CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208647Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMCOLOGY REVIEW

NDA	208647
Submission Date(s)	28th August, 2015; 18th June, 2018
Brand Name	Ezallor
Generic Name	Rosuvastatin
OCP Division	Clinical Pharmacology-2
OND Division	Metabolism and Endocrinology Products (DMEP)
Sponsor	Sun Pharma Global FZE
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Immediate-release, hard gelatin capsule filled with drug-containing (b) (4); 5 mg, 10 mg, 20 mg, 40 mg strengths
Proposed Indication	▪ Patients with hypertriglyceridemia as an adjunct to diet ▪ Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet ▪ Patients with homozygous familial hypercholesterolemia
Dosage and Administration	▪ 5 mg to 40 mg orally once daily, the usual starting dose is 10 mg to 20 mg once daily ▪ Administered at any time of the day, with or without food ▪ Capsule swallowed intact or the contents of the capsule sprinkled onto applesauce or administered via a nasogastric tube
Clinical Pharmacology Reviewer	Shalini Wickramaratne Senarath Yapa, Ph.D.
Clinical Pharmacology Team Leader	Jayabharathi Vaidyanathan, Ph.D.

1. Background

The Applicant, Sun Pharm Global FZE, submitted a 505(b)(2) NDA application on August 28th, 2015 for rosuvastatin oral capsules (Ezallor™, 5 mg, 10 mg, 20 mg, 40 mg). The Office of Clinical Pharmacology reviewed the clinical pharmacology data submitted under NDA 208647 and recommended approval (refer to Clinical Pharmacology Review by Dr. Wickramaratne Senarath Yapa in DARRTs dated May 23rd, 2016). On June 22nd, 2016, the Agency issued a Complete Response letter to NDA 208647 stating that the application could not be approved due to deficiencies relating to facility inspections. On June 18th, 2018, the Applicant submitted a response to the Agency's Complete Response letter. The current submission has no new clinical data for Clinical Pharmacology to review. For the current submission, the Applicant reports the following:

> Pursuant to 21 CFR 314.60(f)(1) SUN has verified and confirm that this amendment does not include any changes as described below:
>
> I. To add a new indication or other condition of use;
> II. To add a new strength;
> III. To make other than minor changes in product formulation; or
> IV. To change the physical form or crystalline structure of the active ingredient

The focus of this review will be to provide recommendations for the proposed label for rosuvastatin capsules (Ezallor™).

2. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP-DCP-2) has reviewed the proposed labeling language for rosuvastatin capsules (Ezallor™) submitted under NDA 208647 and has the following comments to the Applicant.

3. Ezallor™ USPI Label

The Applicant reports that the proposed labeling language for rosuvastatin capsules (Ezallor™) has been revised in accordance with the Crestor® USPI label revised on August 4th, 2017 (action date) in the Drugs@FDA website. A more recently revised (action date: November 9th, 2018) Crestor® USPI label is available in the Drugs@FDA website, therefore the Reviewer's labeling recommendations will be based on the latest version of the Crestor® USPI label. Labeling comments are outlined in Section 4 of the review and have been recommended to be consistent with the Crestor® USPI label as follows:

- Section 7.1 and 7.3: The clinical implication as a result of the drug interaction with cyclosporine and protease inhibitors has been moved to Section 7 (from Section 12.3). (b) (4) has been deleted.
- Section 12.2: Section 12.2 (Pharmacodynamics) has been included in the latest version of the Crestor® USPI label in accordance with recommendations in the Guidance for Industry: Clinical Pharmacology Sections of Labeling for Human Prescription Drug and Biological Products – Contents and Format (December 2016). Therefore, Section 12.2 needs to be included in the Ezallor™ USPI label.
- Section 12.3: Subsections in Section 12.3 (Elimination subsection, Specific Population subheadings, Drug Interaction Studies subheading) have been updated to be consistent with the Crestor® USPI label.
- Section 12.3, Drug Interaction Studies: The clinical implication of 'increased risk of myopathy' has been moved to Sections 7.1 and 7.3 (b) (4) has been deleted to be consistent with the Crestor® USPI label.

  The Applicant is proposing to include the following language (highlighted) in the Ezallor™ label that is not present in the current Crestor® USPI label:

Rosuvastatin is a substrate for [redacted] transporter proteins including the hepatic uptake organic anion-transporting polypeptides (OATP1B1 [redacted] and breast cancer resistance protein (BCRP). Concomitant administration of rosuvastatin with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors) may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy *[see Dosage and Administration (2.5)]* [redacted]

Table 43. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	Rosuvastatin		
		Mean Ratio (ratio with/without coadministered drug) No Effect = 1	
	Dose (mg)[1]	Change in AUC	Change in C_{max}
Cyclosporine - stable dose required (75 mg to 200 mg BID)	10 mg QD for 10 days	7.1[2]	11[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3 to 3.4)[3]	3.2[2] (2.6 to 3.9)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	2.1[2] (1.7 to 2.6)[3]	5[2] (3.4 to 6.4)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6 to 2.2)[3]	2.2[2] (1.8 to 2.7)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4 to 1.7)[3]	2 (1.8 to 2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	1.5 (1 to 2.1)[3]	2.4 (1.6 to 3.6)[3]
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	1.4 (1.2 to 1.6)[3]	2.2 (1.8 to 2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2 to 1.6)[3] 1.3 (1.1 to 1.4)[3]	1.4 (1.2 to 1.5)[3] 1.2 (0.9 to 1.4)[3]
Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	1.2 (0.9 to 1.6)[3]	1.2 (0.8 to 1.6)[3]
[redacted]			
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7 days	10 mg	↔	1.2 (1.1 to 1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	40 mg 40 mg	0.5[2] (0.4 to 0.5)[3] 0.8 (0.7 to 0.9)[3]	0.5[2] (0.4 to 0.6)[3] 0.8 (0.7 to 1)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1 (0.8 to 1.2)[3]	1 (0.7 to 1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1 to 1.3)[3]	1.1 (0.9 to 1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8 (0.7 to 0.9)[3]	0.7 (0.5 to 0.9)[3]

- Section 2.5, Administration Options: The Applicant is proposing labeling language that reports that the granules inside the capsule should be emptied onto one (b) (4) of applesauce (b) (4). The administration options in the label should reflect the manner in which it was studied in the pivotal fasting and fed studies. In the pivotal studies the following was utilized "single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire content on a teaspoonful of applesauce and swallowed without chewing".

4. Labeling Comments

The ~~red strikeout font~~ is used to show the proposed text to be deleted and the underline blue font to show text to be included.

2 DOSAGE AND ADMINISTRATION

2.7 Administration of Sprinkle Capsules

Oral Administration

For patients who have difficulty swallowing capsules, the EZALLOR can be opened, the (b) (4) filled in the capsule sprinkled on one teaspoon (b) (4) of applesauce (b) (4)

7 DRUG INTERACTIONS

7.1 Cyclosporine

Cyclosporine increased rosuvastatin exposure (b) (4) and may result in increased risk of myopathy. Therefore, in patients taking cyclosporine, the dose of EZALLOR should not exceed 5 mg once daily *[see Dosage and Administration (2.4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

7.3 Protease Inhibitors

Coadministration of rosuvastatin with certain protease inhibitors has differing effects on rosuvastatin exposure and may increase risk of myopathy. Simeprevir, which is a hepatitis C virus (HCV) protease inhibitor, or combinations of atazanavir/ritonavir or lopinavir/ritonavir, which are HIV-1 protease inhibitors, increase rosuvastatin exposure (b) (4) *[see Table 4 – Clinical Pharmacology (12.3)]*. For these protease inhibitors, the dose of EZALLOR should not exceed 10 mg once daily. The combinations of fosamprenavir/ritonavir or tipranavir/ritonavir, which are HIV-1 protease inhibitors, produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors *[see Dosage and Administration (2.4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Rosuvastatin dose dependently reduces elevated LDL-cholesterol and reduces total cholesterol and triglycerides and increases HDL-cholesterol *[see Clinical Studies (14)]*. A therapeutic response to rosuvastatin is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that. Individualization of drug dosage should be based on the therapeutic response *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

Elimination

Rosuvastatin is primarily eliminated by excretion in the feces. The elimination half-life of rosuvastatin is approximately 19 hours.

Metabolism

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-

sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.

Excretion
Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). (b) (4)

After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Specific Populations
Racial or Ethnic Groups:
A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group.

(b) (4) **Male and Female Patients**:
There were no differences in plasma concentrations of rosuvastatin between men and women.

Pediatric use information for patients ages 8 to less than 10 years is approved for AstraZeneca's CRESTOR (rosuvastatin calcium) tablets. However, due to AstraZeneca's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Geriatric Patients:
There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).

Patients with Renal Impairment:
Mild to moderate renal impairment (CLcr ≥ 30 mL/min/1.73 m2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr < 30 mL/min/1.73 m2) not receiving hemodialysis compared with healthy subjects (CLcr > 80 mL/min/1.73 m2).

Hemodialysis:
Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Patients with Hepatic Impairment:
In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased.
In patients with Child-Pugh A disease, Cmax and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, Cmax and

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

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Rosuvastatin is a substrate for [redacted] certain transporter proteins including the hepatic uptake organic anion-transporting polyproteins (OATP1B1, OATP1B3, [redacted] and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of rosuvastatin with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors) may result in increased rosuvastatin plasma concentrations [redacted] *[see Dosage and Administration (2.4)and Drug Interactions (7.1, 7.3)]*. [redacted]

Table 4. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect = 1	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
Cyclosporine - stable dose required (75 mg to 200 mg BID)	10 mg QD for 10 days	7.1[2]	11[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3 to 3.4)[3]	3.2[2] (2.6 to 3.9)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	2.1[2] (1.7 to 2.6)[3]	5[2] (3.4 to 6.4)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6 to 2.2)[3]	2.2[2] (1.8 to 2.7)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4 to 1.7)[3]	2 (1.8 to 2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	1.5 (1 to 2.1)[3]	2.4 (1.6 to 3.6)[3]
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	1.4 (1.2 to 1.6)[3]	2.2 (1.8 to 2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2 to 1.6)[3] 1.3 (1.1 to 1.4)[3]	1.4 (1.2 to 1.5)[3] 1.2 (0.9 to 1.4)[3]
Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	1.2 (0.9 to 1.6)[3]	1.2 (0.8 to 1.6)[3]

[redacted]

Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7 days	10 mg	↔	1.2 (1.1 to 1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	40 mg 40 mg	0.5[2] (0.4 to 0.5)[3] 0.8 (0.7 to 0.9)[3]	0.5[2] (0.4 to 0.6)[3] 0.8 (0.7 to 1)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1 (0.8 to 1.2)[3]	1 (0.7 to 1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1 to 1.3)[3]	1.1 (0.9 to 1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8 (0.7 to 0.9)[3]	0.7 (0.5 to 0.9)[3]

[1] Single dose unless otherwise noted.
[2] Clinically significant *[see Dosage and Administration (2) and Warnings and Precautions (5)]*
[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease, 11=11 fold increase in exposure)

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/s/

SHALINI WICKRAMARATNE SENARATH YAPA
12/13/2018

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12/13/2018

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208647
Submission Date(s)	28th August 2015
Brand Name	Ezallor
Generic Name	Rosuvastatin
OCP Division	Clinical Pharmacology - 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Sun Pharma Global FZE
Submission Type; Code	NDA 505(b)(2); Standard
Formulation; Strength(s)	Immediate-release, hard gelatin capsule filled with drug-containing (b) (4); 5 mg, 10 mg, 20 mg, 40 mg strengths
Proposed Indication	▪ Patients with hypertriglyceridemia as an adjunct to diet ▪ Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet ▪ Patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB
Dosage & Administration	▪ 5 mg to 40 mg orally once daily, the usual starting dose is 10 mg to 20 mg ▪ Administered at any time of the day, with or without food ▪ Capsule swallowed intact or the contents of the capsule sprinkled onto applesauce or administered *via* a nasogastric tube ▪ In Asian patients, consider initiating therapy with 5 mg once daily dose ▪ Patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73 m^2) not on hemodialysis, the dose should not exceed 10 mg once daily ▪ Dose should not exceed 5 mg once daily in patients taking cyclosporine, and not exceed 10 mg once daily in patients taking gemfibrozil, atazanavir and ritonavir, lopinavir and ritonavir or simeprevir
Clinical Pharmacology Reviewer	Shalini Wickramaratne Senarath Yapa, Ph.D.
Clinical Pharmacology Team Leader	Jayabharathi Vaidyanathan, Ph.D.

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1. Executive Summary

Rosuvastatin capsules (Ezallor) developed and marketed by Sun Pharma Global FZE, is an HMG Co-A reductase inhibitor indicated as an adjunct to diet for patients with hypertriglyceridemia and primary dysbetalipoproteinemia and for patients with homozygous familial hypercholesterolemia.

This is a 505 (b) (2) NDA referencing Crestor® (NDA 021366).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted under NDA 208647 and recommends approval.

1.2 Phase IV commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Rosuvastatin capsules (Ezallor) an immediate-release, hard gelatin capsule filled with drug-containing (b) (4), are manufactured in strengths of 5 mg, 10 mg, 20 mg, and 40 mg.

The proposed dosage regimen is 5 mg to 40 mg once daily, with the usual starting dose ranging from 10 mg to 20 mg. Rosuvastatin capsules can be taken at any time of the day, with or without food. Rosuvastatin capsules can be swallowed intact or the contents of the capsule sprinkled onto applesauce. The capsules can also be administered *via* a nasogastric tube.

Two pivotal bioequivalence (BE) studies, one under fasting conditions and the other under fed conditions, were conducted to assess the BE between rosuvastatin 40 mg capsules (both as intact capsule and sprinkling contents of capsule on applesauce) *versus* Crestor® 40 mg tablets. BE was also assessed between rosuvastatin 40 mg capsules by sprinkling contents of capsule on applesauce *versus* intact capsule. Bioequivalence was demonstrated for the following treatment comparisons:

a) Study PKD_14_128 demonstrated BE of rosuvastatin 40 mg capsules (intact capsules) *versus* Crestor® 40 mg tablets, rosuvastatin 40 mg capsules (sprinkling contents of capsule on applesauce) *versus* Crestor® 40 mg tablets, and rosuvastatin 40 mg capsules by sprinkling contents of capsule on applesauce *versus* intact capsule under fasting conditions.
b) Study PKD_14_129 demonstrated BE of rosuvastatin 40 mg capsules (intact capsules) *versus* Crestor® 40 mg tablets, rosuvastatin 40 mg capsules (sprinkling contents of capsule on applesauce) *versus* Crestor® 40 mg tablets, and rosuvastatin 40 mg capsules by sprinkling contents of capsule on applesauce *versus* intact capsule under fed conditions.

Biowaiver: The pivotal BE studies were conducted with the highest strength rosuvastatin capsules (40 mg). *In vitro* dissolution data was provided along with a biowaiver request for the lower strengths (5 mg, 10 mg, and 20 mg) rosuvastatin capsules. The biowaiver request and *in vitro* dissolution data were reviewed by the biopharmaceutics reviewer (refer to the biopharmaceutics review in DARRTs).

Key BE information of rosuvastatin capsules are summarized in Table 1.

Table 1: Highlights of Bioequivalence Studies

Study	Treatment Comparisons	PK Parameters	Bioequivalence[3]		
			Ratio of Least-Squares Geometric Means %[1]	90% Geometric C.I.[2]	Intra-Subject CV%
PKD 14 128 Fasting Condition	A *versus* C	AUC_{0-t}	93.40	87.14 to 100.11	18.72
		AUC_{0-inf}	93.14	86.83 to 99.90	18.92
		C_{max}	97.75	89.67 to 106.55	23.36
	B *versus* C	AUC_{0-t}	99.85	94.14 to 105.90	16.26
		AUC_{0-inf}	99.64	94.20 to 105.40	15.49
		C_{max}	107.79	99.19 to 117.13	23.09
	B *versus* A	AUC_{0-t}	106.14	99.18 to 113.58	18.56
		AUC_{0-inf}	106.14	99.48 to 113.25	17.73
		C_{max}	109.26	98.88 to 120.74	27.63
PKD 14 129 Fed Condition	A *versus* C	AUC_{0-t}	106.80	100.01 to 114.04	18.67
		AUC_{0-inf}	106.46	100.10 to 113.22	17.50
		C_{max}	111.09	102.58 to 120.31	22.75
	B *versus* C	AUC_{0-t}	100.25	93.66 to 107.30	19.33
		AUC_{0-inf}	100.27	93.92 to 107.04	18.59
		C_{max}	94.04	86.57 to 102.15	23.64
	B *versus* A	AUC_{0-t}	93.83	88.94 to 98.98	15.15
		AUC_{0-inf}	94.07	89.36 to 99.02	14.51
		C_{max}	84.81	79.53 to 90.44	18.23

[1]Least squares geometric means ratio calculated according to the following formula $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (C)} \times 100$

[2]90% geometric confidence interval using Ln-transformed data

[3]Excluding data from Subject 11

Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)

Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)

Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, page 0043-0045; Ezallor NDA, Module 5.3.1.2, Study pkd-14-129-stf for pivotal fasting study pkd-14-129, Study report body, Study –report, page 0053-0055)

2. Question Based Review (QBR)

2.1 What are the Clinical Pharmacology and Biopharmaceutics studies submitted in the NDA?

The clinical pharmacology and biopharmaceutics program conducted to evaluate the BE and relative bioavailability of rosuvastatin capsules compared to Crestor® tablets included 11 trials. All studies were conducted in healthy volunteers. In addition to the two pivotal BE studies comparing rosuvastatin capsules (intact capsule and sprinkling contents of capsule on applesauce) and Crestor® tablets, the NDA program also comprised of a redosing relative bioavailability Phase 1 study and eight pilot BE Phase 1 studies (Table 2). This review focuses on the two pivotal BE studies and the redosing study.

Table 2: Overview of studies with pharmacokinetic assessments relevant to the clinical pharmacology and biopharmaceutics of rosuvastatin capsules

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Products(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Pivotal Studies							
Phase 1 BE (Fasting Study)	PKD_14_128	Primary: To assess the relative bioavailability between treatment B and A, treatment A and C, and treatment B and C Secondary: To assess the safety of the test product and reference product in healthy adult subjects	A randomized, open-label, three-treatment, three-period, six sequence, single dose, crossover study under fasting conditions with a washout period of 15 days between periods I and II and 7 days between period II and III	▪ Treatment A: Single oral dose of rosuvastatin 40 mg capsule administered as intact capsule in the fasted state (test treatment) ▪ Treatment B: Single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire contents on a teaspoonful (5 mL ± 10%) of applesauce in the fasted state (test treatment) ▪ Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet administered in the fasted state (reference treatment)	48 subjects randomized, 42 subjects completed all three periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (both inclusive)	Treatment A, B, and C: single dose
Phase 1 BE (Fed Study)	PKD_14_129	Primary: To assess the relative bioavailability between treatment B and A, treatment A and C, and treatment B and C Secondary: To assess the safety of the test product and reference product in healthy adult subjects	A randomized, open-label, three-treatment, three-period, six sequence, single dose, crossover study under fed conditions with a washout period of 7 days between period I,II, and III	▪ Treatment A: Single oral dose of rosuvastatin 40 mg capsule administered as intact capsule in the fed state (test treatment) ▪ Treatment B: Single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire contents on a teaspoonful (5 mL ± 10%) of applesauce in the fed state (test treatment)	47 subjects randomized, 45 subjects completed all three periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (both inclusive)	Treatment A, B, and C: single dose

				▪ Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet administered in the fed state (reference treatment)			
Phase 1 BA (Fasting Redosing Study)	PKD_14_291	Primary: To evaluate and verify the aberrant response of Subject No. 11 in rosuvastatin 40 mg capsule fasting relative bioavailability study (PKD_14_128) Secondary: To assess the safety of test product and reference product in healthy adult subjects	A randomized, open-label, three-treatment, three-period, six sequence, single dose, crossover study under fasting conditions with a washout period of 7 days between periods I, II, and III	▪ Treatment A: Single oral dose of rosuvastatin 40 mg capsule administered as intact capsule in the fasted state (test treatment) ▪ Treatment B: Single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire contents on a teaspoonful (5 mL ± 10%) of applesauce in the fasted state (test treatment) ▪ Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet administered in the fasted state (reference treatment)	5 subjects randomized, 5 subjects completed all three periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (both inclusive)	Treatment A, B, and C: single dose
Supportive Studies							
Phase 1 BE (Fasting Study)	PKD_13_179	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor® 40 mg tablet under fasting conditions ▪ To assess the safety of subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fasting conditions with a washout period of 7 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/01A) administered in the fasted state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fasted state	24 subjects were randomized, 23 subjects completed both periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (inclusive)	Test (A) and Reference (B): single dose
Phase 1 BE (Fed Study)	PKD_13_180	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor®	A randomized, open-label, two-treatment, two-period, two sequence, single	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/01A) administered	24 subjects were randomized, 24 subjects	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2	Test (A) and Reference (B): single dose

		40 mg tablet under fed conditions ▪ To monitor the safety of subjects participating in the study	dose, crossover study under fed conditions with a washout period of 7 days between periods I and II	in the fed state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fed state	completed both periods	(inclusive)	
Phase 1 BE (Fasting Study)	PKD_13_278	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor® 40 mg tablet under fasting conditions ▪ To monitor the safety of the subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fasting conditions with a washout period of 7 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/04A) administered in the fasted state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fasted state	18 subjects were randomized, 18 subjects completed both periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (inclusive)	Test (A) and Reference (B): single dose
Phase 1 BE (Fed Study)	PKD_13_279	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor® 40 mg tablet ▪ To monitor the safety of the subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fed conditions with a washout period of 9 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/05A) administered in the fed state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fed state	18 subjects were randomized, 18 subjects completed both periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (inclusive)	Test (A) and Reference (B): single dose
Phase 1 BE (Fasting Study)	PKD_13_295	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor® 40 mg tablet ▪ To monitor the safety of the subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fasting conditions with a washout period of 7 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/03B) administered in the fasted state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fasted state	18 subjects were randomized, 17 subjects completed both periods	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (inclusive)	Test (A) and Reference (B): single dose
Phase 1 BE (Fasting Study)	PKD_13_410	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor®	A randomized, open-label, two-treatment, two-period, two sequence, single	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: RST-C/05A) administered	18 subjects were randomized, 18 subjects	Healthy male subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2	Test (A) and Reference (B): single dose

		40 mg tablet ▪ To monitor the safety of the subjects participating in the study	dose, crossover under fasting conditions with a washout period of 12 days between periods I and II	in the fasted state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fasted state	completed both periods	(inclusive)	
Phase 1 BE (Fasting Study)	PKD_14_017	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule (sprinkled on soft food) and Crestor® 40 mg tablet ▪ To monitor the safety of the subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fasting conditions with a washout period of 8 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: SRD2014B002) administered by opening the capsule and sprinkling the entire contents on a teaspoonful (5mL±10%) of applesauce at room temperature and swallowed without chewing immediately or within 5 minutes after sprinkling the capsule content in the fasted state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fasted state	18 subjects were randomized, 18 subjects completed both periods	Healthy subjects, age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 (inclusive)	Test (A) and Reference (B): single dose
Phase 1 BE (Fed Study)	PKD_14_062	▪ To assess the bioequivalence of rosuvastatin 40 mg capsule and Crestor® 40 mg tablet ▪ To monitor the safety of the subjects participating in the study	A randomized, open-label, two-treatment, two-period, two sequence, single dose, crossover study under fed conditions with a washout period of 7 days between periods I and II	▪ Test (A): Single oral dose of rosuvastatin 40 mg capsule (Batch number: SRD2014B002) administered in the fed state ▪ Reference (B): Single oral dose of Crestor® 40 mg tablet administered in the fed state	18 subjects were randomized, 15 subjects completed both periods	Healthy subjects age 18-45 years, with a BMI of 18.5-25.0 kg/m^2 for males and 17.0-25.0 kg/m^2 for females (inclusive both)	Test (A) and Reference (B): single dose

2.1.1 What are the highlights of the rosuvastatin capsule drug product (Ezallor) as they relate to the clinical pharmacology review?

Rosuvastatin capsule is a hard gelatin capsule filled with rosuvastatin-containing (b) (4) formulated for immediate release. Rosuvastatin capsules are manufactured in strengths of 5 mg, 10 mg, 20 mg, and 40 mg.

2.1.2 What is the composition of the clinical trial formulation and proposed commercial formulation of rosuvastatin capsules (Ezallor)?

Proposed commercial formulation of rosuvastatin capsule:
The composition of the final drug product and the components of the empty hard gelatin capsule of the final drug product are shown in Table 3 and Table 4, respectively.

Table 3: Composition of drug product

Ingredient	Function	mg/capsule				Amount % w/w
		5 mg	10 mg	20 mg	40 mg	
(b) (4)						
Rosuvastatin calcium	API	5.198*1	10.395*1	20.790*1	41.58	(b) (4)
Microcrystalline cellulose, NF	(b) (4)					(b) (4)
(b) (4)						
Crospovidone, NF	(b) (4					
Mannitol, USP	(b) (4)					
Magnesium oxide, USP	(b) (4)					
Ferric oxide	(b) (4)					
Sodium Citrate, USP	(b) (4)					
	(b) (4)					
Hypromellose, USP	(b) (4)					
(b) (4)						
Polyethylene glycol 4000, NF						
Isopropyl alcohol, USP						
Purified water, USP						
	(b) (4)					
Silicon dioxide, NF	(b) (4)					
	(b) (4)					
Capsule filling						
Hard gelatin capsule shells*4	Empty shells	(size'3')	(size '3')	(size '1')	(size '0, El')	

*1 5.198mg Rosuvastatin calcium is equivalent to 5 mg Rosuvastatin.
10.395mg Rosuvastatin calcium is equivalent to 10 mg Rosuvastatin.
20.790mg Rosuvastatin calcium is equivalent to 20 mg Rosuvastatin.
41.580mg Rosuvastatin calcium is equivalent to 40 mg Rosuvastatin.

(b) (4)

*4 Components of empty hard gelatin capsules is provided below

(Source: Ezallor NDA, Module 2.3.P, Drug Product – PDF, Table 2.3.P.1:1, page 4)

Table 4: Components of empty hard gelatin capsules

Components of empty hard gelatin capsules					
Sr.#	Ingredients	Amount/Unit (mg)			
		Hard Gelatin capsule shell for 5 mg (Size:3)	Hard Gelatin capsule shell for 10 mg (Size:3)	Hard Gelatin capsule shell for 20 mg (Size:1)	Hard Gelatin capsule shell for 40 mg (Size:0EL)
1	Gelatin	(b) (4)			
2	Sodium Lauryl Sulphate				
3	Titanium Dioxide				
4	Water				
5	FD&C Red 3				
6	FD&C Blue 1				
7	D&C Red 28				
8	FD&C Red 40				
9	FD & C Green 3				
10	(b) (4) Black Ink*[2]				

(b) (4) Black Ink Composition: Shellac (b) (4) Dehydrated Alcohol (b) (4) Isopropyl Alcohol (b) (4) Butyl Alcohol (b) (4) Propylene Glycol (b) (4) Strong Ammonia Solution (b) (4) Black Iron Oxide (b) (4) Potassium Hydroxide (b) (4) Purified Water (b) (4)

(Source: Ezallor NDA, Module 2.3.P, Drug Product – PDF, Table 2.3.P.1:2, page 5)

Proposed commercial formulation and registration formulation (exhibit batch):

The sponsor reports that there are no differences in the unit dose formula of the exhibit batch and the proposed commercial batch of rosuvastatin capsules 5 mg, 10 mg, 20 mg, and 40 mg. Table 5 shows a complete list of the ingredients used for the manufacture of the exhibit batch and the proposed intended commercial batch.

Table 5: Typical batch formula for intended commercial batches and exhibit batches

Rosuvastatin (b) (4) for Rosuvastatin Capsules, 5 mg, 10 mg, 20 mg and 40 mg		
	Intended commercial batch	Exhibit batch
Batch size		(b) (4)
Components		
Rosuvastatin calcium		
Microcrystalline cellulose, NF (b) (4)		
(b) (4)		
Crospovidone, NF (b) (4)		
(b) (4)		
Mannitol, USP (b) (4)		
Magnesium oxide, USP (b) (4)		
Ferric oxide (b) (4) NF		
Sodium Citrate (b) (4) USP		
(b) (4)		
Hypromellose, USP (b) (4)		
(b) (4)		
Polyethylene glycol (b) (4)		
Isopropyl alcohol, USP		
Purified water, USP		
Silicon dioxide, NF (b) (4)		
(b) (4)		

(b) (4)

(b) (4)

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Reviewer's Comment: *The term 'exhibit batch' refers to all batches submitted in the CMC section of the NDA, including the rosuvastatin 40 mg batch (batch number: JKN2312A) that was used in the two pivotal BE studies.*

The sponsor reports that there are no compositional changes in the formulation batch used in the pivotal BE studies and the proposed commercial formulation batch. The only change between the batches is in the capsule shell description, as shown in Table 6. With the exception of the printing ink amount, the commercial formulation is similar to the 40 mg batch JKN2312A that was used in the pivotal BE studies.

Table 6: Capsule shell description for the pivotal and commercial batch

Strength	Capsule shell description	
	Pivotal batch	Commercial batch
40 mg	EHG capsule, size '0 EL' green / white , axially imprinted (b) (4) on cap and body in bk (b) (4)	EHG capsule, size '0 EL' green / white , axially imprinted with '987' on cap and body in bk (b) (4)
20 mg	EHG capsule, size '1' blue / off white, axially imprinted (b) (4) cap and body in BK (b) (4)	EHG capsule, size '1' blue / off white, axially imprinted with '986' on cap and body in BK (b) (4)
10 mg	EHG capsule, size '3 ' purple / off white , axially imprinted (b) (4) on cap and body in bk (b) (4)	EHG capsule, size '3 ' purple / off white , axially imprinted with '985' on cap and body in bk (b) (4)
5 mg	EHG capsule, size '3 ' pink / off white , axially imprinted (b) (4) lines on cap and body in bk (b) (4)	EHG capsule, size '3 ' pink / off white , axially imprinted with '984' on cap and body in bk (b) (4)

(Source: Ezallor NDA, Module 2.3.P, Drug Product – PDF, page 24)

2.1.3 What are the findings from the OSIS inspections?

An OSIS inspection was requested for the clinical and analytical sites for the pivotal BE studies (PKD_14_128, PKD_14_129). Inspection of the clinical sites also included auditing of the redosing study protocol (PKD_14_291). The analytical and clinical data from the audited studies were found to be reliable. Therefore the OSIS reviewers recommended that the analytical and clinical portion of studies PKD_14_128 and PKD_14_129 are acceptable for further Agency review.

2.1.4 What are the proposed mechanism of action and therapeutic indications?

Proposed mechanism of action: Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL, and second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Proposed therapeutic indications:

- Patients with hypertriglyceridemia as an adjunct to diet,
- Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as

an adjunct to diet,

- Patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB

Limitations of use: Rosuvastatin capsules have not been studied in Fredrickson Type I and V dyslipidemias

2.1.5 What are the proposed dosages and routes of administration?

Proposed dosages:

This dosing recommendation is similar to those for the RLD, Crestor®. The proposed dose range for rosuvastatin capsules is 5 mg to 40 mg orally once daily. The usual starting dose is 10 mg to 20 mg. Rosuvastatin capsules can be administered as a single dose at any time of the day, with or without food.

When initiating therapy, or switching from another HMG-CoA reductase inhibitor therapy, the appropriate rosuvastatin capsule starting dose should be first utilized, and only then titrated according to the patient's response and individualized goal of therapy. After initiation or upon titration of rosuvastatin capsule, lipid levels should be analyzed within 2 to 4 weeks and the dose adjusted accordingly. The 40 mg dose should be used only for those patients who have not achieved their LDL-C goal with the 20 mg dose.

In addition, the following recommendations are proposed by the sponsor:

- Patients with HoFH the recommended starting dose is 20 mg once daily,
- In Asian patients, consider initiation of therapy with the 5 mg once daily dose due to increased rosuvastatin plasma concentrations. Take into consideration the increased systemic exposure in this patient population when treating patients not adequately controlled at doses up to 20 mg/day,
- Patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73 m^2) not on hemodialysis, the dosing should be started at 5 mg once daily and not exceed 10 mg once daily,
- Patients taking cyclosporine, the dose should not exceed 5 mg once daily. Patients taking gemfibrozil, atazanavir and ritonavir, lopinavir and ritonavir or simeprevir should initiate therapy with the 5 mg once daily dose, the dose should not exceed 10 mg once daily.

Proposed Routes of administration:

- *Oral administration*: The capsules can be swallowed intact or for patients who have difficulty swallowing capsules, the capsule can be opened and the (b) (4) sprinkled on one (b) (4) of applesauce (b) (4) The (b) (4) with applesauce should be swallowed immediately, without chewing. The mixture should not be stored for future use. If the mixture is not used in its entirety, the remaining mixture should be discarded immediately.
- *Nasogastric tube (≥16 French) administration:* The capsules can be opened and the intact (b) (4) emptied into a syringe and mixed with 40 mL of water. Replace

the plunger and shake the syringe vigorously, the [redacted] may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16-French) and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the [redacted], the nasogastric tube should be flushed with additional water. Use in other liquids [redacted] is [redacted] not recommended.

2.2 General Clinical Pharmacology

2.2.1 What is known about the PK characteristics of rosuvastatin following administration of the commercially listed drug, Crestor® tablets?

In clinical pharmacology studies, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral administration. The absolute bioavailability of rosuvastatin is approximately 20%. The systemic exposure (C_{max} and AUC) increased in an approximately proportional manner to Crestor® dose. Rosuvastatin systemic exposure (AUC) is not affected by administration of Crestor® with food and did not differ following evening or morning drug administration. The mean volume of distribution at steady-state is approximately 134 liters. Rosuvastatin is 88% bound to plasma protein (mostly albumin) and this binding is reversible and independent of plasma concentrations. Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite of rosuvastatin is N-desmethyl rosuvastatin which is formed principally by cytochrome P450/2C9 enzyme. Following administration of Crestor®, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is from the parent compound, with *in vitro* studies demonstrating that the metabolite has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). Following IV administration, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route. The elimination half-life of rosuvastatin is approximately 19 hours.

Refer to the label and clinical pharmacology review of Crestor® (NDA 021366) for information on the effect of intrinsic factors such as race, gender, age, renal impairment and, hepatic impairment on the PK of rosuvastatin.

2.2.2 Were the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes, rosuvastatin concentrations were measured in plasma to assess the PK parameters. Refer to Section 2.6 for analytical method details.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No dedicated studies were conducted with rosuvastatin capsule to evaluate the PK in

special populations such as in geriatrics, pediatrics, different race, and in patients with renal impairment and hepatic impairment. Since this is a 505 (b)(2) application, the sponsor cross-referenced the NDA for Crestor® (NDA 021366) for information relating to special population (race, genetic polymorphism, renal and hepatic impairment).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure (PK) and/or response (PD) and what is the impact of any differences in exposure on pharmacodynamics?

No dedicated studies were conducted with rosuvastatin capsule to evaluate the impact of herbal products, smoking, and alcohol on the PK of rosuvastatin. The sponsor conducted a study to investigate the effect of food on the PK of rosuvastatin. This is discussed in

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2.5 General Biopharmaceutics

The sponsor conducted eight pilot relative BE studies using developmental formulations of rosuvastatin capsules. Refer to Table 2 for an overview of the study objectives, study design, and subject numbers. Five of the pilot studies were conducted under fasting conditions and three pilot studies were conducted under fed conditions. Rosuvastatin 40 mg capsules as intact capsules were used as the test formulation in all studies except for in study PKD_14_017 where the contents of the capsule were sprinkled on applesauce. Crestor® 40 mg tablets were used as the reference product in all the studies. A summary of the BE results for the pilot BE studies conducted under fasting conditions and fed conditions are presented in Table 7 and Table 8, respectively. The sponsor reports that under fasting conditions two formulations (Table 7) and under fed conditions three formulations (Table 8) demonstrated BE to Crestor® 40 mg tablets. In study PKD_14_062 the test vs. reference ratios for AUC and C_{max} were within the 80 – 125% bounds, however the values of the 90% CI were slightly higher than 125% (Table 8). The sponsor reports that these results are likely to be attributed to the limited number of subjects and concluded that when tested in a larger study population the formulation would likely meet the BE criteria.

Table 7: Summary of pilot randomized, two-way crossover, fasting, BE studies of rosuvastatin 40 mg capsules and Crestor® 40 mg tablets

Study Number (Dates of Conduct)	Rosuvastatin Treatments (Batch/Lot Number)	No. (Completed) Age (yrs) BMI (kg/m^2)	Pharmacokinetic Analysis		
			Parameter	Statistical Comparison (Test *vs.* Reference)	
				Ratio of LSM[1] (%)	90% CI[2]
Fasting Conditions					
PKD_13_179 (15 May – 26 May 2013)	Rosuvastatin 40 mg Capsules (RST-C/01A)	24 (23) 33.2 ± 5.28 21.72 ± 2.160	C_{max}	71.54	60.99 – 83.91
			AUC_{0-t}	79.73	70.11 – 90.66
	Crestor® 40 mg Tablets (113386)		$AUC_{0-\infty}$	80.63	71.10 – 91.44
PKD_13_278 (29 Jul. – 09 Aug. 2013)	Rosuvastatin 40 mg Capsules (RST-C/04A)	18 (18) 30.9 ± 7.13 21.10 ± 2.307	C_{max}	79.79	68.36 – 93.13
	Crestor® 40 mg Tablets (113386)		AUC_{0-t}	89.56	81.73 – 98.13
			$AUC_{0-\infty}$	89.41	81.78 – 97.75
PKD_13_295 (07 Aug. – 18 Aug. 2013)	Rosuvastatin 40 mg Capsules (RST-C/03B)	18 (17) 31.8 ± 6.44 21.52 ± 2.409	C_{max}	69.85	60.15 – 81.12
			AUC_{0-t}	77.60	70.53 – 85.37
	Crestor® 40 mg Tablets (113386)		$AUC_{0-\infty}$	78.38	71.30 – 86.17
PKD_13_410 (03 Oct. – 19 Oct. 2013)	Rosuvastatin 40 mg Capsules (RST-C/05A)	18 (18) 31.4 ± 7.59 22.14 ± 1.702	C_{max}	96.46	81.64 – 113.98
			AUC_{0-t}	98.14	87.77 – 109.73
	Crestor® 40 mg Tablets (113386)		$AUC_{0-\infty}$	98.82	88.67 – 110.14
PKD_14_017 (20 Jan. – 01 Feb. 2014)	Rosuvastatin 40 mg Capsules (SRD2014B002)	18 (18) 33.4 ± 5.83 21.72 ± 2.374	C_{max}	91.98	80.33 – 105.32
			AUC_{0-t}	95.75	88.22 – 103.91
	Crestor® 40 mg Tablets (BK0033)		$AUC_{0-\infty}$	96.85	89.16 – 105.21

[1]Calculated using least square means according to the formula: $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (B))} \times 100$
[2]90% Geometric Confidence Interval using Ln-transformed data

(Source: Ezallor NDA, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods– PDF, page 40)

Table 8: Summary of pilot randomized, two-way crossover, fed, BE studies of rosuvastatin 40 mg capsules and Crestor® 40 mg tablets

Study Number (Dates of Conduct)	Rosuvastatin Treatments (Batch/Lot Number)	No. (Completed) Age (yrs) BMI (kg/m^2)	Pharmacokinetic Analysis		
			Parameter	Statistical Comparison (Test vs. Reference)	
				Ratio of LSM[1] (%)	90% CI[2]
PKD_13_180 (15 May – 26 May 2013)	Rosuvastatin 40 mg Capsules (RST-C/01A)	24 (24) 32.8 ± 5.30 21.96 ± 2.204	C_{max}	103.59	93.31 – 115.00
			AUC_{0-t}	104.84	97.45 – 112.79
	Crestor® 40 mg Tablets (113386)		$AUC_{0-\infty}$	105.39	97.90 – 113.46
PKD_13_279 (21 Sep. – 04 Oct. 2013)	Rosuvastatin 40 mg Capsules (RST-C/05A)	18 (18) 29.4 ± 5.02 21.79 ± 2.124	C_{max}	100.28	88.46 – 113.68
			AUC_{0-t}	109.51	100.01 – 119.91
	Crestor® 40 mg Tablets (113386)		$AUC_{0-\infty}$	109.73	100.11 – 120.28
PKD_14_062 (06 Mar. – 17 Mar. 2014)	Rosuvastatin 40 mg Capsules (SRD2014B002)	18 (15) 32.1 ± 6.52 22.85 ± 2.098	C_{max}	106.76	88.94 – 128.14
			AUC_{0-t}	108.65	92.59 – 127.50
	Crestor® 40 mg Tablets (BK0033)		$AUC_{0-\infty}$	109.78	94.15 – 128.00

[1]Calculated using least square means according to the formula: $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (B))} \times 100$
[2]90% Geometric Confidence Interval using Ln-transformed data

(Source: Ezallor NDA, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods– PDF, page 41)

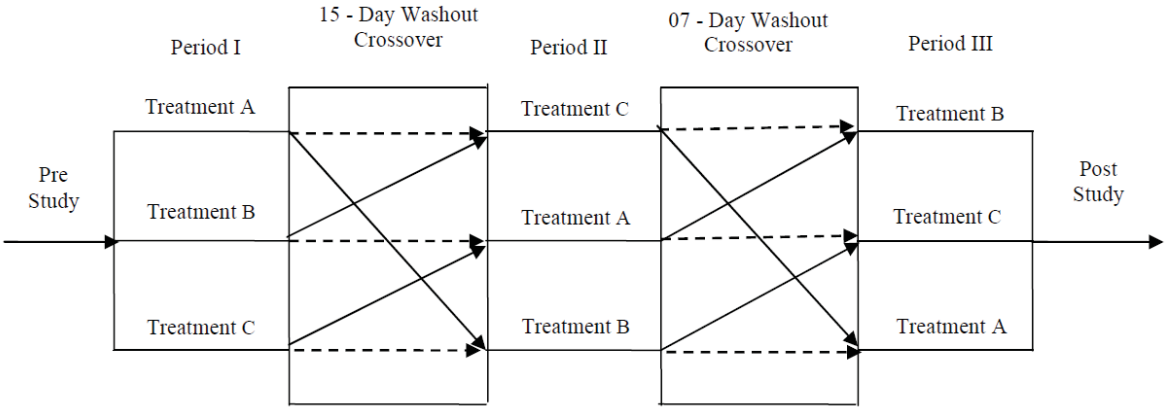
2.5.1 Was bioequivalence established between rosuvastatin capsules (both intact capsule and sprinkling contents of capsule on applesauce) and Crestor® tablets and between rosuvastatin capsules when sprinkling contents of capsule on applesauce and intact capsule in the fasted state?

One pivotal BE study using the final formulation of rosuvastatin capsule (batch number: JKN2312A, rosuvastatin capsule 40 mg) was conducted to evaluate the fasting-state BE of rosuvastatin capsule 40 mg (intact capsule and sprinkling contents of capsule on applesauce) compared to the reference listed drug Crestor® tablet 40 mg. This pivotal study is described below.

Study PKD_14_128:

This was a randomized, open-label, three treatment, three period, six sequence, single dose, crossover relative bioavailability study under fasting conditions. The study design is shown in Figure 1. Treatment A, B (batch number: JKN2312A) and C (lot number: BK0033) (Figure 1) were administered after subjects were fasted for at least 10 hours and subjects continued to fast for 4 hours after dosing. Water was not allowed from 1 hour prior to dosing and until 1 hour after dosing. The 48 healthy male subjects were randomized to 1 of the 6 sequences (ABC, BCA, CAB, ACB, CBA, BAC). Following dosing in Periods I, II, and III, PK blood samples were collected for 76 hours. There was a washout period of 15 days between period I and II and 7 days between period II and III. Out of the 48 subjects who were dosed, 42 subjects completed all three periods of the study, and 45 subjects completed at least two periods of the study. Plasma samples of the 45 subjects who completed at least two periods of the study were assayed for rosuvastatin

plasma concentrations.



Treatment A: Single oral dose of rosuvastatin 40 mg capsule administered with 240 mL (±2 mL) of water at ambient temperature in the morning (bioequivalence test treatment)

Treatment B: Single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire contents on a teaspoonful (5mL ± 10%) of applesauce at room temperature and swallowed without chewing immediately or within 5 minutes after sprinkling the capsule content followed by 240 mL (± 2mL) of water at ambient temperature in the morning (bioequivalence test treatment)

Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet administered with 240 mL (± 2mL) of water at ambient temperature in the morning (bioequivalence reference treatment)

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, page 0018)

Figure 1: Study design for pivotal fasting BE study (PKD_14_128)

The mean (±SD) rosuvastatin plasma concentration versus time profile is presented in Figure 2. Summary statistics by treatment for rosuvastatin PK parameters are provided in Table 9.

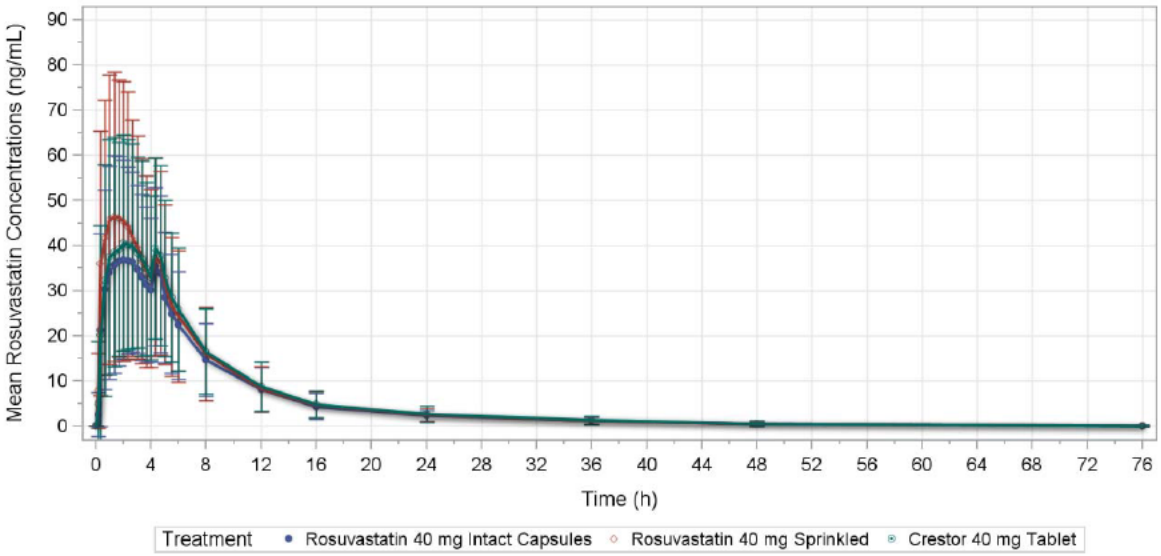


Figure 2: Mean plasma concentration time profile of rosuvastatin following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects in the fasted state (n=45) (PKD_14_128)

Table 9: Summary statistics for rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects in the fasted state (PKD 14 128)

Treatment (No. of subjects)	Rosuvastatin PK Parameters[1]				
	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
A (n=43)	44.89 (24.33)	348.87 (195.15)	359.67 (197.86)	2.33 (0.33 – 4.67)	10.69 (4.85)
B (n=45)	54.96 (34.59)	394.13 (233.37)	405.55 (235.64)	1.67 (0.33 – 5.00)	10.26 (4.51)
C (n=44)	50.13 (29.11)	387.08 (211.20)	402.16 (218.04)	2.50 (0.33 – 5.00)	11.00 (7.32)

[1]Mean (±SD) values for all PK estimates except for T_{max} which is reported as Median (range) values
Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)
Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)
Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet
Numbers are shown with two decimal places
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, pages 0058-0060)

One subject, Subjec (b) (6), was identified as a statistical outlier (Grubb's outlier test) (Figure 3). Rosuvastatin PK parameter for Subject (b) (6) stratified by treatment is shown in (Table 10). The sponsor states that all necessary clinical and bioanalytical investigations failed to provide an explanation for the anomalous response for Subject (b) (6) following administration of rosuvastatin 40 mg capsule (intact capsule, Treatment A). Statistical analysis of PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of rosuvastatin with inclusion of data from Subject (b) (6) are presented in Table 11. Inclusion of data from Subject (b) (6) results

in the BE criteria not been met for rosuvastatin 40 mg capsule (intact capsule) and Crestor® 40 mg tablet and for rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) and rosuvastatin 40 mg capsule (intact capsule) (Table 11). Bioequivalence for rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) and Crestor® 40 mg tablet was demonstrated (Table 11).

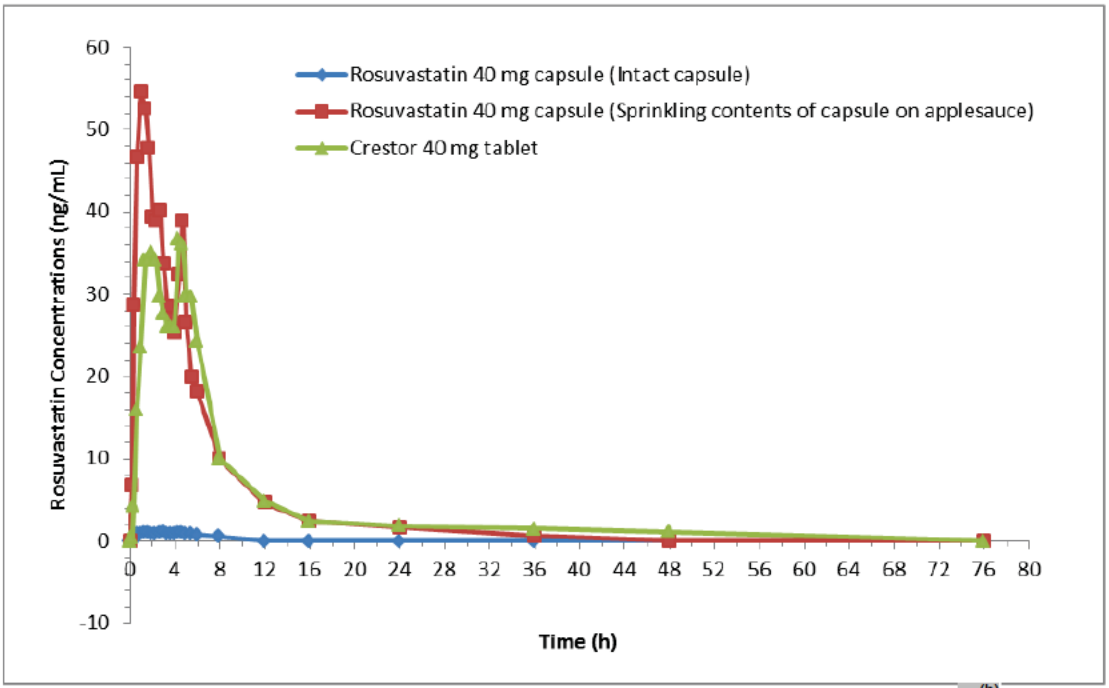


Figure 3: Plasma concentration time profile of rosuvastatin for Subject (b) (6) after oral administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in the fasted state (PKD_14_128)

Table 10: Rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in Subject (b) (6) in the fasted state (PKD_14_128)

Treatment	Rosuvastatin PK Parameters				
	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
A	1.08	6.25	9.96	3.00	4.64
B	54.56	302.29	310.26	1.00	9.61
C	36.65	293.66	353.24	4.33	35.97

Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)
Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)
Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet
Numbers are shown with two decimal places
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Individual efficacy response data, Individual-pharmacokinetic-data, pages 0002-0007)

Table 11: Bioequivalence and fasting effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (Subject (b) (6) data included in the analysis) in the fasted state (PKD 14 128)

	Ln-Transformed Data					
Treatment A vs. C (n=42)						
PK Variables	**Least Squares Geometric Means[3]**		**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
	Treatment A	**Treatment C**				
AUC_{0-t}	283.22	333.77	84.86	71.99 to 100.02	46.96	0.1004
AUC_{0-inf}	296.55	347.89	85.24	73.06 to 99.46	43.80	0.0891
C_{max}	37.26	41.66	89.45	76.08 to 105.18	46.18	0.2532
Treatment B vs. C (n=44)						
	Treatment B	**Treatment C**	**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
AUC_{0-t}	339.79	339.51	100.08	94.50 to 106.00	16.09	0.9807
AUC_{0-inf}	351.75	353.51	99.50	94.21 to 105.10	15.31	0.8789
C_{max}	46.41	42.69	108.72	100.16 to 118.01	23.12	0.0939
Treatment B vs. A (n=43)						
	Treatment B	**Treatment A**	**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
AUC_{0-t}	328.40	282.33	116.32	98.68 to 137.11	47.68	0.1296
AUC_{0-inf}	340.08	295.38	115.13	99.31 to 133.47	42.43	0.1164
C_{max}	44.30	36.99	119.74	100.09 to 143.25	52.49	0.0984

[1]Least squares geometric means ratio calculated according to the following formula (example for Treatment A and C): $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (C)})} \times 100$

[2]90% geometric confidence interval using Ln-transformed data

[3]Least-square geometric means calculated from least-squares mean as $e^{(\text{least-square mean})}$

[4]p-value is for product effect

Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)

Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)

Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, page 0058-0060)

Reviewer's comment: *This study does not demonstrate BE between rosuvastatin 40 mg capsules (intact capsules) and Crestor® 40 mg tablets and between rosuvastatin 40 mg capsules sprinkling contents of capsule on applesauce and intact capsule. Bioequivalence was demonstrated between rosuvastatin 40 mg capsule (sprinkling content of capsule on applesauce) and Crestor® 40 mg tablet. Bioequivalence analysis (Appendix 1, Table 1A) conducted by the reviewer showed comparable outcomes to that reported by the sponsor (Table 11) for treatment comparisons A versus C and B versus A. For treatment comparison B versus C the 90% geometric C.I was wider (sponsor - AUC_{0-t} 94.50 to*

106.00, $AUC_{0\text{-}inf}$ 94.21 to 105.10, C_{max} 100.16 to 118.01; reviewer - $AUC_{0\text{-}t}$ 86.90 to 113.85, $AUC_{0\text{-}inf}$ 87.34 to 111.87, C_{max} 93.39 to 124.52) and CV% larger (sponsor - $AUC_{0\text{-}t}$ 16.09, $AUC_{0\text{-}inf}$ 15.31, C_{max} 23.12; reviewer - $AUC_{0\text{-}t}$ 39.06, $AUC_{0\text{-}inf}$ 35.76, C_{max} 42.01) than that reported by the sponsor, however BE was demonstrated between treatment B and C.

The sponsor performed a redosing study to evaluate and verify the anomalous response of Subjec (b) (6) The redosing study (Study number: PKD_14_291) was a randomized, open-label, three treatment, three period, six sequence, single dose, crossover relative bioavailability study conducted under fasting condition. The redosing study consisted of 5 subjects, Subject (b) (6), 2 control subjects and 2 standby control subjects who had participated in the fasting pivotal BE study (Study number: PKD_14_128). Treatment A, B (batch number: JKN2312A) and C (lot number: BK0033) were administered after subjects were fasted for at least 10 hours and subjects continued to fast for 4 hours after dosing. Water was not allowed from 1 hour prior to dosing and until 1 hour after dosing. Treatment A, B, and C was the same as for the fasting pivotal BE study and subjects received the treatments in the same sequence as in the fasting pivotal BE study. Plasma samples of Subject (b) (6) and the first two control subjects (Subject (b) (6) and (b) (6)) were assayed for rosuvastatin plasma concentrations. The blood samples of the two standby subjects were not analyzed since the control subjects did not dropout or withdraw from the study. The sponsor had specified a pre-defined criteria to conclude Subject (b) (6) as an outlier (Figure 4).

Subject can be concluded as outlier / anomalous if both the following conditions met.

- In the re-dosing study, if the % B / A and A / C ratio of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ for anomalous subjects falls between the minimum and maximum value of the main bio study (i.e. excluding the anomalous subject).
- The % B / A and A / C ratio of C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ in the re-dosing study for the two control subjects (who completes entire study) falls between the minimum and maximum test/reference ratios of main study (i.e. excluding the anomalous subject).

Figure 4: Criteria to conclude the subject as an outlier in the redosing study (PKD_14_291). (Main bio study: Refers to the fasting pivotal BE study (PKD_14_128). Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule) (test treatment), Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) (test treatment), Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet (reference treatment))

Rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule, Treatment A) in Subject (b) (6), and Subject's (b) (6) and (b) (6) (control subjects) are presented in Table 12. The sponsor reports that the PK parameters are comparable in all three subjects (Table 12). The percentage ratio of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} for B/A and A/C treatments for the three subjects are presented in Table 13. The sponsor reports that the A/C% ratio for C_{max} for Subject (b) (6) is not within the minimum and maximum test/reference ratio of the fasting pivotal BE study (Table 13). Therefore Subject (b) (6) could not be considered an outlier.

Table 12: Rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule, Treatment A) in Subject (b) (6) and two control subjects (Subject (b) (6) in the redosing study (PKD 14 291) in the fasted state

Subject	Rosuvastatin PK Parameters				
	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	T_{max} (h)	$t_{1/2}$ (h)
(b) (6)	35.61	343.78	348.14	0.67	7.52
	23.11	126.07	134.66	4.67	8.28
	39.47	285.39	291.71	0.67	7.70

Refe dix 2 for rosuvastatin PK parameters for rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) and Crestor® 40 mg tablet
Numbers are shown with two decimal places
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Patients excluded from efficacy analysis, Subjects-excluded-from-pk-or-stat-analysis, page 0026)

Table 13: Test/reference ratio of AUC_{0-t}, AUC_{0-inf}, and C_{max} in the redosing study (PKD_14_291) vs. range (minimum and maximum) of test/reference ratio of AUC_{0-t}, AUC_{0-inf}, and C_{max} in the fasting pivotal BE study (PKD_14_128, excluding Subject (b) (6)'s data)

For comparison B vs A

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Subject	**Ratio% B/A**	**Ratio% B/A**	**Ratio% B/A**
(b) (6) (Anomalous)	133.79	135.34	202.98
(b) (6) (Control)	170.19	166.16	130.89
(b) (6) (Control)	74.61	75.25	74.82
Range (Min)#	**58.10**	**56.46**	**48.55**
Range (Max)#	**213.69**	**214.74**	**295.69**

For comparison A vs C

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Subject	**Ratio% A/C**	**Ratio% A/C**	**Ratio% A/C**
(b) (6) (Anomalous)	84.09	77.85	43.57
(b) (6) (Control)	89.59	92.41	137.67
(b) (6) (Control)	83.65	83.68	66.66
Range (Min)#	**52.32**	**53.34**	**47.13**
Range (Max)#	**167.54**	**172.95**	**194.28**

Values taken from data of Main Study (Study Number: PKD_14_128) excluding anomalous subject number (b) (6)
* Not estimable as reference data is not available.
** Not estimable as test and reference data are not available

Refer to Appendix 3 for the test/reference ratio calculation for AUC_{0-t}, AUC_{0-inf}, and C_{max} conducted by the reviewer – outcomes were comparable to that reported by the sponsor
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Patients excluded from efficacy analysis, Subjects-excluded-from-pk-or-stat-analysis, page 0018)

As noted in the Table above, the redosing study results do not meet the pre-specified

criteria to conclude Subject [redacted] as an outlier. Despite these findings the sponsor's overall conclusion was that Subject [redacted] could be considered an outlier since the PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule, Treatment A) were comparable between Subject [redacted] and the 2 control subjects in the redosing study (Table 12). Based on this, the sponsor reports that the data for Subject [redacted] in the original fasting pivotal BE study was anomalous and therefore proceeded to conduct a sensitivity analysis excluding Subject [redacted] data. Summary statistics by treatment for rosuvastatin PK parameters excluding Subject [redacted] data are provided in Table 14. Statistical analysis of PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of rosuvastatin excluding Subject [redacted]'s data are presented in Table 15. The sponsor reports that excluding Subject [redacted] data results in the BE criteria been met for all three treatment comparisons. The T_{max} was comparable after administration of rosuvastatin 40 mg capsule (intact capsule) as compared to Crestor® 40 mg tablet (Table 14). The T_{max} occurred approximately one hour earlier after administration of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) when compared to Crestor® 40 mg tablet (Table 14).

Table 14: Summary statistics for rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (Subject [redacted] data excluded in the analysis) in the fasted state (PKD 14 128)

Treatment (No. of subjects)	Rosuvastatin PK Parameters[1]				
	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
A (n=42)	45.93 (23.63)	357.03 (189.95)	368.00 (192.48)	2.33 (0.33 – 4.67)	10.83 (4.81)
B (n=44)	54.97 (34.99)	396.22 (235.64)	407.72 (237.91)	1.67 (0.33 – 5.00)	10.27 (4.57)
C (n=43)	50.44 (29.38)	389.26 (213.20)	403.30 (220.49)	2.33 (0.33 – 5.00)	10.42 (6.30)

[1]Mean (±SD) vales for all PK estimates except for T_{max} which is reported as Median (range) values
Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)
Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)
Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet
Numbers are shown with two decimal places
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, pages 0043-0045)

Table 15: Bioequivalence and fasting effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (Subject (b) (6) data excluded in the analysis) in the fasted state (PKD_14_128)

	Ln-Transformed Data					
Treatment A vs. C (n=41)						
PK Variables	**Least Squares Geometric Means[3]**		**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
	Treatment A	**Treatment C**				
AUC_{0-t}	318.59	341.10	93.40	87.14 to 100.11	18.72	0.1055
AUC_{0-inf}	329.58	353.87	93.14	86.83 to 99.90	18.92	0.0956
C_{max}	41.51	42.47	97.75	89.67 to 106.55	23.36	0.6583
Treatment B vs. C (n=43)						
	Treatment B	**Treatment C**	**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
AUC_{0-t}	345.69	346.22	99.85	94.14 to 105.90	16.26	0.9655
AUC_{0-inf}	357.72	358.99	99.64	94.20 to 105.40	15.49	0.9155
C_{max}	46.83	43.45	107.79	99.19 to 117.13	23.09	0.1366
Treatment B vs. A (n=42)						
	Treatment B	**Treatment A**	**Ratio of Least-Squares Geometric Means %[1]**	**90% Geometric C.I.[2]**	**Intra-Subject CV%**	**p-value[4]**
AUC_{0-t}	332.19	312.98	106.14	99.18 to 113.58	18.56	0.1469
AUC_{0-inf}	343.93	324.04	106.14	99.48 to 113.25	17.73	0.1295
C_{max}	44.45	40.68	109.26	98.88 to 120.74	27.63	0.1432

[1]Least squares geometric means ratio calculated according to the following formula (example for Treatment A and C): $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (C)})} \times 100$

[2]90% geometric confidence interval using Ln-transformed data

[3]Least-square geometric means calculated from least-squares mean as $e^{(\text{least-square mean})}$

[4]p-value is for product effect

Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)

Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)

Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Study report body, Study –report, page 0043-0045)

Reviewer's Comment: The sponsor reports that they initially conducted all necessary clinical and bioanalytical investigations but failed to find a reason for the anomalous response observed for Subject (b) (6) The sponsor then proceeded to conduct a redosing study and the findings of this study showed that the PK of rosuvastatin in Subject (b) (6) was comparable to the two control subjects. We acknowledge that the requirements in the pre-defined criteria for Subject (b) (6) was not met, however the comparability of the PK estimates for Subject (b) (6) and the control subjects confirm that observations in the pivotal fasting BE study (PKD_14_128) occurred at random. The outlier issue was discussed with the Office of Clinical Pharmacology senior leadership team (OCP-SLT) and it was agreed that Subject (b) (6) can be considered as an outlier.

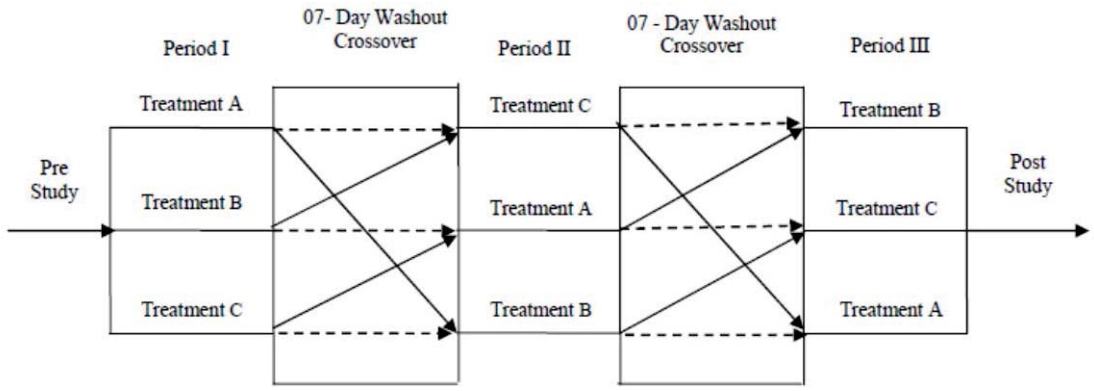
The sponsor has thus demonstrated BE between rosuvastatin 40 mg capsules (both intact capsule and sprinkling contents of capsule on applesauce) and Crestor® 40 mg tablets and between rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) and rosuvastatin 40 mg capsule (intact capsule) under fasting conditions. Bioequivalence analysis (Appendix 1, Table 1B) conducted by the reviewer showed comparable outcomes to that reported by the sponsor (Table 15) for all treatment comparisons.

2.5.2 Was bioequivalence established between rosuvastatin capsules (intact capsule and sprinkling contents of capsule on applesauce) and Crestor® tablets and between rosuvastatin capsules when sprinkling contents of capsule on applesauce and intact capsule in the fed state?

One pivotal BE study using the final formulation of rosuvastatin capsule (batch number: JKN2312A, rosuvastatin 40 mg capsule) was conducted to evaluate the fed state BE of rosuvastatin 40 mg capsule (intact capsule and sprinkling contents of capsule on applesauce) compared to the reference listed drug Crestor® 40 mg tablet. This pivotal study is described below.

Study PKD_14_129:

This was a randomized, open-label, three treatment, three period, six sequence, single dose, crossover relative bioavailability study under fed conditions. The study design is shown in Figure 5. Subjects were fasted for at least 10 hours and treatment A, B, and C (Figure 5) were administered 30 minutes after administration of a high-calorie high fat breakfast (986.59 Kcal). Subjects were fasted for a period of at least 5 hours post-dose. Water was not allowed from 1 hour prior to dosing and until 1 hour after dosing. The 48 healthy male subjects were randomized to 1 of the 6 sequences (ABC, BCA, CAB, ACB, CBA, BAC). Following dosing in Periods I, II, and III, PK blood samples were collected for 76 hours. There was a washout period of 7 days between periods I, II, and III. Out of the 48 subjects dosed, 45 subjects completed all three periods of the study, and 46 subjects completed at least two periods of the study. Plasma samples of the 45 subjects who completed all three periods of the study were assayed for rosuvastatin plasma concentrations.



Treatment A: Single oral dose of rosuvastatin 40 mg capsule administered with 240 mL (±2 mL) of water at ambient temperature in the morning (bioequivalence test treatment)

Treatment B: Single oral dose of rosuvastatin 40 mg capsule administered by opening the capsule and sprinkling the entire content on a teaspoonful (5 mL± 10%) of applesauce at room temperature and swallowed without chewing immediately or within 5 minutes after sprinkling the capsule content followed by 240 mL (±2 mL) of water at ambient temperature in the morning (bioequivalence test treatment)

Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet administered with 240 mL (±2 mL) of water at ambient temperature in the morning (bioequivalence reference treatment)

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-129-stf for pivotal fed study pkd-14-129, Study report body, Study –report, page 0019)

Figure 5: Study design for pivotal fed BE study (PKD_14_129)

The mean (±SD) rosuvastatin plasma concentration versus time profile is presented in Figure 6. Summary statistics by treatment for rosuvastatin PK parameters are provided in Table 16. Statistical analysis of PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of rosuvastatin and presented in Table 17.

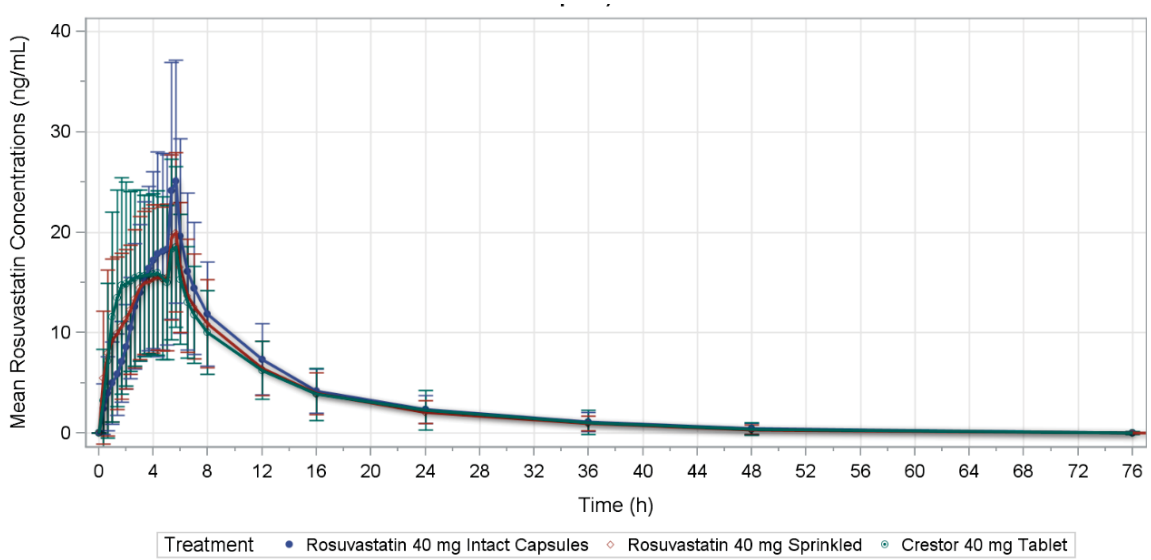


Figure 6: Mean plasma concentration time profile of rosuvastatin following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects in the fed state (n=45) (PKD_14_129)

Table 16: Summary statistics for rosuvastatin PK parameters following administration of rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects in the fed state (PKD_14_129)

Treatment (No. of subjects)	Rosuvastatin PK Parameters[1]				
	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
A (n=45)	26.09 (12.73)	224.19 (110.44)	234.69 (112.46)	5.67 (2.67 – 6.00)	10.29 (2.89)
B (n=45)	21.57 (9.26)	208.08 (93.44)	219.10 (96.90)	5.67 (0.67 – 5.67)	10.28 (4.18)
C (n=45)	23.31 (10.24)	214.01 (119.03)	223.80 (119.83)	4.67 (0.33 – 5.67)	10.07 (3.53)

[1]Mean (±SD) vales for all PK estimates except for T_{max} which is reported as Median (range) values
Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)
Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)
Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet
Numbers are shown with two decimal places
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-129-stf for pivotal fasting study pkd-14-129, Study report body, Study –report, pages 0053-0055)

Table 17: Bioequivalence and fed effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (PKD 14 129)

	Ln-Transformed Data					
Treatment A vs. C (n=45)						
PK Variables	Least Squares Geometric Means[3]		Ratio of Least-Squares Geometric Means %[1]	90% Geometric C.I.[2]	Intra-Subject CV%	p-value[4]
	Treatment A	Treatment C				
AUC_{0-t}	202.70	189.80	106.80	100.01 to 114.04	18.67	0.0996
AUC_{0-inf}	213.33	200.40	106.46	100.10 to 113.22	17.50	0.0950
C_{max}	23.58	21.23	111.09	102.58 to 120.31	22.75	0.0319
Treatment B vs. C (n=45)						
	Treatment B	Treatment C	Ratio of Least-Squares Geometric Means %[1]	90% Geometric C.I.[2]	Intra-Subject CV%	p-value[4]
AUC_{0-t}	190.25	189.78	100.25	93.66 to 107.30	19.33	0.9516
AUC_{0-inf}	200.85	200.31	100.27	93.92 to 107.04	18.59	0.9455
C_{max}	19.99	21.26	94.04	86.57 to 102.15	23.64	0.2182
Treatment B vs. A (n=45)						
	Treatment B	Treatment A	Ratio of Least-Squares Geometric Means %[1]	90% Geometric C.I.[2]	Intra-Subject CV%	p-value[4]
AUC_{0-t}	189.88	202.37	93.83	88.94 to 98.98	15.15	0.0517
AUC_{0-inf}	200.41	213.05	94.07	89.36 to 99.02	14.51	0.0513
C_{max}	19.95	23.53	84.81	79.53 to 90.44	18.23	0.0001

[1]Least squares geometric means ratio calculated according to the following formula (example for Treatment

A and C): $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (C)}} \times 100$
[2]90% geometric confidence interval using Ln-transformed data
[3]Least-square geometric means calculated from least-squares mean as $e^{(\text{least-square mean})}$
[4]p-value is for product effect
Treatment A: Single oral dose of rosuvastatin 40 mg capsule (intact capsule)
Treatment B: Single oral dose of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)
Treatment C: Single oral dose of Crestor® (rosuvastatin calcium) 40 mg tablet
(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-129-stf for pivotal fasting study pkd-14-129, Study report body, Study –report, page 0053-0055)

The sponsor concluded that under fed conditions, BE is demonstrated between rosuvastatin 40 mg capsule (both as intact capsule and sprinkling contents of capsule on applesauce) and Crestor® 40 mg tablet. However, the 90% CI for the C_{max} ratio between rosuvastatin 40 mg capsule (sprinkling contents on applesauce) and rosuvastatin 40 mg capsule (intact capsule) did not meet the pre-defined BE criteria. The sponsor reports that no clinical significance is attributed to the fact that the lower limit for the 90% CI for the C_{max} ratio is slightly below the 80-125% range (Table 17). The T_{max} was delayed by one hour after administration of rosuvastatin 40 mg capsule (both intact capsule and sprinkling contents on applesauce) when compared to Crestor® 40 mg tablet in the fed state (Table 16).

Reviewer's Comment: *The sponsor has demonstrated BE between rosuvastatin 40 mg capsule (intact capsule) and Crestor® 40 mg tablets under fed conditions. Although BE was not demonstrated between rosuvastatin 40 mg capsule (intact capsule) and rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) under fed conditions, the difference in C_{max} is unlikely to result in any clinical significance. Bioequivalence analysis (Appendix 1, Table 3A) conducted by the reviewer showed comparable outcomes to that reported by the sponsor (Table 17) for all treatment comparisons.*

2.6 Analytical

2.6.1 Is the analytical method for rosuvastatin used for the pivotal BE studies appropriately validated?

Plasma concentrations of rosuvastatin in the fasted and fed BE studies (PKD_14_128, PKD_14_129, and PKD_14_291 (redosing study)) were quantified using bioanalytical methods based on liquid chromatography/tandem mass spectrometry (LC/MS/MS). Rosuvastatin and the internal standard, rosuvastatin D3, were extracted from human plasma containing K_2 EDTA anticoagulant by solid phase extraction. Several bioanalytical methods were used for the extraction and analysis of rosuvastatin, with the methods differing with respect to the chromatography systems and settings, and mass spectrometry detectors and setting used (Table 18).

Table 18: Summary of bioanalytical methods and validation reports used in the pivotal studies

Pivotal Study Number	Analytical Method (Date)	Method Validation	Dates of Sample Receipt (No. of Samples)	Date of Sample Testing (No. of Samples)
Fasted Studies				
PKD_14_128	ATP_13_RVT Rev. 00 (11 June 2014) ATP_14_RVT Rev. 00 (16 June 2014) ATP_15_RVT Rev. 00 (17 June 2014) ATP_16_RVT Rev. 00 (2 July 2014)	MV_RVT_081C PMV_RVT_081C PMV_RVT_081CA PMV_RVT_081CB	Originals: 19 – 25 Jun 2014 (3510)\ Duplicates: 7 July 2014 (3509)	3 Jul – 17 Jul 2014 (3430 samples)
PKD_14_291	ATP_14_RVT Rev. 00 (16 June 2014)	MV_RVT_081C PMV_RVT_081C PMV_RVT_081CA PMV_RVT_081CB	Originals: 21-25 Nov 2014 (389 samples) Duplicates: 21-25 Nov 2014 (389 samples)	28 Nov – 1 Dec 2014 (233 samples)
Fed Studies				
PKD_14_129	ATP_13_RVT Rev. 00 (11 June 2014) ATP_14_RVT Rev. 00 (16 June 2014) ATP_15_RVT Rev. 00 (17 June 2014)	MV_RVT_081C PMV_RVT_081C PMV_RVT_081CA PMV_RVT_081CB	Originals: 6 – 18 Jun 2014 (3839 samples) Duplicates: 6 – 18 Jun 2014 (3838 samples)	18 Jun – 4 Jul 2014 (3779 samples)

ATP_13_RVT Rev.00: Estimation of rosuvastatin in human K2EDTA plasma using ultra performance liquid chromatography method with tandem mass spectrometry – API-3200
ATP_14_RVT Rev.00: Estimation of rosuvastatin in human K2EDTA plasma using Ultra high performance liquid chromatography method with tandem mass spectrometry – API-4000
ATP_15_RVT Rev.00: Estimation of rosuvastatin in human K2EDTA plasma using ultra performance liquid chromatography method with tandem mass spectrometry – micromass Quattro premier-XE
ATP_16_RVT Rev.00: Estimation of rosuvastatin in human K2EDTA plasma using ultra high performance liquid chromatography method with tandem mass spectrometry – API4000
MV_RVT_081C: Method validation; PMV-RVT_081C/081CA/081CB: Partial method validation
(Source: Ezallor NDA, Module 2.7.1, Summary of biopharmaceutic studies and associated analytical methods, page 25)

The bioanalytical methods were validated for rosuvastatin concentrations ranging from 0.400 ng/mL to 120.060 ng/mL. Rosuvastatin concentrations were determined by linear regression, with a weighting factor of $1/x^2$. The bioanalytical methods were validated for analyzing rosuvastatin in plasma samples in terms of recovery, linearity, accuracy, precision, and sensitivity. An overview of the bioanalytical method validation (MV_RVT_081C) and bioanalytical partial method validation (PMV_RT_081C, PMV_RT_081CA, PMV_RT_081CB) parameters are presented in Table 19 and Table 20, respectively.

Table 19: Overview of bioanalytical method validation MV_RVT_081C for rosuvastatin

Analyte	Rosuvastatin	
Internal Standard (IS)	Rosuvastatin D_3	
Limit of quantitation (ng/mL)	LLOQ : 0.400 LLOQ[1]:0.400 ULOQ: 120.060 ULOQ[1]: 120.003	
Relative recovery of analyte	QC Low A: 76.8%, QC Med B: 75.4%, QC High : 86.5%	
Absolute recovery of analyte	QC Low A: 75.2%, QC Med B: 73.3%, QC High : 82.3%	
Relative recovery of IS	78.4%	
Absolute recovery of IS	76.0%	
Standard curve concentrations (ng/mL)	0.400, 0.800, 4.002, 18.009, 54.427, 76.038, 92.046, 120.060 0.400, 0.800, 4.000, 18.001, 54.402, 76.002, 92.003, 120.003[1]	
QC concentrations (ng/mL)	Low QC A: 1.200 Low QC B: 3.599 Medium QC A : 25.989 Medium QC B : 55.977 High QC : 95.961 DQC: 194.921	Low QC A: 1.199[1] Low QC B: 3.597[1] Medium QC A : 25.977[1] Medium QC B : 55.951[1] High QC : 95.916[1]
QC Intraday precision	1.2% – 11.7%	
QC Interday precision	1.2% – 18.8%	
QC Intraday accuracy	91.0% – 102.9%	
QC Interday accuracy	86.0% – 103.4%	
Bench-top stability	8 hours at room temperature (in Plasma) 2 hours at room temperature (in Blood)	
Stock solution stability	10 days at -20°C	
Post-Processed stability	70 hours at 6°C	
Post Extraction Bench Top Stability	8 hours at room temperature	
Freeze-thaw stability (cycles)	3 cycles at -20±5°C, -35±5°C and -65±10°C	
Long term storage stability	83 days at -20±5°C, -35±5°C and -65±10°C	
Dilution integrity	1.5-3 × ULOQ concentration (194.921 ng/mL) diluted 5 folds	
	% Accuracy : 1/5th : 92.0%	
	% Precision: 1/5th: 3.2%	
Selectivity	No interference observed in blank plasma samples	

Source: Method Validation Report MV_RVT_081C
[1]Freshly prepared for long term stability in matrix experiment

(Source: Ezallor NDA, Module 2.7.1, Summary of biopharmaceutic studies and associated analytical methods, page 26)

Table 20: Overview of bioanalytical partial method validations (PMV_RT_081C, PMV RT 081CA, PMV RT 081CB) for rosuvastatin

Parameter	PMV_RT_081C	PMV_RT_081CA	PMV_RT_081CB
Analyte	Rosuvastatin	Rosuvastatin	Rosuvastatin
Internal Standard (IS)	Rosuvastatin D_3	Rosuvastatin D_3	Rosuvastatin D_3
Limit of quantitation (ng/mL)	LLOQ : 0.408 ULOQ: 119.852	LLOQ : 0.408 ULOQ: 119.852	LLOQ : 0.400 ULOQ: 119.674
Standard curve concentrations (ng/mL)	0.408, 0.815, 4.077, 18.345, 55.034, 77.455, 93.762, 119.852	0.408, 0.815, 4.077, 18.345, 55.034, 77.455, 93.762, 119.852	0.400, 0.800, 4.002, 18.011, 54.434, 76.047, 92.057, 119.674
QC concentrations (ng/mL)	Low QC A: 1.213 Low QC B: 3.693 Medium QC A : 25.875 Medium QC B : 56.601 High QC : 97.031	Low QC A: 1.213 Low QC B: 3.639 Medium QC A : 25.875 Medium QC B : 56.601 High QC : 97.031	QC Low-A : 1.201 QC Low-B : 3.602 QC Med-A : 28.174 QC Med-B : 56.028 QC High : 96.048 DQC : 197.599
QC Intraday precision	1.2 – 8.4%	0.7% – 5.3%	1.8 – 10.5%
QC Interday precision	1.1 – 11.6%	0.4% – 9.0%	1.6 – 10.5%
QC Intraday accuracy	88.6 – 103.7%	92.5% – 109.2%	91.4 – 110.0%
QC Interday accuracy	88.6 – 105.4%	92.5% – 109.5%	91.4 – 110.0%
Post-Processed stability	--	61 hours at 6°C	--
Selectivity	No interference observed in blank plasma samples		

Source: Partial Method Validation Reports PMV_RVT_081C, PMV_RVT_081CA, PMV_RVT_081CB
[1]Freshly prepared for long term stability in matrix experiment

(Source: Ezallor NDA, Module 2.7.1, Summary of biopharmaceutic studies and associated analytical methods, page 27)

Reviewer's comment: *For bioanalytical method validation MV_RVT_081C (Table 19) the QC interday precision is reported as 1.2% – 18.8% (%C.V.). The 18.8% value (%C.V.) is associated with the LLOQ samples. Therefore the precision for the LLOQ sample did not exceeded 20% of the C.V. Additionally, the precision for the remaining QC samples (low QC, medium QC, high QC, upper limit QC, diluted QC) did not exceeded 15% of the C.V.*

3. Labeling Comments

The following are the labeling recommendations relevant to clinical pharmacology for NDA208647. The ~~red strikeout font~~ is used to show the proposed test to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

2.7 Administration of Sprinkle Capsules

Oral Administration

For patients who have difficulty swallowing capsules, the rosuvastatin capsules can be opened, the (b) (4) filled in the capsule sprinkled on one teaspoon (b) (4) of applesauce and (b) (4) swallowed immediately, without chewing. The mixture should not be stored for future use. If the (b) (4) /applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

Nasogastric Tube (≥16 French) Administration

For patients who have a nasogastric tube in place, Rosuvastatin capsules can be opened and the intact (b) (4) emptied into a syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The (b) (4) in rosuvastatin may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16-French) and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the (b) (4) the nasogastric tube should be flushed with additional water. USE IN OTHER LIQUIDS (b) (4) IS (b) (4) NOT RECOMMENDED.

12.3 Pharmacokinetics

Drug-Drug Interactions:
Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Rosuvastatin is a substrate for certain (b) (4) transporter proteins including the hepatic uptake transporter organic anion-transporting polyproteins 1B1 (OATP1B1) and efflux transporter (b) (4) breast cancer resistance protein (BCRP). Concomitant administration of rosuvastatin with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors) may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy [*see Dosage and Administration (2.5)*]. (b) (4) (b) (4)

(b) (4)

Table 2. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	Rosuvastatin		
		Mean Ratio (ratio with/without coadministered drug) No Effect = 1	
	Dose (mg)[1]	Change in AUC	Change in C_{max}
Cyclosporine - stable dose required (75 mg to 200 mg BID)	10 mg QD for 10 days	7.1[2]	11[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3 to 3.4)[3]	3.2[2] (2.6 to 3.9)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	2.1[2] (1.7 to 2.6)[3]	5[2] (3.4 to 6.4)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6 to 2.2)[3]	2.2[2] (1.8 to 2.7)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4 to 1.7)[3]	2 (1.8 to 2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	1.5 (1 to 2.1)[3]	2.4 (1.6 to 3.6)[3]
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	1.4 (1.2 to 1.6)[3]	2.2 (1.8 to 2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2 to 1.6)[3] 1.3 (1.1 to 1.4)[3]	1.4 (1.2 to 1.5)[3] 1.2 (0.9 to 1.4)[3]
Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	1.2 (0.9 to 1.6)[3]	1.2 (0.8 to 1.6)[3]
[redacted]			
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7	10 mg	↔	1.2

(b) (4)

days			(1.1 to 1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid Administered simultaneously	40 mg	0.5[2] (0.4 to 0.5)[3]	0.5[2] (0.4 to 0.6)[3]
Administered 2 hours apart	40 mg	0.8 (0.7 to 0.9)[3]	0.8 (0.7 to 1)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1 (0.8 to 1.2)[3]	1 (0.7 to 1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1 to 1.3)[3]	1.1 (0.9 to 1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8 (0.7 to 0.9)[3]	0.7 (0.5 to 0.9)[3]

[1] Single dose unless otherwise noted.
[2] Clinically significant [*see Dosage and Administration (2) and Warnings and Precautions (5)*]
[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease, 11=11 fold increase in exposure)

17 PATIENT COUNSELING INFORMATION

Administration Options

Oral Administration

For patients who have difficulty swallowing capsules, the rosuvastatin capsules can be opened, the [(b) (4)] filled in the capsule sprinkled on one teaspoon [(b) (4)] of applesauce and [(b) (4)] swallowed immediately, without chewing. The mixture should not be stored for future use. If the [(b) (4)]/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

Rosuvastatin Capsules - Nasogastric Tube (≥16 French) Administration

For patients who have a nasogastric tube in place, Rosuvastatin capsules can be opened and the intact [(b) (4)] emptied into a syringe and mixed with 40 mL of water. Replace the plunger and shake the syringe vigorously. The [(b) (4)] in rosuvastatin may start dissolving which is acceptable. Attach the syringe to a nasogastric tube (≥16-French) and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the [(b) (4)] the nasogastric tube should be flushed with additional water. USE IN OTHER LIQUIDS [(b) (4)] IS [(b) (4)] NOT RECOMME

PATIENT INFORMATION

Instructions for Use

Rosuvastatin capsules with applesauce:

For patients who have difficulty swallowing capsules, the rosuvastatin capsules can be opened, the [(b) (4)] filled in the capsule sprinkled on one teaspoon [(b) (4)] of applesauce and [(b) (4)] swallowed immediately, without chewing. The mixture should not be stored for future use. If the [(b) (4)]/applesauce mixture is not used in its entirety, the remaining mixture should be discarded immediately.

4. Appendix

Appendix 1: Bioequivalence and fasting/fed effect comparison for study PKD_14_128 and PKD_14_129 conducted by the reviewer

Table 1A: Bioequivalence and fasting effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (Subject (b) (6) data included in the analysis) in the fasted state (PKD 14 128)

	Ln-Transformed Data[1]				
Treatment A vs. C (n=42)					
PK Variables	**Least Squares Geometric Means[4]**		**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
	Treatment A	**Treatment C**			
AUC_{0-t}	284.197	334.612	84.93	74.03 to 97.35	39.06
AUC_{0-inf}	297.680	348.783	85.35	75.24 to 96.80	35.76
C_{max}	37.443	41.781	89.62	77.44 to 103.73	42.01
Treatment B vs. C (n=44)					
	Treatment B	**Treatment C**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	332.847	334.612	99.47	86.90 to 113.85	39.06
AUC_{0-inf}	344.776	348.783	98.85	87.34 to 111.87	35.76
C_{max}	45.046	41.781	107.82	93.39 to 124.52	42.01
Treatment B vs. A (n=43)					
	Treatment B	**Treatment A**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	332.847	284.197	117.12	102.30 to 134.20	39.06
AUC_{0-inf}	339.925	295.678	114.96	101.53 to 130.24	35.62
C_{max}	44.272	37.016	119.60	103.51 to 138.16	41.78

[1]PK parameters calculated using Phoenix32

[2]Least squares geometric means ratio calculated according to the following formula (example for Treatment A and C): $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (C)})} \times 100$

[3]90% geometric confidence interval using Ln-transformed data

[4]Least-square geometric means calculated from least-squares mean as $e^{(\text{least-square mean})}$

Table 2A: Bioequivalence and fasting effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects (Subject (b) (6) data excluded in the analysis) in the fasted state (PKD_14_128)

	Ln-Transformed Data[1]				
Treatment A vs. C (n=41)					
PK Variables	**Least Squares Geometric Means[4]**		**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
	Treatment A	**Treatment C**			
AUC_{0-t}	318.668	342.170	93.13	87.23 to 99.44	18.04
AUC_{0-inf}	329.946	355.093	92.92	87.12 to 99.11	17.60
C_{max}	41.631	42.624	97.67	89.32 to 106.81	24.79
Treatment B vs. C (n=43)					
	Treatment B	**Treatment C**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	340.199	342.170	99.42	93.17 to 106.04	18.04
AUC_{0-inf}	352.041	355.093	99.14	93.06 to 105.60	17.60
C_{max}	45.639	42.624	107.07	98.01 to 116.93	24.79
Treatment B vs. A (n=42)					
	Treatment B	**Treatment A**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	340.199	318.668	106.76	99.99 to 113.96	18.04
AUC_{0-inf}	344.129	323.722	106.30	99.77 to 113.30	17.53
C_{max}	44.466	40.622	109.46	100.21 to 119.57	24.63

[1]PK parameters calculated using Phoenix32

[2]Least squares geometric means ratio calculated according to the following formula (example for Treatment A and C): $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (C)} \times 100$

[3]90% geometric confidence interval using Ln-transformed data

[4]Least-square geometric means calculated from least-squares mean as $e^{(least\text{-}square\ mean)}$

Table 3A: Bioequivalence and fed effect comparison for rosuvastatin 40 mg capsule (intact capsule), rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce), and Crestor® 40 mg tablet in healthy subjects in the fed state (PKD_14_129)

	Ln-Transformed Data[1]				
Treatment A vs. C (n=45)					
PK Variables	**Least Squares Geometric Means[4]**		**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
	Treatment A	**Treatment C**			
AUC_{0-t}	202.599	189.641	106.83	100.43 to 113.63	17.62
AUC_{0-inf}	213.234	200.193	106.51	100.43 to 112.97	16.79
C_{max}	23.573	21.235	111.01	103.07 to 119.57	21.47
Treatment B vs. C (n=45)					
	Treatment B	**Treatment C**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	190.149	189.641	100.27	94.27 to 106.59	17.62
AUC_{0-inf}	200.758	200.193	100.28	94.60 to 106.37	16.79
C_{max}	19.967	21.235	94.03	87.23 to 101.31	21.47
Treatment B vs. A (n=45)					
	Treatment B	**Treatment A**	**Ratio of Least-Squares Geometric Means %[2]**	**90% Geometric C.I.[3]**	**Intra-Subject CV%**
AUC_{0-t}	190.149	202.599	93.85	88.22 to 99.77	17.62
AUC_{0-inf}	200.758	213.234	94.15	88.77 to 99.77	16.79
C_{max}	19.967	23.573	84.70	78.65 to 91.30	21.47

[1]PK parameters calculated using Phoenix32

[2]Least squares geometric means ratio calculated according to the following formula (example for Treatment A and C): $e^{(LSM\ Treatment\ (A) - LSM\ Treatment\ (C)} \times 100$

[3]90% geometric confidence interval using Ln-transformed data

[4]Least-square geometric means calculated from least-squares mean as $e^{(least\text{-}square\ mean)}$

Appendix 2: PK parameters following administration of rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce) and Crestor® 40 mg tablet in Subject (b) (6), (b) (6) and (b) (6) in the redosing study (PKD_14_291) in the fasted state

Subject	Rosuvastatin PK Parameters				
	Rosuvastatin 40 mg capsule (sprinkling contents of capsule on applesauce)				
	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	T_{max} (h)	$t_{1/2}$ (h)
(b) (6)	72.27	459.93	471.18	0.67	8.21
	30.25	214.56	223.75	1.67	14.74
	29.53	212.92	219.50	1.33	6.09
	Crestor® 40 mg tablet				
	81.72	408.82	447.19	0.33	19.16
	16.78	140.72	145.72	4.67	6.06
	59.21	341.15	348.61	0.67	11.52

Numbers are shown with two decimal places

(Source: Ezallor NDA, Module 5.3.1.2, Study pkd-14-128-stf for pivotal fasting study pkd-14-128, Patients excluded from efficacy analysis, Subjects-excluded-from-pk-or-stat-analysis, page 0027-0028)

Appendix 3: Test/reference ratio of AUC_{0-t}, AUC_{0-inf}, and C_{max} in the redosing study (PKD_14_291) conducted by the reviewer

For Comparison B vs. A[1]			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Subject	Ratio% B/A	Ratio% B/A	Ratio% B/A
(b) (6)	133.79	135.34	202.98
	170.19	166.16	130.89
	74.61	75.26	74.82

For Comparison A vs. C[1]			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Subject	Ratio% A/C	Ratio% A/C	Ratio% A/C
(b) (6)	84.09	77.85	43.57
	89.59	92.29	137.67
	83.65	83.68	66.66

[1]PK parameters calculated using Phoenix32

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

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/s/

SHALINI WICKRAMARATNE SENARATH YAPA
05/23/2016

JAYABHARATHI VAIDYANATHAN
05/23/2016