

Source: Applicant; Clinical Study Report, 083-18, p. 11

Table 2. Pharmacokinetic Parameters for Test Product and Unconjugated Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	8.3922	7.9226	105.93	(97.89 , 114.62)	26.40	99.83
Ln(AUC_{0-t})(ng.hr/mL)	139.6338	137.7857	101.34	(95.97 , 107.01)	18.05	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	148.2384	146.3142	101.32	(94.76 , 108.33)	22.16	99.99

Source: Applicant; Clinical Study Report, 083-18, p. 12

Table 3. Pharmacokinetic Parameters for Test Product and Total Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	144.3903	119.9918	120.33	(112.57 , 128.63)	22.31	99.99
Ln(AUC_{0-t})(ng.hr/mL)	1170.8763	1126.9451	103.90	(99.02 , 109.01)	15.98	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	1246.2267	1197.8670	104.04	(98.89 , 109.45)	16.88	100.00

Source: Applicant; Clinical Study Report, 083-18, p. 12

No serious adverse events (SAEs) or adverse events leading to discontinuation were reported during the study. A summary of adverse events experienced across all 3 BE studies is summarized in Tables 10-11.

084-18 (40/10 Fed)

Study 084 was a single-center (India), open-label, randomized, single dose, two-period, crossover study to evaluate the PK of the 40 mg/10 mg FCDP compared to PK observed with coadministration of the RLDs. The study was conducted under fed conditions. The trial design was identical to study 083 (**Figure 1**).

Seventy-two (72) healthy male volunteers enrolled, and 58 subjects (81%) completed the study. Seven patients (10%) were discontinued for positive urine alcohol/drug screen, 5 patients (7%) were lost to follow-up, 1 patient (1%) was discontinued due to a protocol violation, and 1 patient (1%) discontinued due to an adverse event.

BE results provided by the Applicant are included in tables below (**Tables 4-6**).

Table 4. Pharmacokinetic Parameters for Test Product and Rosuvastatin Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	33.4962	36.7560	91.13	(84.40 , 98.40)	25.06	99.88
Ln(AUC_{0-t})(ng.hr/mL)	363.9669	378.6409	96.12	(90.70 , 101.87)	18.84	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	368.7176	384.3824	95.92	(90.55 , 101.62)	18.71	100.00

Source: Applicant; Clinical Study Report, 084-18, p. 11

Table 5. Pharmacokinetic Parameters for Test Product and Unconjugated Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	9.4145	8.7577	107.50	(98.33 , 117.52)	29.28	99.26
Ln(AUC_{0-t})(ng.hr/mL)	125.0732	124.9076	100.13	(94.62 , 105.97)	18.39	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	132.1198	131.6890	100.33	(94.83 , 106.14)	18.13	100.00

Source: Applicant; Clinical Study Report, 084-18, p. 12

Table 6. Pharmacokinetic Parameters for Test Product and Total Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	160.2453	148.6317	107.81	(99.72 , 116.57)	25.52	99.85
Ln(AUC_{0-t})(ng.hr/mL)	1134.4868	1159.8387	97.81	(93.20 , 102.66)	15.66	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	1213.5829	1221.8376	99.32	(94.41 , 104.50)	16.45	100.00

Source: Applicant; Clinical Study Report, 084-18, p. 12

No SAEs were reported during the study. One patient discontinued due to an adverse event (moderate diarrhea and abdominal pain). A summary of adverse events experienced across all 3 BE studies is summarized in Tables 10-11.

085-18 (5/10 Fasting)

Study 085 was a single-center (India), open-label, randomized, single dose, two-period, crossover study to evaluate the PK of the 5 mg/10 mg FCDP compared to PK observed with coadministration of the RLDs. The study was conducted under fasting conditions. The trial design was identical to studies 083 and 084 (**Figure 1**).

Seventy-two (72) healthy male volunteers enrolled, and 64 subjects (89%) completed the study. Four patients (6%) were lost to follow-up, and 4 patients (6%) were discontinued due to positive urine alcohol/drug screen.

> *Reviewer comment: The high discontinuation rate across all 3 BE studies raises questions about trial integrity, particularly given that most patients were lost to follow-up or discontinued due to positive alcohol/drug screening. However, the Office of Study Integrity and Surveillance (OSIS) recently inspected the clinical site and identified no concerning findings.*

BE results provided by the Applicant for study 085 are included in tables below (**Tables 7-9**).

Table 7. Pharmacokinetic Parameters for Test Product and Rosuvastatin Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	8.3407	7.9592	104.79	(98.24 , 111.78)	22.04	99.99
Ln(AUC_{0-t})(ng.hr/mL)	72.3571	66.8046	108.31	(102.32 , 114.65)	19.36	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	75.8454	69.6212	108.94	(103.07 , 115.14)	18.84	100.00

Source: Applicant; Clinical Study Report, 085-18, p. 11

Table 8. Pharmacokinetic Parameters for Test Product and Unconjugated Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	7.8760	7.4821	105.27	(96.38, 114.97)	30.41	99.35
Ln(AUC_{0-t})(ng.hr/mL)	150.0159	141.1016	106.32	(101.00, 111.91)	17.43	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	161.4829	151.0037	106.94	(101.11, 113.10)	18.54	100.00

Source: Applicant; Clinical Study Report, 085-18, p. 12

Table 9. Pharmacokinetic Parameters for Test Product and Total Ezetimibe Reference Product.

Pharmacokinetic parameter	Geometric Least Squares Means (Test,T)	Geometric Least Squares Means (Refe,R)	Ratio (T/R) (%)	90% Confidence Limits (T vs. R)	Intra Subject CV %	Power (%)
Ln(C_{max})(ng/mL)	134.7210	124.6790	108.05	(100.83, 115.79)	23.65	99.98
Ln(AUC_{0-t})(ng.hr/mL)	1109.7925	1074.4103	103.29	(98.26, 108.58)	16.96	100.00
Ln(AUC_{0-inf})(ng.hr/mL)	1193.2103	1142.0656	104.48	(99.42, 109.79)	16.85	100.00

Source: Applicant; Clinical Study Report, 085-18, p. 12

No SAEs or adverse events leading to discontinuation were reported during the study. A summary of adverse events experienced across all 3 BE studies is summarized in Tables 10-11.

Table 10. Overview of Adverse Events,[1] Safety Population,[2] Trials 083, 084, and 085.

	40/10 Fasting		40/10 Fed		5/10 Fasting	
	Test N=65	Ref N=67	Test N=64	Ref N=69	Test N=67	Ref N=71
Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AE	4 (6.2)	1 (1.5)	3 (4.7)	1 (1.4)	2 (3.0)	3 (4.2)
Moderate or severe AEs[3]	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.4)	1 (1.5)	1 (1.4)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to discontinuation	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug. AE were monitored for 72 hours after each single dose administration.

[2] Includes subjects who received at least one dose of study drug (test or reference).

[3] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; Ref, reference product; SAE, serious adverse event

Table 11. Adverse Events,[1] Safety Population,[2] Trials 083, 084, and 085.

Event	Test N=196 n (%)	Ref N=207 n (%)	Risk Difference[3] (95% CI)
Hyperglycemia	3 (1.5)	0 (0.0)	1.5 (-0.2, 3.2)
Elevated CK >3x	2 (1.0)	0 (0.0)	1.0 (-0.4, 2.4)
Diarrhea	2 (1.0)	0 (0.0)	1.0 (-0.4, 2.4)
Elevated liver enzymes	1 (0.5)	0 (0.0)	0.5 (-0.5, 1.5)
Abdominal pain	1 (0.5)	0 (0.0)	0.5 (-0.5, 1.5)
Headache	1 (0.5)	0 (0.0)	0.5 (-0.5, 1.5)
Rash	1 (0.5)	1 (0.5)	0.0 (-1.3, 1.4)
Elevated CK >10x	0 (0.0)	1 (0.5)	-0.5 (-1.4, 0.5)
Elevated bilirubin	0 (0.0)	1 (0.5)	-0.5 (-1.4, 0.5)
Hyperkalemia	0 (0.0)	1 (0.5)	-0.5 (-1.4, 0.5)

Source: Reviewer's analysis

[1] Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug. AE were monitored for 72 hours after each single dose administration.

[2] Includes subjects who received at least one dose of study drug (test or reference).

[3] Test product vs. reference product

Abbreviations: AE, adverse event; CK, creatine kinase; N, number of subjects in group; n, number of subjects with at least one event; Ref, reference product; SAE, serious adverse event

No SAEs were observed in the 3 BE studies. One adverse discontinuation, due to moderate diarrhea, occurred in a subject after receiving the test product. In the 40 mg/10 mg BE studies, a small imbalance in adverse events was observed between the test product and the RLDs, with more events experienced after use of the test product (**Table 10**). Overall, adverse events observed across the BE studies were consistent with the known safety profiles of rosuvastatin and ezetimibe (**Table 11**). The most common events experienced with test drug exposure, but not RLD exposure, were hyperglycemia, elevated CK, and diarrhea. However, these events were experienced by ≤3 patients and are known to occur with ezetimibe and/or rosuvastatin exposure.

ACTE

ACTE[1] was a 6-week, multicenter, 4-arm, active control, randomized, parallel group trial that assessed the efficacy of ezetimibe add-on versus statin up-titration in patients on baseline rosuvastatin. The trial enrolled 440 patients on baseline rosuvastatin 5-10 mg at moderate to high CV risk with a baseline LDL-C of 100-160 mg/dL (for patients at moderate CV risk) or LDL-C of 70-160 mg/dL (patients at high CV risk). Patients were randomized to either a statin dose increase or addition of ezetimibe 10 mg, resulting in 4 treatment arms: rosuvastatin 5 mg plus ezetimibe 10 mg, rosuvastatin 5 mg → 10 mg, rosuvastatin 10 mg plus ezetimibe 10 mg, and rosuvastatin 10 mg → 20 mg. The trial included a 4-5 week run-in period for statin optimization. The primary endpoint was mean percent reduction in LDL-C from baseline to Week 6.

The trial screened 1925 patients and enrolled 440 (77% screen failure rate). Reasons for screen failure were not provided. Ninety-seven percent (97%) of patients completed the study. The primary reasons for study discontinuation were adverse events (1.4%), withdrawal of consent (0.9%), and lost to follow-up (0.5%). Patients in the ezetimibe add-on arms were more likely to discontinue for an adverse event than patients in the statin alone arms (2.3% [5/221] vs. 0.5% [1/219]).

Enrolled patients were generally older and White, and 62% were male. Most patients enrolled in ACTE were high CV risk (85%). Amongst patients on baseline rosuvastatin 10 mg (Stratum II), more patients in the rosuvastatin up-titration arm had baseline LDL-C <100 mg/dL, while more ezetimibe add-on patients had baseline LDL-C of 100-160 mg/dL. Otherwise, patient demographics and baseline disease characteristics were well-balanced across the treatment arms (**Tables 12-13**).

[1] Bays, HE, Davidson, MH, Massad, R, et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE study). Am J Cardiol 2011; 108: 523-530.

Table 12. Baseline Demographics and Disease Characteristics, ACTE Trial.

Table 1
Baseline characteristics (all randomized patients)

Characteristic	Stratum I		Stratum II	
	R5 + EZ10 (n = 99)	R10 (n = 98)	R10 + EZ10 (n = 122)	R20 (n = 121)
Men	64 (65%)	58 (59%)	66 (54%)	84 (69%)
Women	35 (35%)	40 (41%)	56 (46%)	37 (31%)
Age (years)	60.5 ± 9.3	60.5 ± 10.0	62.0 ± 9.1	61.4 ± 9.4
Race				
American Indian or Alaska	7 (7%)	1 (1%)	2 (2%)	6 (5%)
Asian	1 (1%)	3 (3%)	0	1 (1%)
Black or African American	6 (6%)	3 (3%)	4 (3%)	3 (2%)
Multiracial	19 (19%)	24 (24%)	10 (8%)	12 (10%)
White	66 (67%)	67 (68%)	106 (87%)	99 (82%)
Body mass index (kg/m^2)	29.8 ± 5.3	28.1 ± 4.7	28.8 ± 5.1	29.5 ± 5.4
Risk group				
High risk with atherosclerotic vascular disease*	50 (51%)	48 (49%)	100 (82%)	99 (82%)
High risk without atherosclerotic vascular disease†	27 (27%)	24 (24%)	12 (10%)	15 (12%)
Moderately high risk without atherosclerotic vascular disease‡	22 (22%)	26 (27%)	10 (8%)	7 (6%)
Baseline low-density lipoprotein cholesterol (mg/dl)				
<70	2 (2%)	9 (9%)	16 (13%)	11 (9%)
70–<100	31 (31%)	34 (35%)	41 (34%)	62 (51%)
100–<130	50 (50%)	46 (47%)	43 (35%)	32 (26%)
130–160	14 (14%)	7 (7%)	20 (16%)	13 (11%)
>160	2 (2%)	2 (2%)	2 (2%)	3 (2%)

Source: The ACTE Study, Am J Cardiol 2011, p. 526
Stratum I patients were on rosuvastatin 5 mg at baseline.
Stratum II patients were on rosuvastatin 10 mg at baseline.

Table 13. Baseline Lipid Parameters, ACTE Trial.

Table 2
Baseline lipid parameters and high-sensitivity C-reactive protein (all randomized patients)

Baseline	R5 + EZ10 (n = 99)*	R10 (n = 98)*	R10 + EZ10 (n = 122)*	R20 (n = 121)*
Low-density lipoprotein cholesterol (mg/dl)†	107 ± 23	102 ± 23	101 ± 27	98 ± 25
Total cholesterol (mg/dl)	188 ± 29	182 ± 29	183 ± 32	178 ± 31
Triglycerides (mg/dl)‡	133 ± 80	143 ± 87	131 ± 69	116 ± 73
High-density lipoprotein cholesterol (mg/dl)	52 ± 15	48 ± 12	54 ± 17	52 ± 13
Non–high-density lipoprotein cholesterol (mg/dl)	135 ± 27	134 ± 29	129 ± 32	126 ± 33
Apolipoprotein B (mg/dl)	112 ± 22	109 ± 23	107 ± 24	103 ± 24
Apolipoprotein AI (mg/dl)	162 ± 32	153 ± 26	161 ± 33	157 ± 25
Low-density lipoprotein/high-density lipoprotein cholesterol	2.2 ± 0.7	2.3 ± 0.7	2.1 ± 0.9	2.0 ± 0.7
Total/high-density lipoprotein cholesterol	3.8 ± 1.1	4.0 ± 1.0	3.7 ± 1.2	3.6 ± 1.1
Non–high-density lipoprotein/high-density lipoprotein cholesterol	2.8 ± 1.1	3.0 ± 1.0	2.7 ± 1.2	2.6 ± 1.1
Apolipoprotein B/apolipoprotein AI	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
High-sensitivity C-reactive protein (mg/L)‡	1.8 ± 2.8	2.1 ± 3.0	1.7 ± 3.1	1.7 ± 2.2

Source: The ACTE Study, Am J Cardiol 2011, p. 526

Efficacy results from the ACTE trial are provided below (**Table 14**). The analysis was conducted in the mITT population, defined as all randomized subjects who received at least one dose of study drug, with baseline data available. The imputation method was not specified. Percent reduction in LDL-C for pooled analyses was the primary endpoint, and percent reduction in LDL-C for strata were secondary endpoints. Multiplicity was controlled using the step-down procedure.

In both strata, addition of ezetimibe add-on therapy resulted in a larger LDL-C reduction from baseline than up-titration of rosuvastatin dosage. Amongst patients taking rosuvastatin 5 mg at

baseline, addition of ezetimibe 10 mg resulted in -17.9% LDL-C reduction vs. -5.6% with an increase to rosuvastatin 10 mg. Amongst patients taking rosuvastatin 10 mg at baseline, addition of ezetimibe 10 mg resulted in -23.7% LDL-C reduction vs. -6.3% with an increase to rosuvastatin 20 mg (**Table 14**).

> *Reviewer comment: Efficacy results must be interpreted with caution, since the analysis was not conducted in the ITT population. Additionally, the full treatment effect of high-intensity rosuvastatin would only be expected with 20 mg or 40 mg, since rosuvastatin 10 mg is considered moderate-intensity. However, the trial successfully demonstrates that both rosuvastatin and ezetimibe are capable of contributing to LDL-C lowering.*

Table 14. Percent Change from Baseline to Week 6, Selected Lipid Parameters, ACTE Trial.

Table 3
Percentage of change from treated baseline at week 6 in lipid parameters and high-sensitivity C-reactive protein (full analysis set population)

Parameter	Percentage of Change from Treated Baseline*						Treatment Difference†		
	Stratum I (R5 run-in)		Stratum II (R10 run-in)		Pooled		Stratum I	Stratum II	Pooled
	R5 + EZ10 (n = 98)‡	R10 (n = 96)‡	R10 + EZ10 (n = 121)‡	R20 (n = 121)‡	All R5,10 + EZ10 (n = 219)‡	All R10,20 (n = 217)‡	R5 + EZ10 vs R10	R10 + EZ10 vs R20	All R + EZ10 vs all R
Low-density lipoprotein cholesterol	−17.9	−5.6	−23.7	−6.3	−21.0	−5.7	−12.3§	−17.5§	−15.2§
Total cholesterol	−10.7	−3.9	−14.3	−4.1	−12.6	−3.9	−6.8¶	−10.1§	−8.7§
Non–high-density lipoprotein cholesterol	−13.6	−5.2	−20.5	−5.7	−17.1	−5.2	−8.4‖	−14.8§	−12.0§
Triglycerides	−1.6	−3.6	−9.8	−2.9	−6.3	−3.2	1.9	−7.0	−3.1
Apolipoprotein B	−11.8	−5.2	−15.7	−4.0	−13.8	−4.4	−6.6‖	−11.6§	−9.4§
High-density lipoprotein cholesterol	−2.7	1.8	1.6	1.9	−0.5	1.7	−4.5#	−0.3	−2.1
Apolipoprotein AI	2.5	0.3	0.0	1.0	−1.2	0.6	−2.8	−1.0	−1.8
Low-density lipoprotein/high-density lipoprotein cholesterol	−13.8	−5.8	−24.1	−6.3	−19.4	−6.2	−7.9‖	−17.8§	−13.2§
Total/high-density lipoprotein cholesterol	−5.5	−4.1	−14.9	−4.3	−10.7	−4.2	−1.4	−10.6§	−6.4¶
Non–high-density lipoprotein/high-density lipoprotein cholesterol	−7.1	−5.1	−20.8	−5.1	−14.6	−5.1	−2.0	−15.7§	−9.5¶
Apolipoprotein B/apolipoprotein AI	−8.3	−4.8	−14.6	−3.7	−11.8	−4.2	−3.5	−10.8§	−7.5§
High-sensitivity C-reactive protein	−13.1	−13.4	−13.2	−14.1	−14.1	−13.0	0.4	0.8	−1.1

Source: The ACTE Study, Am J Cardiol 2011, p. 527

The following tables (**Tables 15-16**) summarize safety information provided in the ACTE trial manuscript. The authors compared adverse events experienced in the rosuvastatin + ezetimibe treatment arms to rosuvastatin alone treatment arms. There were no trial deaths and no difference in SAEs between arms. More patients treated with combination therapy experienced discontinuations due to an adverse event (2.3% vs. 0.5%). Reasons for drug discontinuation in the ezetimibe arms were constipation, allergic dermatitis, eczema, myalgia, and arthralgia. There was also a small imbalance in adverse events, 14.9% vs. 14.2%, with more events experienced in the ezetimibe add-on arms. Patients treated with rosuvastatin + ezetimibe experienced more gastrointestinal, allergic, and rash adverse events, consistent with ezetimibe's known safety profile. There were no significant differences in aminotransferase or CK elevations between treatment arms (**Table 16**).

> *Reviewer comment: The observed safety data is consistent with the known safety profiles of rosuvastatin and ezetimibe from approved labeling.*

Table 15. Summary of Adverse Events, ACTE Trial, Ezetimibe Add-On versus Rosuvastatin Alone.

Table 4
Safety end points: adverse experiences (all-patients-as-treated population)

Adverse Experience*	All R5,10 + EZ10 (n = 221)	All R10,20 (n = 219)	Difference (95% CI)†
≥1 Events	33 (14.9%)	31 (14.2%)	0.8 (−5.9, 7.5)
Drug-related‡	10 (4.5%)	6 (2.7%)	1.8 (−1.9, 5.7)
Serious	0	2 (0.9%)	−0.9 (−3.3, 0.8)
Serious drug-related‡	0	0	0.0 (−1.7, 1.7)
Discontinuations§	5 (2.3%)	1 (0.5%)	1.8 (−0.5, 4.8)
Drug-related‡	5 (2.3%)	0	
Serious	0	0	
Serious drug-related‡	0	0	
Deaths	0	0	

* All AEs collected up to end of 14-day follow-up window were included in analysis.

Source: The ACTE Study, Am J Cardiol 2011, p. 528

Table 16. Adverse Events of Special Interest, ACTE Trial.

Table 5
Safety end points: prespecified adverse experiences (all patients-as-treated population)

Variable	All R5,10 + EZ10 (n = 221*)	All R10,20 (n = 219*)	Difference (95% CI)	p Value†
Alanine aminotransferase or aspartate aminotransferase ≥3 times upper limit of normal, consecutive‡	1/219 (0.5%)	0/214	0.5 (−1.3, 2.5)	0.327
Alanine aminotransferase ≥3 times upper limit of normal, consecutive‡	1/219 (0.5%)	0/214	0.5 (−1.3, 2.5)	0.327
Aspartate aminotransferase ≥3 times upper limit of normal, consecutive‡	0/219	0/214	0	
Creatine kinase ≥10 times upper limit of normal	0/219	1/214 (0.5%)	−0.5 (−2.6, 1.3)	0.315
Creatine kinase ≥10 times upper limit of normal, with muscle symptoms	0/219	0/214	0	
Creatine kinase ≥10 times upper limit of normal, with drug-related muscle symptoms§	0/219	0/214	0	
Hepatitis-related adverse experiences	0	2 (0.9)	−0.9 (−3.3, 0.8)	0.155
Gallbladder-related adverse experiences	0	0	0	
Gastrointestinal-related adverse experiences	9 (4.1%)	3 (1.4%)	2.7 (−0.4, 6.4)	0.082
Allergic reaction or rash adverse experiences	3 (1.4%)	1 (0.5%)	0.9 (−1.3, 3.6)	0.318

Source: The ACTE Study, Am J Cardiol 2011, p. 529

GRAVITY

GRAVITY[2] was a 12-week, multicenter, 4-arm, active control, randomized, parallel group trial that assessed the efficacy of ezetimibe add-on after 6 weeks of statin monotherapy. The trial enrolled 833 patients at high CV risk with a baseline LDL-C of 130 to 219 mg/dL. Patients were randomized to 1 of 4 treatment arms: rosuvastatin 10 mg plus ezetimibe 10 mg, rosuvastatin 20 mg plus ezetimibe 10 mg, simvastatin 40 mg plus ezetimibe 10 mg, or simvastatin 80 mg plus

[2] Ballantyne, CM, Hoogeveen, RC, Raya, JL, et al. Efficacy, safety and effect on biomarkers related to cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20 mg plus ezetimibe 10 mg vs. simvastatin 40 or 80 mg plus ezetimibe 10 mg in high-risk patients: results of the GRAVITY randomized study. Atherosclerosis 2014; 232: 86-93.

ezetimibe 10 mg. The trial included a 6-week run-in period for diet optimization; patients were required to discontinue baseline lipid-modifying therapy (LMT) during the run-in period. After randomization, patients were treated with 6 weeks of statin monotherapy followed by 6 weeks of statin plus ezetimibe. The primary endpoint was mean percent reduction in LDL-C from baseline to Week 12.

The trial screened 1743 patients and enrolled 833 (52% screen failure rate). Reasons for screen failure were not provided. Ninety percent (90%) of patients completed the study. The primary reasons for study discontinuation were adverse events (3.7%), withdrawal of consent (2.5%), lost to follow-up (1.2%), protocol violation (0.7%), non-compliance (0.4%), and safety concern (0.2%). Patients in the rosuvastatin 20 mg + ezetimibe arm were more likely to discontinue for an adverse event than patients in the other treatment arms (5.1% [11/214] vs. 3% for other arms).

Enrolled patients were generally older and White, and 55% were male. Baseline LDL-C was 162.7 to 164.8 mg/dL. Overall, patient demographics were well-balanced across the treatment arms (**Table 17**).

Table 17. Baseline Demographics and Disease Characteristics, GRAVITY Trial.

Table 1
Patient demographics and baseline characteristics.

	RSV 10 mg/EZE 10 mg ($n = 214$)	RSV 20 mg/EZE 10 mg ($n = 214$)	SIM 40 mg/EZE 10 mg ($n = 202$)	SIM 80 mg/EZE 10 mg ($n = 203$)
Demographics[a]				
Age, years; mean (SD)	62.2 (10.1)	61.8 (9.9)	61.9 (9.4)	62.0 (9.2)
Male, *n* (%)	123 (57.5)	117 (54.7)	105 (52.0)	113 (55.7)
Race, *n* (%)				
Caucasian	127 (59.3)	136 (63.6)	115 (56.9)	127 (62.6)
Hispanic	45 (21.0)	45 (21.0)	45 (22.3)	36 (17.7)
Black	20 (9.3)	18 (8.4)	18 (8.9)	19 (9.4)
Asian	3 (1.4)	1 (0.5)	5 (2.5)	6 (3.0)
Other	19 (8.9)	14 (6.5)	19 (9.4)	15. (7.4)
Body mass index, kg/m^2; mean (SD)	30.3 (6.0)	31.0 (6.6)	30.2 (6.2)	31.0 (6.5)
Blood pressure, mmHg; mean (SD)				
Systolic	137.7 (17.7)	136.6 (16.0)	137.9 (18.5)	137.6 (18.2)
Diastolic	81.7 (10.2)	81.6 (9.9)	81.0 (10.7)	81.2 (10.6)
Baseline laboratory parameters, mg/dl; mean (SD)[b]	$n = 210$	$n = 204$	$n = 199$	$n = 201$
LDL-C	162.7 (22.7)	164.8 (24.7)	164.8 (23.6)	163.1 (24.1)
HDL-C	48.4 (12.7)	48.1 (13.2)	49.1 (13.5)	48.2 (12.2)
Total cholesterol	248.1 (28.3)	251.6 (30.3)	251.3 (28.2)	247.7 (24.9)
Triglycerides	184.8 (79.0)	192.5 (80.0)	187.2 (78.4)	181.9 (81.2)
nonHDL-C	199.8 (28.4)	203.5 (29.1)	202.3 (28.4)	199.5 (25.2)
ApoB	127.3 (20.7)	129.4 (21.7)	127.8 (20.0)	126.4 (18.3)
ApoA-I	144.0 (26.4)	143.4 (27.2)	145.6 (27.5)	143.2 (24.5)
hsCRP, mg/l; median (range)	2.8 (0.2–103.0)	2.6 (0.2–68.7)	2.6 (0.2–47.1)	2.5 (0.3–44.1)
Baseline biomarkers, median (IQR)[c]	$n = 130$	$n = 132$	$n = 124$	$n = 129$
C4 (ng/ml)	57.4 (82.4)	57.1(81.4)	55.0(82.8)	56.6(64.7)
7-ketocholesterol (ng/ml)	48.3 (25.5)	48.7 (31.3)	47.1 (30.5)	45.4 (24.1)
β-sitosterol (μg/ml)	2.2 (1.4)	2.1 (1.1)	2.3 (1.3)	2.1 (1.4)
Free cholesterol (mg/dl)	60.0 (17.7)	62.8 (15.1)	61.4 (14.5)	62.4 (12.6)
Lanosterol (μg/ml)	1.0 (0.8)	1.1 (0.8)	1.1 (1.0)	1.1 (0.9)
Lp-PLA$_2$ activity (nmol/min/ml)	217.5 (76.8)	224.5 (66.1)	211.1 (67.9)	208.3 (68.2)
Lp-PLA$_2$ concentration (ng/ml)	272.7 (120.5)	259.4 (116.2)	283.8 (150.7)	285.5 (124.1)

Source: The GRAVITY Study, Atherosclerosis 2014, p. 89

Efficacy results from the GRAVITY trial are provided below (**Table 18**). The analysis was conducted in the mITT population, defined as all randomized subjects who received at least one dose of study drug, with baseline data and at least one post-baseline measurement available. Missing data was imputed using LOCF. Percent reduction in LDL-C from baseline to Week 12 was the primary endpoint. Week 6 data was included as descriptive only. Control for multiplicity was not specified.

After six weeks of rosuvastatin monotherapy (10 mg or 20 mg), LDL-C was reduced by -46.5% to -53.6% (baseline LDL-C compared to Week 6). After addition of ezetimibe add-on therapy to rosuvastatin 10 or 20 mg from Weeks 6-12, LDL-C was further reduced by -59.7% to -63.5% (baseline LDL-C compared to Week 12) (**Table 18**).

> *Reviewer comment: Data suggests that ezetimibe add-on to rosuvastatin confers additional LDL-C lowering efficacy compared to rosuvastatin monotherapy. However, the additional lowering may also be a treatment duration effect, i.e. the result of an additional 6 weeks of rosuvastatin therapy. Efficacy results may also be overestimated given the authors' statistical analysis approach, which was not conducted in the ITT population and used LOCF for missing data imputation.*

Table 18. Percent Change in LDL-C from Baseline to Week 6 (Statin Monotherapy) and Week 12 (Statin + Ezetimibe), GRAVITY Trial.

		Treatment group			
		RSV 10 mg/ EZE 10 mg (*n* = 210)	RSV 20 mg/ EZE 10 mg (*n* = 204)	SIM 40 mg/ EZE 10 mg (*n* = 199)	SIM 80 mg/ EZE 10 mg (*n* = 201)
Baseline (mean of weeks –2 and 0)	mean (SD), mg/dl	162.7 (22.7)	164.8 (24.7)	164.8 (23.6)	163.1 (24.1)
	range, mg/dl	122 to 222	107 to 264	110 to 238	93 to 228
Monotherapy (mean of weeks 4 and 6)	*N*	206	199	197	200
	mean (SD), mg/dl	87.2 (24.7)	76.4 (20.0)	97.4 (23.6)	86.7 (25.7)
	range, mg/dl	42 to 202	26 to 142	53 to 175	42 to 183
% change from baseline to monotherapy	mean (SD), mg/dl	–46.5 (13.1)[a]	–53.6 (10.5)[b]	–40.9 (12.4)	–46.4 (16.2)
	range, mg/dl	–71.6 to 21.7	–81.5 to –11.5	–66.9 to 10.3	–70.9 to 28.0
Combination therapy (mean of weeks 10 and 12)	*N*	210	204	199	201
	mean (SD), mg/dl	65.2 (23.3)	59.4 (24.1)	73.7 (26.9)	68.7 (32.2)
	range, mg/dl	25 to 188	16 to 207	29 to 172	26 to 226
% change from baseline to combination therapy	mean (SD), mg/dl	–59.7 (14.2)[c]	–63.5 (16.7)[b]	–55.2 (15.8)	–57.4 (20.5)
	range, mg/dl	–84.3 to 10.9	–90.3 to 58.7	–78.6 to 14.9	–82.5 to 28.0

EZE = ezetimibe; RSV = rosuvastatin; SD = standard deviation; SIM = simvastatin.
[a] $p < 0.001$ vs. SIM 40 mg/EZE 10 mg.
[b] $p < 0.001$ vs. SIM 40 mg/EZE 10 mg and SIM 80 mg/EZE 10 mg.
[c] $p = 0.002$ vs. SIM 40 mg/EZE 10 mg.

Source: The GRAVITY Study, Atherosclerosis 2014, Supplemental Materials, Supplemental Table 1

The tables below display safety information summarized in the GRAVITY trial manuscript. The authors provided adverse event comparisons between the 4 treatment arms for the initial 6-week monotherapy phase (**Table 19**) and the subsequent 6-week combination therapy phase (**Table**

20). The incidence of SAEs was similar in the monotherapy (statin alone) and combination therapy phases (statin + ezetimibe). Adverse discontinuations and overall AEs were lower in the combination therapy phase, suggesting that addition of ezetimibe to background statin does not result in increased drug discontinuations or adverse events. The authors also reported no imbalance in myopathy with addition of ezetimibe to statin therapy (1 event with rosuvastatin 10 mg alone vs. 1 event with rosuvastatin 20 mg + ezetimibe 10 mg).

> *Reviewer comment: The observed safety data does not suggest any unknown or unique safety signals with coadministration of rosuvastatin and ezetimibe.*

Table 19. Summary of Adverse Events, Monotherapy Phase, GRAVITY Trial.

Number of patients reporting AE, *n* (%)	Treatment in monotherapy phase[a]			
	RSV 10 mg (*n* = 213)	RSV 20 mg (*n* = 212)	SIM 40 mg (*n* = 199)	SIM 80 mg (*n* = 203)
All AEs	70 (32.9)	80 (37.7)	59 (29.6)	62 (30.5)
AEs leading to withdrawal from study	5 (2.3)	9 (4.2)	2 (1.0)	3 (1.5)
Drug-related AEs	18 (8.5)	13 (6.1)	7 (3.5)	15 (7.4)
Serious AEs	3 (1.4)	5 (2.4)	1 (0.5)	3 (1.5)
AEs occurring in ≥2% of patients				
Myalgia	5 (2.3)	10 (4.7)	3 (1.5)	7 (3.4)
Headache	4 (1.9)	4 (1.9)	5 (2.5)	4 (2.0)
Arthralgia	5 (2.3)	4 (1.9)	1 (0.5)	4 (2.0)
Nasopharyngitis	3 (1.4)	3 (1.4)	4 (2.0)	3 (1.5)
Nausea	4 (1.9)	5 (2.4)	1 (0.5)	1 (0.5)
Dizziness	1 (0.5)	5 (2.4)	1 (0.5)	2 (1.0)
Upper respiratory tract infection	1 (0.5)	1 (0.5)	4 (2.0)	3 (1.5)
Bronchitis	1 (0.5)	1 (0.5)	4 (2.0)	2 (1.0)
Influenza	2 (0.9)	1 (0.5)	4 (2.0)	1 (0.5)
Muscle spasms	1 (0.5)	2 (0.9)	4 (2.0)	1 (0.5)

Source: The GRAVITY Study, Atherosclerosis 2014, Supplemental Materials, Supplemental Table 4

Table 20. Summary of Adverse Events, Combination Therapy Phase, GRAVITY Trial.

Number of patients reporting AE, *n* (%)	Treatment in combination therapy phase[b]			
	RSV 10 mg/ EZE 10 mg (*n* = 200)	RSV 20 mg/ EZE 10 mg (*n* = 191)	SIM 40 mg/ EZE 10 mg (*n* = 189)	SIM 80 mg/ EZE 10 mg (*n* = 192)
All AEs	60 (30.0)	57 (29.8)	63 (33.3)	62 (32.3)
AEs leading to withdrawal	2 (1.0)	2 (1.0)	4 (2.1)	4 (2.1)
Drug-related AEs	11 (5.5)	13 (6.8)	6 (3.2)	15 (7.8)
Serious AEs	4 (2.0)	1 (0.5)	7 (3.7)	4 (2.1)
AEs occurring in ≥2% of patients				
Myalgia	4 (2.0)	5 (2.6)	4 (2.1)	3 (1.6)
Nasopharyngitis	2 (1.0)	5 (2.6)	2 (1.1)	3 (1.6)
Influenza	0 (0.0)	4 (2.1)	3 (1.6)	0 (0.0)
Oedema peripheral	1 (0.5)	0 (0.0)	2 (1.1)	4 (2.1)

[a] One patient received study medication other than per protocol during the monotherapy phase.
[b] Three patients received study medication other than per protocol during the combination therapy phase.

Source: The GRAVITY Study, Atherosclerosis 2014, Supplemental Materials, Supplemental Table 5

EXPLORER

EXPLORER[3] was a 6-week, multicenter, 2-arm, active control, randomized, parallel group trial that assessed the efficacy of ezetimibe add-on therapy versus statin alone. The trial enrolled 469 patients at high CV risk with a baseline LDL-C of 160-249 mg/dL. Patients were randomized to rosuvastatin 40 mg or rosuvastatin 40 mg plus ezetimibe 10 mg. The trial included a 6 week run-in period for diet optimization; patients were required to discontinue baseline LMT during the run-in period. The primary endpoint was the proportion of patients who achieved an LDL-C <100 mg/dL at Week 6.

The trial screened 1197 patients and enrolled 469 (61% screen failure rate). Reasons for screen failure were not provided. Ninety-seven percent (97%) of patients completed the study. The primary reasons for study discontinuation were adverse events (1.9%) and withdrawal of consent (0.2%). Patients in the ezetimibe add-on arm were more likely to discontinue for an adverse event than patients in the rosuvastatin alone arm (2.5% [6/239] vs. 1.3% [3/230]).

Enrolled patients were generally older and White, and the majority were male. Patients in the ezetimibe add-on arm were more likely to have baseline HDL <40 mg/dL, and patients in the rosuvastatin alone arm were more likely to be diabetic. Otherwise, patient demographics were well-balanced across the treatment arms (**Table 21**).

[3] Ballantyne, CM, Weiss, R, Moccetti, T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk for cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007; 99:673-680.

Table 21. Baseline Demographics, EXPLORER Trial.

Table 1
Patient characteristics at baseline (randomized population)

Variable	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 239)
Age (yrs) (mean ± SD)	63.5 ± 10.6	63.1 ± 10.2
Men	55.7%	58.6%
Caucasian	91.7%	93.3%
Body mass index (kg/m²) (mean ± SD)	29.7 ± 4.9	28.8 ± 4.7
Creatinine clearance		
>80 ml/min	49.1%	51.0%
50 to ≤80 ml/min	43.5%	42.7%
30 to <50 ml/min	7.0%	6.3%
<30 ml/min	0%	0%
Metabolic syndrome at baseline*	63.5%	59.0%
Diabetes mellitus	39.6%	34.4%
Men ≥45 yrs, women ≥55 yrs	92.6%	91.6%
Hypertension (≥140/90 mm Hg or on antihypertensive medication)	87.0%	86.6%
HDL cholesterol <40 mg/dl (1.0 mmol/L)	18.7%	24.3%

Source: The EXPLORER Study, Am J Cardiol 2007, p. 675

Efficacy results from the EXPLORER trial are provided below (**Table 22**). The analysis was conducted in the mITT population, defined as all randomized subjects who received at least one dose of study drug, with baseline data, and at least one post-baseline measurement available. Missing data was imputed using LOCF. Percent reduction in LDL-C was included as a secondary endpoint; control for multiplicity was not specified.

Addition of ezetimibe 10 mg to rosuvastatin 40 mg resulted in greater LDL-C reduction at Week 6 compared to treatment with rosuvastatin 40 mg alone, -70% vs. -57% (**Table 22**).

> *Reviewer comment: The EXPLORER trial suggests that both ezetimibe and rosuvastatin contribute to LDL-C lowering. However, efficacy results may be overestimated, as the authors did not conduct statistical analyses in the ITT population and used LOCF for missing data imputation.*

Table 22. Percent Reduction in Selected Lipid Parameters, Baseline to Week 6, EXPLORER Trial.

Table 2
Percentage change from baseline in lipid, lipoprotein and inflammatory marker levels after six weeks of treatment (intention-to-treat population)

Lipids/lipoproteins	Rosuvastatin 40 mg Group (n = 230)			Rosuvastatin 40 mg/Ezetimibe 10 mg Group (n = 235)			p Value†
	Mean at		Mean Change from Baseline	Mean at		Mean Change from Baseline	
	Baseline	Wk 6		Baseline	Wk 6		
LDL cholesterol (mg/dl)*	191	82	−57%	189	57	−70%	<0.001
TC (mg/dl)*	278	162	−42%	276	134	−51%	<0.001
HDL cholesterol (mg/dl)*	50	53	+9%	49	54	+11%	0.151
Non-HDL cholesterol (mg/dl)*	228	109	−52%	226	80	−65%	<0.001
TGs (mg/dl)*	186	138	−25%	186	114	−35%	<0.001
LDL/HDL cholesterol	4.1	1.6	−60%	4.1	1.1	−72%	<0.001
TC/HDL cholesterol	5.9	3.2	−45%	5.9	2.6	−56%	<0.001
Non-HDL/HDL cholesterol	4.9	2.2	−55%	4.9	1.6	−67%	<0.001
Apolipoprotein B (mg/dl)	173	95	−45%	176	76	−56%	<0.001
Apolipoprotein A-I (mg/dl)	166	169	+3%	166	167	+2%	0.202
Apolipoprotein B/apolipoprotein A-I	1.1	0.6	−46%	1.1	0.5	−57%	<0.001
hs-CRP (mg/L) (median)	2.4	1.7	−29%	2.5	1.2	−46%	<0.001

Source: The EXPLORER Study, Am J Cardiol 2007, p. 677

The tables below display safety information provided in the EXPLORER trial manuscript (**Tables 23-25**). There was one trial death due to myocardial infarction in a rosuvastatin + ezetimibe-treated patient. Slightly more SAEs (2.1% vs. 1.7%) and adverse discontinuations (2.5% vs. 1.3%) were experienced by patients randomized to the rosuvastatin + ezetimibe arm. However, fewer AEs were experienced overall by the rosuvastatin + ezetimibe arm (31.5% vs. 33.5%) (**Table 23**). Across the trial, the most frequent AEs were myalgia, nausea, ALT increased, and angina. Increased ALT was experienced more frequently in the ezetimibe arm (2.5% vs. 0.4%); the remainder of AEs were experienced with similar or lower incidence than the rosuvastatin alone arm (**Table 24**). The authors also presented data on changes in laboratory parameters (**Table 25**). Consistent with AE findings, more ezetimibe patients experienced ALT >3x ULN (1.3% [3/238] vs. 0% [0/230]). There were no differences in CK elevations, creatinine increase, or proteinuria.

> *Reviewer comment: Results suggest a possible increased risk for aminotransferase elevation with use of rosuvastatin and ezetimibe concomitantly. This finding is consistent with ezetimibe's approved labeling, which reports ALT/AST elevation >3x ULN of 1.3% for ezetimibe plus statins compared to 0.4% for statin alone.*

Table 23. Summary of Adverse Events, EXPLORER Trial.

Table 3
Number of patients with adverse events (randomized safety population)

Variable	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 238)
Any adverse event	77 (33.5%)	75 (31.5%)
Rosuvastatin-related adverse event only	21 (9.1%)	2 (0.8%)
Rosuvastatin- and ezetimibe-related adverse event*	N/A	16 (6.7%)
Serious adverse event	4 (1.7%)	5 (2.1%)
Rosuvastatin-related serious adverse event only	0	0
Rosuvastatin- and ezetimibe-related serious adverse event*	N/A	0
Adverse event leading to death	0	1 (0.4%)
Rosuvastatin-related adverse event only, leading to death	0	0
Rosuvastatin- and ezetimibe-related adverse event leading to death*	N/A	0
Discontinuation due to adverse event	3 (1.3%)	6 (2.5%)
Rosuvastatin-related adverse event only, leading to discontinuation	3 (1.3%)	0
Rosuvastatin- and ezetimibe-related adverse event, leading to discontinuation*	N/A	2 (0.8%)

* No event was considered related only to ezetimibe.

Source: The EXPLORER Study, Am J Cardiol 2007, p. 677

Table 24. Most Frequent Adverse Events, EXPLORER Trial.

Table 4
Most frequent reported (≥2.0% in any group) adverse events (randomized safety population)

Variable	No. (%) of Patients With Adverse Events	
	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 238)
Myalgia	7 (3.0%)	7 (2.9%)
Nausea	5 (2.2%)	6 (2.5%)
ALT increased	1 (0.4%)	6 (2.5%)
Angina pectoris	6 (2.6%)	1 (0.4%)

Source: The EXPLORER Study, Am J Cardiol 2007, p. 677

Table 25. Changes in Laboratory Parameters, EXPLORER Trial.

Table 5
Clinically relevant changes in laboratory values (randomized safety population)

Variable	No. (%) of Patients With Changes in Laboratory Values	
	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 238)
ALT elevations at any time		
>3 × Upper limit of normal	0 (0.0%)	3 (1.3%)
CK elevations at any time		
>5 × Upper limit of normal	2 (0.9%)	2 (0.8%)
>10 × Upper limit of normal	0 (0.0%)	0 (0.0%)
Serum creatinine increase at any time		
>50%–100% from baseline	3 (1.3%)*	1 (0.4%)†
>100% from baseline	0 (0.0%)	0 (0.0%)
Proteinuria at week 6‡	10 (4.5%)	1 (0.4%)

* Above upper limit of normal in 2 patients.
† Above upper limit of normal in this patient.
‡ Change in dipstick-positive urine protein from none or trace at baseline to ++ or greater.

Source: The EXPLORER Study, Am J Cardiol 2007, p. 678

Drug Utilization Query

The Applicant provided results from a drug utilization query that aimed to estimate the number of U.S.-based patients taking rosuvastatin and ezetimibe concomitantly. Insurance claims data from [redacted] (b) (4), a home delivery and pharmacy benefit management service, was searched for adult patients with ≥1 claim for rosuvastatin and ezetimibe within the previous one year, prescribed at the same time. The Applicant reported that [redacted] (b) (4) unique adult patients achieved this criterion.

> *Reviewer comment: Ezetimibe's label indicates that it may be combined with any drug in the statin class; however, specific efficacy and safety data on rosuvastatin combination therapy is not included. The Applicant's drug utilization query supports that providers are prescribing the drugs together in clinical practice.*
>
> [redacted] (b) (4) *likely underestimates the actual number of concomitant prescriptions, since data is only available for patients or providers within the* [redacted] (b) (4) *network. Additional limitations include the lack of patient-level data – although prescribed by healthcare providers concurrently, whether the drugs were actually received and taken simultaneously by the patient is unknown.*

AUDITS

The Office of Study Integrity and Surveillance (OSIS) concluded that data from the audited BE studies were reliable to support a regulatory decision. No objectionable conditions were

identified, and no Form FDA 483 was issued. The inspection outcome was No Action Indicated (NAI).

CMC

The CMC drug product reviewer, Dr. Luong, identified the following approvability deficiencies in the Roszet application:

> **APPROVABILITY DEFICIENCIES:**
> 1. There were analytical method validation deficiencies noted in the FDA Form 483, 6 observations with 11 items of evidence that the firm practices 'testing into compliance' and 'data manipulation'. In particular, there is a possibility that the true data sets of degradation products (b) (4) impurity in the stability batches of the ROSZET tablets could exceed the 0.5% qualification threshold. Consequently, no product shelf-life can be granted at this point.
>
> **INFORMATION NEEDED TO RESOLVE DEFICIENCIES:**
> 1. You will need to re-perform the analytical method validation for suitability of the reference standards / working standards, assay, chromatographic purity, content uniformity, and dissolution.
>
> 2. You will need to repeat runs and re-analyze the existing stability samples after revalidation of the analytical method, 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 normal (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.

Additionally, at least one manufacturing facility was found unacceptable during pre-approval facilities inspections. The Applicant received a Form FDA 483 which cited 11 deficiencies across three major aspects of the pre-approval inspection. The inspection outcome was Official Action Indicated (OAI). A second drug substance manufacturer was also OAI. The facilities inspection reviewer, Dr. Khan, recommends withholding of approval.

Based on drug product and facilities deficiencies, the Office of Pharmaceutical Quality (OPQ) recommends a Complete Response (CR) action. Please refer to Dr. Luong's and Dr. Khan's reviews for additional details.

PHARMACOLOGY/TOXICOLOGY

No new pharmacology/toxicology data were provided in the NDA.

FINANCIAL DISCLOSURE

The Applicant provided a signed form FDA 3454 certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

LABELING

Detailed review of labeling will be deferred to a later review cycle. However, the following clinical labeling issues were considered:

1. Primary hyperlipidemia indication: [redacted]

2. [redacted]

3. Contraindications for pregnancy and nursing: The pregnancy and nursing contraindications are in the process of being removed from statin labeling. Roszet labeling would need to match the rosuvastatin and ezetimibe labeling at the time of approval if the aforementioned labeling changes were implemented before an approval action.

4. Pediatric use: Section 8.4 [redacted]

5. Inclusion of [redacted] in Section 14 should be removed, [redacted]

6. Inclusion of [redacted] in Section 14.2 should be removed.

7. Description of [redacted] in Section 14 should be removed.

PROPRIETARY NAME

Division of Medication Error Prevention and Analysis (DMEPA) reviewed "Roszet" from a promotional and safety perspective and determined that the name is acceptable.

PEDIATRIC STUDY REQUIREMENTS

An agreed iPSP was not in place at the time of NDA submission. The Applicant requested a full waiver for pediatric non-familial hypercholesterolemia [redacted] and a partial waiver for pediatric HoFH ages 0 to [redacted] years as studies are impossible or highly impractical. In consultation with the Pediatric Review Committee (PeRC), the Division agreed with the request as it is unlikely that Roszet would be prescribed to a substantial number of patients in this age group, and pharmacotherapy has not been shown superior to behavioral and lifestyle interventions in children in this age group.

The Applicant also requested a deferral of pediatric [redacted] HoFH [redacted] 17 years until the pediatric and orphan exclusivities have expired. [redacted]

(b) (4)

In consultation with PeRC, the Division agreed with the request. If approved, the Applicant will be issued two PREA PMRs with a final report submission date that corresponds to the exclusivity expiration (b) (4)

POST-MARKETING REQUIREMENTS

The following PREA PMRs were agreed upon with PeRC input. PMRs will be issued during a later review cycle.

(b) (4)

2. Assessment of Roszet (rosuvastatin and ezetimibe) for the treatment of homozygous familial hypercholesteremia in pediatric patients (b) (4) to 17 years of age (inclusive).

a. Final Protocol submission: n/a
b. Study Completion: n/a
c. Final Report Submission: (b) (4)

RECOMMENDATION

Although ezetimibe is approved broadly for coadministration with statins, approval studies did not explicitly test the safety and efficacy of ezetimibe and rosuvastatin combination therapy. The Applicant provided published literature to support the safety and efficacy of coadministration. In submitted literature studies, a multiple-dose regimen of chronic daily administration of concomitant rosuvastatin and ezetimibe was administered for the treatment of hyperlipidemia. Study results demonstrated that both rosuvastatin and ezetimibe contribute to LDL-C reduction. Published literature also supports the safety of coadministration. Two published studies compared the safety profiles of rosuvastatin plus ezetimibe to rosuvastatin alone, and one published study compared the safety profile of rosuvastatin plus ezetimibe to that of another statin (simvastatin) plus ezetimibe. The studies demonstrate that concomitant rosuvastatin and ezetimibe does not result in unexpected or unique safety signals, and the safety profile of combination therapy is consistent with the safety profiles of the individual drug products. Note that the Applicant's proposed Roszet dosing regimen is consistent with doses reported in the referenced literature studies. The Applicant also provided data from a drug utilization query that supports that rosuvastatin and ezetimibe are prescribed together in clinical practice.

From a clinical standpoint, Roszet is approvable based on a favorable benefit/risk framework. However, I concur with OPQ's recommendation for a CR action based on method validation and drug stability concerns, which limit our confidence in the drug's reliable and safe manufacturing. Recommendations to address the CR will be provided by OPQ.

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/

LAURA B HIGGINBOTHAM
05/05/2020 05:02:40 PM

JOHN M SHARRETTS
05/05/2020 10:14:30 PM
I concur with the findings.