CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208647Orig1s000

CLINICAL REVIEW(S)

Medical Officer 505(b)(2) NDA Review
Division of Metabolism and Endocrine Products

NDA – 208647

Name of drug – Ezallor (rosuvastatin capsules)

Applicant – Sun Pharma Global FZE

Date of Submission – June 18, 2018

PDUFA Goal Date – December 18, 2018

Medical Reviewer – Mary D. Roberts, M.D.

This is a Class 2 Resubmission for approval of Ezallor (rosuvastatin) capsules in dosage in dosage strengths of 5, 10, 20, and 40 mg for 3 treatment indications:

- Hypertriglyceridemia: Adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia
- Primary dysbetalipoproteinemia (Type III hyperlipoproteinemia: An adjunct to diet for the treatment of adult patients with primary dysbetalipoproteinemia
- Homozygous familial hypercholesterolemia: Adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia

The product is designed to facilitate dosing in patients who may find it difficult to swallow a tablet, as the capsule may be swallowed intact or the contents sprinkled onto applesauce or administered via a nasogastric tube. The applicant is relying on the published literature and FDA's safety and efficacy findings for the Reference Listed Drug (RLD), Crestor (rosuvastatin calcium – in tablet form), along with the results of a 30-day non-clinical bridging study and two pivotal clinical bioavailability studies. Crestor manufactured by AstraZeneca, was approved under NDA 21366 in 2003.

In the initial application cycle, the applicant established bioequivalence between Ezallor and Crestor. There were no clinical, clinical pharmacology, or non-clinical deficiencies (please see the clinical review dated May 27, 2016 for further details). However, the Office of Pharmaceutical Quality (OPQ) recommended a complete response due to deficiencies at the manufacturing facility. A Complete Response Letter was issued June 22, 2016.

The applicant, with this current Class 2 resubmission, has addressed the deficiencies and has undergone an inspection of the manufacturing facility, which resulted in a No Action

Indicated classification. In the resubmitted NDA, the facilities reviewer found the firms used in the manufacturing process and quality testing to be acceptable. The OPQ review team recommends approval based on the updated information.

No new pharmacology/toxicology, clinical pharmacology has been submitted to the application. The applicant has provided an updated safety assessment of rosuvastatin that did not reveal a safety concern which would change the risk-benefit profile for this product. The establishment of bioequivalence still holds per the review of the biopharmaceutical review team.

Labeling has been reviewed, including a review of the pediatric carve out language and PLLR labeling by Division of Pediatrics & Maternal Health (DPMH) and Office of the Chief Counsel (OCC). Their recommendations on labeling regarding the language and placement of the pediatric disclaimers have been conveyed to the applicant.

The applicant proposed to use the name Ezallor which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was determined to be acceptable.

The application was reviewed by the PeRC PREA subcommittee on 18 November 2015 and was granted a full waiver for pediatric studies for the sought after treatment indications because studies are impossible or highly impractical. However, in 2017, the innovator conducted a trial using Crestor to treat pediatric patients 7 years to 17 years of age with homozygous familial hypercholesterolemia and received a pediatric HoFH treatment indication. Therefore, it was the opinion of DPMH that the justification for not conducting pediatric trials under PREA for this indication should be revised. The PeRC PREA subcommittee reviewed this application on 12 December 2018. A partial waiver of studies of HoFH in patients from birth to less than 7 years of age because studies would be impossible or highly impractical was granted, as well as a deferral for patients 7 years and older until the pediatric and orphan exclusivities expire. Once these exclusivities expire, the labeling can be updated to include the protected pediatric information and the PREA requirement can be considered fulfilled.

RECOMMENDATION

No deficiencies were noted in the clinical review of this product. Ezallor was well tolerated and was consistent with the known safety profile of the reference listed drug, Crestor. Issues with the manufacturing facility for this product, have been resolved per the OPQ review team. This reviewer concurs with the OPQ review team for approval of this product.

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

/s/

MARY D ROBERTS
12/17/2018

JOHN M SHARRETTS
12/17/2018

Medical Officer 505(b)(2) NDA Review
Division of Metabolism and Endocrine Products

NDA – 208647

Name of drug – Ezallor (rosuvastatin capsules)

Applicant – Sun Pharma Advanced Research Company Ltd. (SPARC)

Date of Submission – August 28, 2015

PDUFA Goal Date – June 28, 2016

Medical Reviewer – Mary D. Roberts, M.D.

Sun Pharma Advanced Research Company, Ltd. (SPARC) has submitted a 505(b)(2) New Drug Application (NDA) to the Division on August 28, 2015, for a new formulation, rosuvastatin capsules, in dosage strengths of 5, 10, 20, and 40 mg for 3 treatment indications:

- Hypertriglyceridemia: Adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia
- Primary dysbetalipoproteinemia (Type III hyperlipoproteinemia: An adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia
- Homozygous familial hypercholesterolemia: Adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia

The product is designed to facilitate dosing in patients who may find it difficult to swallow a tablet, as the capsule may be swallowed intact or the contents sprinkled onto applesauce, or administered via a nasogastric tube. The applicant is relying on the published literature and FDA's safety and efficacy findings for the Reference Listed Drug (RLD), Crestor (rosuvastatin calcium – in tablet form), along with the results of a 30-day non-clinical bridging study and two pivotal clinical bioavailability studies. Crestor manufactured by AstraZeneca, was approved under NDA 21366 in 2003.

Drug in study

The drug product is rosuvastatin capsules, referred to in this document as RosuvaCaps. Rosuvastatin acts by competitively blocking the HMG-CoA reductase enzyme. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, a critical step in cholesterol biosynthesis. Therefore inhibition of HMG-CoA's enzymatic action by rosuvastatin reduces cholesterol formation in the liver and results in up-regulation of

LDL receptors which transports LDL-C from the blood into the liver, lowering LDL-C values in the bloodstream.

Regulatory history

- 23 December 2013, a pre-IND meeting was requested. A PIND file was opened for this product and the applicant was advised to submit background information regarding the proposed development plan with questions for the Division.
- Following submission of questions to the Division, written responses dated 21 February 2014, were sent to the applicant requesting submission of an Initial Pediatric Study Plan, confirming the need for a comparative bridging toxicity study, and the acceptability of two bioavailability studies for the 505(b)(2) application: (a) a single-dose fasting study comparing RosuvaCaps 40 mg (test) intact and sprinkled on applesauce compared with Crestor 40 mg (reference), and (b) a single-dose study comparing RosuvaCaps 40 mg (test) intact and sprinkled on applesauce compared to Crestor 40 mg (reference) under fed conditions for filing the submission. Questions regarding biowaivers for the lower doses of RosuvaCaps and dissolution studies were addressed. The Division agreed that if the RosuvaCaps and Crestor were shown to be bioequivalent in all dosing conditions, additional clinical studies would not be required prior to submission of the NDA. The Division requested a summary of safety for rosuvastatin be included in a NDA submission using information from the applicant's studies, available published literature, databases, and labeled safety information from the reference listed drug.
- On 18 May 2015, a pre-NDA teleconference was held, preliminary comments to questions were sent 13 May 2015, and the final meeting minutes were received 15 June 2015. The meeting discussed the Division's expectations regarding dissolution testing, information required to support a biowaiver request, and adequacy of the nasogastric in-use studies. The Division commented that if data submitted at the time of the original NDA submission used only applesauce as the soft food tested, the labeling may be explicitly restrictive. The Division reiterated that the adequacy of the non-clinical and clinical studies to support approval of the product would ultimately be a review issue.

Biopharmaceutical Studies Submitted to NDA 208647

The applicant submitted 8 pilot studies conducted with developmental formulations of the to-be-marketed product. These studies are not the subject of this review as they are not considered the basis for establishing bioequivalence with the listed drug. The clinical pharmacology review briefly discusses these studies; please refer to this review for further details if needed.

The applicant submitted 2 pivotal studies to support approval of RosuvaCaps.

- PKD_14_128 – Single-dose bioequivalence study under fasting conditions
- PKD_14_129 – Single-dose bioequivalence study under fed conditions

These studies as well as a redosing study were reviewed in detail by Dr. Shalini Wickramaratne Senarath Yapa from the Office of Clinical Pharmacology. The clinical pharmacology review team recommends approval of this product, following thorough review and consideration, including a discussion of the appropriateness of excluding an outlier's data with the Office of Clinical Pharmacology senior leadership team. Please see Dr. Wickramaratne Senarath Yapa's review for further details.

The biowaiver request for the lower strengths of rosuvastatin was submitted along with in vitro dissolution data to support the request. Following review of in vitro dissolution data by the biopharmaceutics reviewer, the biowaiver request was granted.

Sun Pharma has submitted debarment certification for both of these studies.

STUDY SUMMARIES

PK_14_128

This was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover, bioequivalence (BE) study of the following 3 formulations of rosuvastatin.

- Treatment A: RosuvCaps 40 mg intact,
- Treatment B: RosuvaCaps 40 mg sprinkled on applesauce, and
- Treatment C: Crestor® 40 mg tablets

Treatments were administered under fasting conditions to 48 (42 completed) healthy Indian men. Subjects fasted for at least 10 hours before dosing and at least 4 hours post-dose in each period. The interval between dosing periods was at least 7 days. No subjects had taken any prescription medications and over-the-counter products 14 days prior to dosing in Period I, up to last sample collection in each period and during the washout periods.

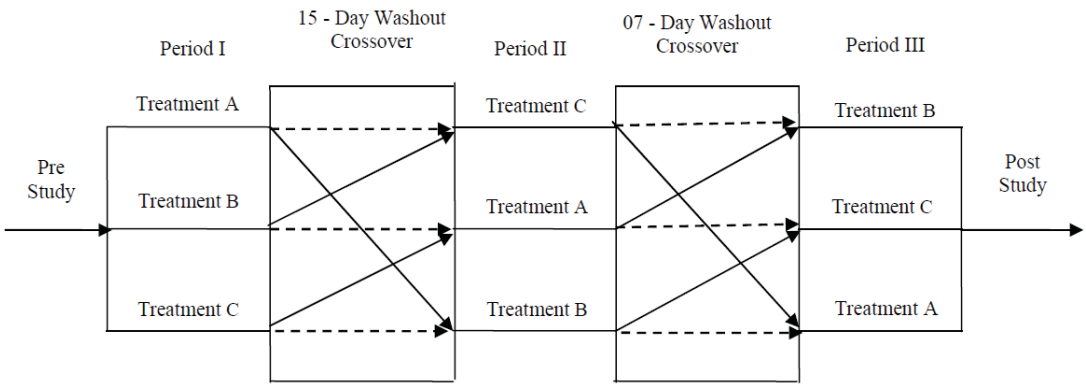


Figure 1. PK_14_128 Study schematic

As shown in Table 1, the 90% confidence interval for the geometric mean ratio of the BE metrics between test and reference products were within the prespecified bounds of 80% -125%. Therefore, RosuvaCaps was bioequivalent to Crestor under fasting conditions.

Table 1. RosuvaCaps PK parameters from the pivotal fasted study PKD_14_128

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

[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 (b) (6)

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: Adapted from Table 1, Dr. Shalini Wickramaratne Senarath Yapa's NDA 208647 clinical pharmacology review

Demographics

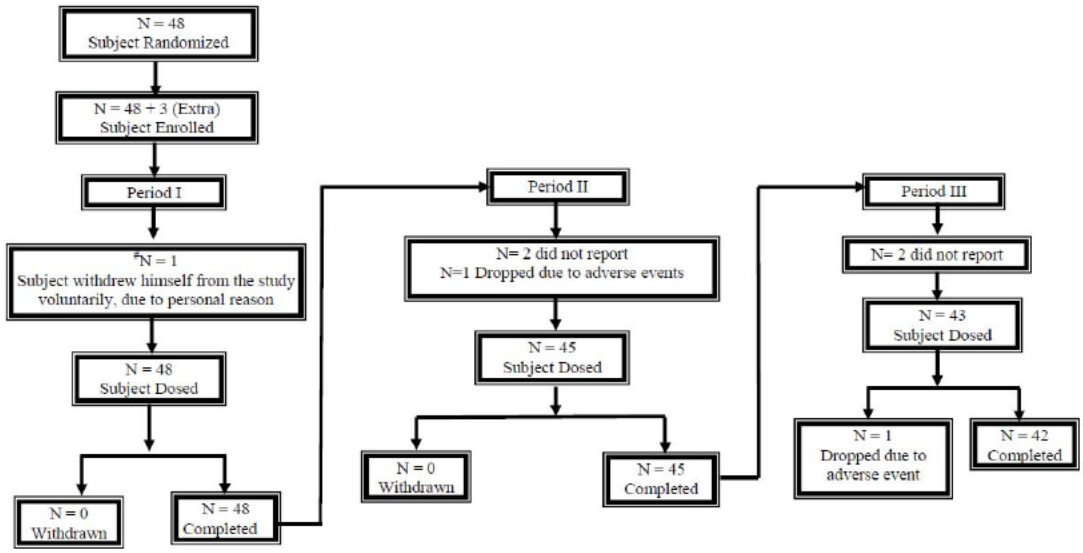
A total of 48 healthy Indian men were dosed. The mean age was 33.8 years (range 23-44 years), BMI was 22.09 kg/m^2 (range 18.7 -25 kg/m^2).

Safety

Disposition

A total of 48 adult healthy Indian men were dosed, of these 6 subjects discontinued.

The following flow chart describes when discontinuations occurred during the study.



N = 42 Subjects Completed the Study.

#Subject number (b) (6) withdrew himself from the study voluntarily, due to personal reason before dosing in period-I and was replaced with extra subject (subject number (b) (6))

Four of the subjects did not report a reason for discontinuation. Two subjects ((b) (6) and (b) (6)) discontinued due to adverse events (abdominal pain, vomiting). Narratives of the 6 subjects who discontinued are summarized below.

- Subject (b) (6): 42 year old Asian man received RosuvaCaps 40 mg sprinkled in the first treatment period and Crestor 40 mg tablets in Period II. Two days after receiving dosing with RosuvaCaps sprinkled, the patient had elevated ALT and AST (see table below) both <2xULN. These events were judged by the Investigator to be mild in intensity and possibly related to study treatment. The elevation in liver transaminases was considered resolved at the Period II check-in with a normal AST and only slightly elevated ALT. Two days following dosing with Crestor 40 mg, the patient had elevated ALT and AST. He withdrew from the study with reason given as "other". A post-study assessment, 6 days following Period II dosing showed elevated ALT and slightly elevated AST. No further follow-up was done.

Table 2. Subject (b) (6) laboratory values

Laboratory Values:

Visit		Date / Time	Liver Function		
			ALT (U/L)	AST (U/L)	Total bilirubin (mg/dL)
Screening (pre-dose)		(b) (6)	42.57	32.61	0.19
Period I	Check in (pre-dose)		42.57	32.61	--
	Check out (2 days post dose 1)		**72.32***	**76.78***	--
Period II	Check in (13 days post dose 1)		**45.22**	36.31	**--**
	Check out (2 days post dose 2)		**62.04**	**60.46**	--
Period III	Check in (5 days post dose 2)	Not dosed in Period III†			
	Check out (2 days post dose 3)				
Follow up (6 days post dose 2)		(b) (6)	**81.79**	**47.31**	--

Normal Range: ALT: 9.00 – 43.00 U/L; AST: 9.00 – 37.00 U/L; total bilirubin: 0.20 – 1.20 mg/dL
* Reported as an AE; **Bold**=value outside normal range
†Subject withdrew from study on (b) (6)

- Subjec (b) (6): 28 year old Asian man who received a single dose of RosuvaCaps 40 mg intact. The patient did not report any adverse events. There were no abnormalities in laboratory or vital signs. The patient did not report to Period II.
- Subject (b) (6): 24 year old Asian man received RosuvaCaps 40 mg sprinkled in the first treatment period. Fourteen days after dosing with RosuvaCaps sprinkles and before dosing in Period II, the patient experienced the adverse events of abdominal pain and vomiting, which led to study withdrawal due to these events and administration of concomitant medications (1 dose each of IM diclofenac and IV ondansetron). These events resolved the same day. At follow-up the next day, the patient had an AST of 91.65 U/L (>2x and <3x ULN), increased white blood cell (17.8 units not provided) and neutrophil counts (16) and decreased lymphocyte count (0.8). The subject was reported to be clinically well and asymptomatic, with stable vital signs. He was prescribed oral ciprofloxacin 500 mg, linezolid 600 mg, and ranitdine 150 mg to be all taken twice daily for 10 days. The subject returned for follow-up 25 days after receiving the 1 time dose of RosuvaCaps 40 sprinkles. The patient was asymptomatic, AST level was normal at 23.92 U/L as well as other laboratory values.
- Subjec (b) (6) 29 year old Asian man who received a single dose of Crestor 40 mg. The patient did not report any adverse events. There were no abnormalities in laboratory values or vital signs. The patient did not report to Period II.
- Subject (b) (6): 35 year old Asian man who received treatment with Crestor 40 mg in Period 1 and RosuvaCaps sprinkled in Period II and received RosuvaCaps intact in Period III. Approximately 20 minutes after receiving RosuvaCaps intact the patient vomited twice with no other complaints and stable vital signs. The patient did not have any other adverse events and within 30 minutes symptoms had resolved. The patient did not have abnormalities in laboratory values throughout the study.
- Subject (b) (4) 43 year old Asian man who received a single dose of RosuvaCaps sprinkled in Period I, RosuvaCaps intact in Period II, and was not dosed in Period III as he elected to withdraw from the study with the reason for discontinuation as "other" 5 days after receiving the RosuvaCaps intact 40 mg dose in Period II. The patient returned for a post-study assessment, 14 days following Period II dosing with RosuvaCaps intact. The laboratory values were notable for an elevated ALT

(right at 3x ULN) and AST (>3xULN <5xULN). No bilirubin was drawn. The events were judged by the Investigator to be mild in intensity. The patient was reportedly well and laboratory assessments were to be repeated in 10 days. The patient returned after a phone call was placed and had laboratory values repeated 33 days after the RosuvaCaps 40 mg intact dose. The ALT and AST values were within normal limits and events were considered resolved.

Table 3. Subject (b) (6) laboratory values

Laboratory Values:

Visit		Date / Time	Liver Function		
			ALT (U/L)	AST (U/L)	Total bilirubin (mg/dL)
Screening (pre-dose)		(b) (6)	15.90	18.55	0.14
Period I	Check in (pre-dose)		15.90	18.55	--
	Check out (2 days post dose 1)		18.13	17.78	--
Period II	Check in (13 days post dose 1)		12.29	16.66	--
	Check out (2 days post dose 2)		14.46	15.26	--
Period III	Check in (5 days post dose 2)	Not dosed in Period III†			
	Check out (2 days post dose 3)				
Follow up 1 (14 days post dose 2)		(b) (6)	**133.06***	**127.71***	--
Follow up 2 (33 days post dose 2)			19.37	29.16	

Normal Range: ALT: 9.00 – 43.00 U/L; AST: 9.00 – 37.00 U/L; total bilirubin: 0.20 – 1.20 mg/dL
* Reported as an AE; **Bold**=value outside normal range
†Subject withdrew from study on (b) (6)

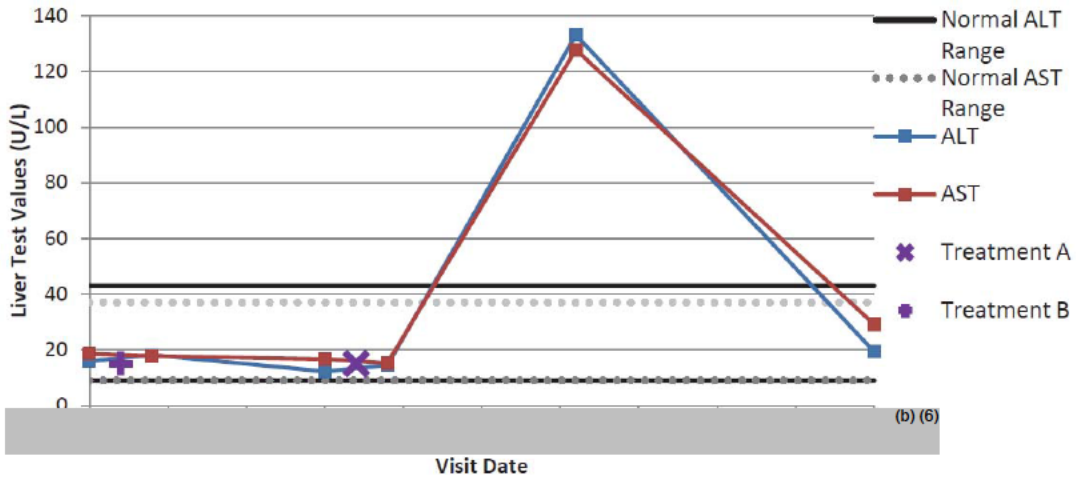


Figure 2. Subject (b) (6) graph of lab values over time

Adverse Events

Volunteers were queried about adverse events (AE) during clinical examinations, during daily vital sign recordings, check out (~48 h post-dose), ambulatory blood sample (76 hours post dose) and washout period. Blood samples for safety assessments included a complete blood count, chemistry profile (glucose, urea, creatinine, total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, total cholesterol), and urinalysis which were done at screening and at the end of the study (complete blood

count, ALT, AST, urea, creatinine, urinalysis). Pre-dose and 48 hours post-dose in each treatment period, ALT and AST levels were collected.

Reviewer comment: CK values were not collected. However, no subjects reported musculoskeletal related adverse events.

No serious adverse events (AE) were reported. A total of 48 subjects were exposed to at least 1 dose of a rosuvastatin test or reference product. The number of subjects exposed within each treatment formulation differs due to patient discontinuation. A total of 16 post-dose (includes AE outside the treatment emergent period) adverse events were reported in 7 subjects. Two (4.2%) subjects as summarized above (subject # (b) (6)) discontinued due to adverse events (vomiting and abdominal pain/vomiting). The majority of AEs were related to elevations in liver transaminases which occurred in a total of 6 (12.5%) subjects.

The following tables list the treatment-emergent AEs. One subject is not included in the treatment-emergent time period. This subject (b) (6) had asymptomatic elevated ALT and AST 14 days following dosing with RosuvaCaps intact (Treatment A).

Tables with treatment-emergent AEs

Table 4. Summary of subjects with treatment-emergent adverse events

	Intact RosuvaCaps N=45 n (%)	Sprinkled RosuvaCaps N=46 n (%)	Crestor N=45 n (%)
SAE	0	0	0
TEAE	2 (4.4)	3 (6.5)	2 (4.4)
DAE	1 (2.4)	1 (2.2)	0

Source: Adapted from PK_14_128 Table, Page 51
Subject (b) (6) is excluded from this table as this AE was considered to occur outside the treatment-emergent period

Table 5. Number (%) of subjects with treatment-emergent adverse events

	Intact RosuvaCaps N=45 n (%)	Sprinkled RosuvaCaps N=46 n (%)	Crestor N=45 n (%)
Total subjects with TEAE	**2 (4.4)**	**3 (6.5)**	**2 (4.4)**
Vomiting	1 (2.2)	1 (2.2)	0
Abdominal pain	0	1 (2.2)	0
ALT increased	1 (2.2)	1 (2.2)	2 (4.4)
AST increased	0	3 (6.5)	1 (2.2)
WBC increased	0	1 (2.2)	0
Neutrophil decreased	0	1 (2.2)	0
Lymphocyte decreased	0	1 (2.2)	0

Source: Adapted from PK_14_128 Table
Subject (b) (6) is excluded from this table as this AE was considered to occur outside the treatment-emergent period

PK_14_129 – Food Effect study

This was an open-label, single-dose, randomized, three-period, six-sequence, three-treatment, crossover, food effect bioavailability study. A single dose of either of the 3 following formulations of rosuvastatin was administered 30 minutes after a high fat/calorie breakfast to 47 healthy Indian men.

- Treatment A: RosuvCaps 40 mg intact,
- Treatment B: RosuvaCaps 40 mg sprinkled on applesauce, and
- Treatment C: Crestor® 40 mg tablets

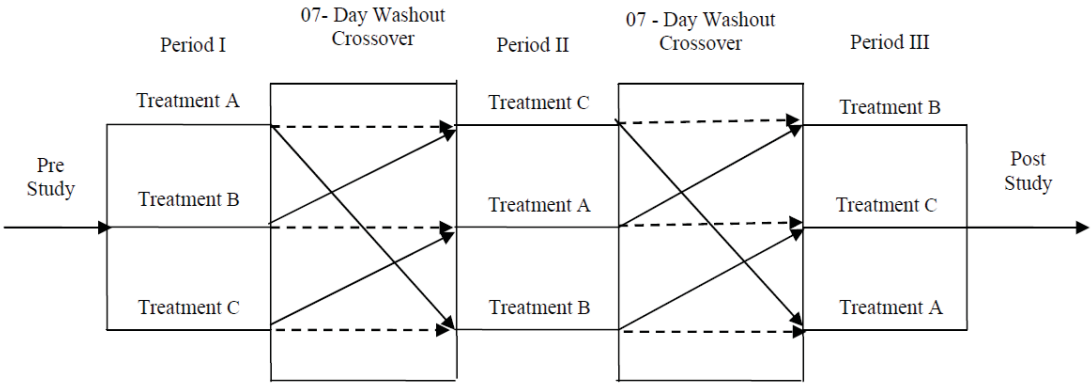


Figure 3. PK_14_129 Study schematic

Table 6: RosuvaCaps PK parameters from the pivotal fed study PKD_14_129

Study	Treatment Comparisons	PK Parameters	Bioequivalence		
			Ratio of Least-Squares Geometric Means %[1]	90% Geometric C.I.[2]	Intra-Subject CV%
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 $e^{(\text{LSM Treatment (A)} - \text{LSM Treatment (C)})} \times 100$

[2]90% geometric confidence interval using Ln-transformed data
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: Adapted from Table 1, Dr. Shalini Wickramaratne Senarath Yapa's NDA 208647 clinical pharmacology review 208647

As shown in Table 6, the 90% confidence interval for the geometric mean ratio under fed conditions for the test and reference products were within the prespecified bounds of 80% -125%. Therefore, RosuvaCaps was bioequivalent to Crestor under fed conditions.

Demographics

A total of 48 healthy Indian men were randomized. The mean age was 30 years (range 18-43 years), BMI was 21.8 kg/m^2 (range 18.6 -26.5 kg/m^2).

Safety
Disposition
A total of 48 subjects were randomized, 47 subjects were dosed, and 45 subjects completed all 3 periods of the study. One subject discontinued prior to any dosing due to incomplete consumption of breakfast in Period 1, two subjects discontinued post-dose – 1 for an adverse event during Period II and the other did not report for treatment in Period II.

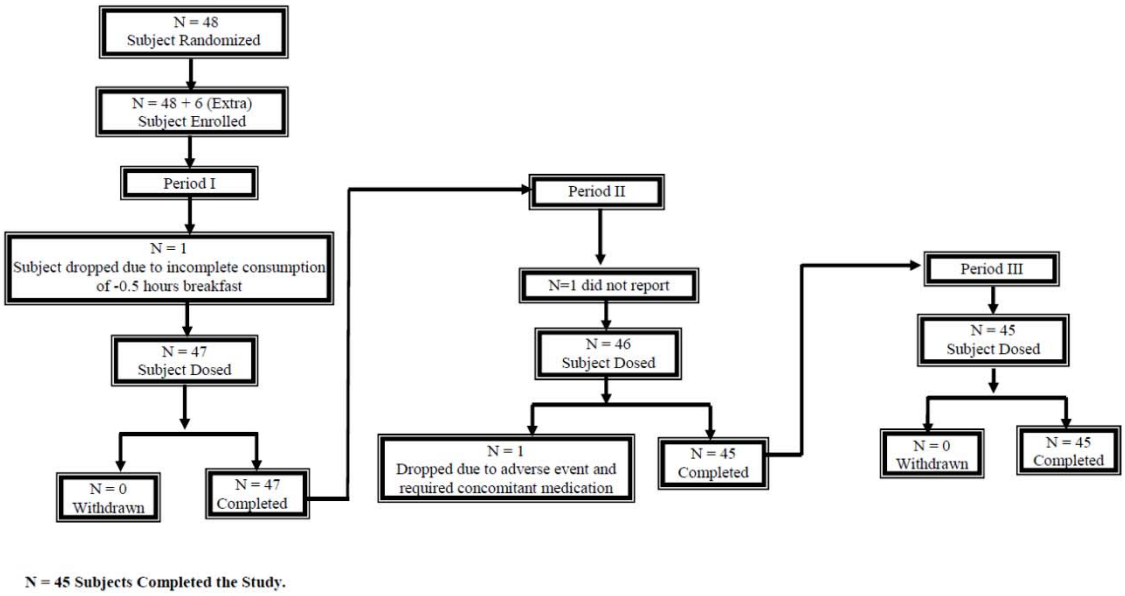


Figure 4. Disposition of subjects PK_14_129
Source: CSR PK_14_129, Chart 16.2.1

Volunteers were queried about adverse events (AE) during clinical examinations, during daily vital sign recordings, check out (~48 h post-dose), ambulatory blood sample (76 hours post dose) and washout period. Blood samples for safety assessments included a complete blood count, chemistry profile (glucose, urea, creatinine, total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, total cholesterol), and urinalysis which were done at screening and at the end of the study (complete blood count, ALT, AST, urea, creatinine, urinalysis). Pre-dose and 48 hours post-dose in each treatment period, ALT and AST levels were collected.

Reviewer comment: CK values were not collected. However, no subjects reported musculoskeletal related adverse events.

No serious adverse events (AE) were reported. A total of 47 subjects were exposed to at least 1 dose of a rosuvastatin test or reference product. The number of subjects exposed within each treatment formulation differs due to patient discontinuation. A total of 9 subjects (19.1%) experienced 19 post-dose adverse events which were all considered

during the treatment-emergent period. One subject discontinued due to adverse events (vomiting). The majority of AEs were related to elevations in liver transaminases which occurred in a total of 8 (17.0%) subjects, 3 subjects had elevations in transaminases in two treatment periods.

The following tables list the treatment-emergent AEs.

Table 7. Overall number (%) of subjects with treatment-emergent adverse events

	Intact RosuvaCaps N=47 n (%)	Sprinkles RosuvaCaps N=46 n (%)	Crestor N=45 n (%)
SAE	0	0	0
TEAE	4 (8.5)	5 (10.9)	3 (6.7)
DAE	0	1 (2.2)	0

Source: Adapted from PK_14_129 Table Section 14.3.1

Table 8. Number (%) of subjects with treatment-emergent adverse events by preferred terms

	Intact RosuvaCaps N=45 n (%)	Sprinkles RosuvaCaps N=46 n (%)	Crestor N=45 n (%)
Total subjects with TEAE	**4 (8.5)**	**5 (10.9)**	**3 (6.7)**
Vomiting	0	1 (2.2)	0
ALT increased	4 (8.5)	4 (8.7)	3 (6.7)
AST increased	3 (6.4)	1 (2.2)	3 (6.7)

Source: Adapted from PK_14_129 Table Section 14.3.1

Subjects with elevations in liver transaminases – Pivotal Studies

There were 14 (14.7%) of the 95 Indian men treated with a rosuvastatin formulation with an elevation in liver transaminases. This table includes Subject (b) (6) with elevated LFTs in the post-study follow-up period, 14 days after receiving a single dose of 40 mg RosuvaCaps intact.

Subject	Lab Test	Screening	Period I		Period II		Period III		Follow Up	
			Check in	Check out	Check in	Check out	Check in	Check out	Follow up 1:	Follow up 2:
Study PKD_14_128										
Subject (b) (6)	AST	32.61	32.61	**76.78* (B)**	36.31	**60.46 (C)**	--	--	**47.31**	--
	ALT	42.57	42.57	**72.32*(B)**	**45.22**	**62.04 (C)**	--	--	**81.79**	--
Subject (b) (6)	AST	32.48	32.48	22.42	25.80	--	--	--	**91.65* (B)**	23.92
Subject (b) (6)	AST	18.55	18.55	17.78	16.66	15.26	--	--	**127.71* (N/A)**	29.16
	ALT	15.90	15.90	18.13	12.29	14.46	--	--	**133.06* (N/A)**	19.37
Subject (b) (6)	AST	22.87	22.87	36.46	31.12	**89.80 (B)**	33.08	**107.00* (C)**	22.18	--
	ALT	15.21	15.21	31.46	19.78	**66.75 (B)**	30.11	**82.62* (C)**	15.25	--
Subject (b) (6)	ALT	**55.12**	38.26	**86.95* (A)**	**43.15**	**62.11 (B)**	**58.89**	**69.64 (C)**	--	--
Subject	ALT	16.42	16.42	**90.32* (C)**	32.86	**61.06 (B)**	**71.94**	**78.27 (C)**	--	--
Study PKD_14_129										
Subject (b) (6)	ALT	30.01	34.61	**55.29 (C)**	**60.45**	**90.50* (B)**	**63.17**	**72.51 (A)**	--	--
Subject	ALT	22.29	23.53	32.49	26.62	36.55	**47.94**	**119.04* (A)**	**65.25**	--
Subject (b) (6)	AST	25.91	25.91	**57.96 (A)**	32.81	**72.95* (C)**	**48.33**	**88.47* (B)**	34.74	--
	ALT	28.09	28.09	**68.82 (A)**	**44.78**	**111.40* (C)**	**60.50**	**140.31* (B)**	**62.44**	--
Subject (b) (6)	AST	**47.15**	**47.15**	**80.08* (A)**	**52.15**	**55.63 (B)**	**48.33**	**66.02 (C)**	--	--
	ALT	**51.17**	**51.17**	**106.39* (A)**	**74.75**	**92.03* (B)**	**60.50**	**75.98 (C)**	--	--
Subject (b) (6)	ALT	13.39	13.39	12.43	13.50	16.01	12.01	**87.37* (B)**	14.39	--
Subject	AST	33.82	33.82	**226.19* (C)**	**37.98**	**57.01 (A)**	23.17	31.05	--	--
	ALT	30.42	30.42	**202.68* (C)**	**77.86**	**80.99 (A)**	27.97	27.36	--	--
Subject (b) (6)	AST	32.40	32.40	27.27	29.64	27.28	32.53	**166.12* (A)**	19.07	--
	ALT	23.41	23.41	24.18	24.75	28.80	29.13	**171.40* (A)**	21.88	--
Subject (b) (6)	AST	**40.97**	**40.97**	**165.75* (C)**	**38.18**	**116.42* (A)**	**43.46**	29.19	--	--
	ALT	33.79	33.79	**249.93* (C)**	**70.27**	**180.92* (A)**	**76.70**	32.40	--	--

Normal Ranges: ALT: 9.00 - 43.00 (U/L); AST: 9.00 -37.00 (U/L)
*Adverse event (lab test value is > 2× the upper limit of normal range or based on the discretion of the investigator)
-- = Dropped/withdrawn subject
A=treatment with Rosuvastatin Capsules, 40 mg Intact
B=treatment with Rosuvastatin Capsules, 40 mg Sprinkled
C=treatment with Crestor® Tablets, 40 mg
N/A=no treatment

The incidence of treatment-emergent adverse events of liver enzyme elevations was equally distributed across treatment formulations as shown in the table below.

Table 9. Treatment emergent adverse events – pivotal BE studies pooled

Adverse Event	n (%)		
	Rosuvastatin Capsules, 40 mg		Crestor® Tablets, 40 mg
	Intact	Sprinkled	
N	**92**	**92**	**90**
Investigations			
Alanine aminotransferase increased	5 (5.4)	5 (5.4)	5 (5.5)
Aspartate aminotransferase increased	3 (3.3)	4 (4.3)	4 (4.4)
White blood cell count increased	0	1 (1.1)	0
Neutrophil count increased	0	1 (1.1)	0
Lymphocyte count decreased	0	1 (1.1)	0
Gastrointestinal Disorders			
Vomiting	1 (1.1)	2 (2.2)	0
Abdominal pain	0	1 (1.1)	0

Source: Studies PKD_14_128 and PKD_14_129 Clinical Reports

There were no treatment emergent elevations in ALT >3x ULN, in study PKD_14_128 (fasting), and only one patient with an elevation in AST >3xULN.

In study PKD_14_129 (fed), there were 4 subjects with ALT >3x ULN, one of which was >5x ULN with concomitant increase in AST (Subject (b) (6)). Narratives of subjects with ALT >3x ULN are presented below. All subjects were asymptomatic. In subjects were follow-up information was available, these elevations resolved.

Review of the narratives show there were 2 subjects treated with Crestor with elevations in ALT >3x ULN (Subject (b) (6) and (b) (6); 1(Subject (b) (6)) following treatment with RosuvaCaps sprinkled, and 2 (Subject (b) (6) and (b) (6) following dosing with RosuvaCaps intact. There were no clinically relevant differences, in this reviewer's opinion, in the incidence of categorical elevations across treatment formulations.

The applicant was asked to compare the PK data of subjects with and without elevated liver enzymes, to determine if there were exposure differences that could account for the elevations in liver enzymes. As shown in the graphs below, subjects with elevated liver enzymes did not consistently have higher average levels of rosuvastatin exposure compared to subjects without elevated liver enzymes.

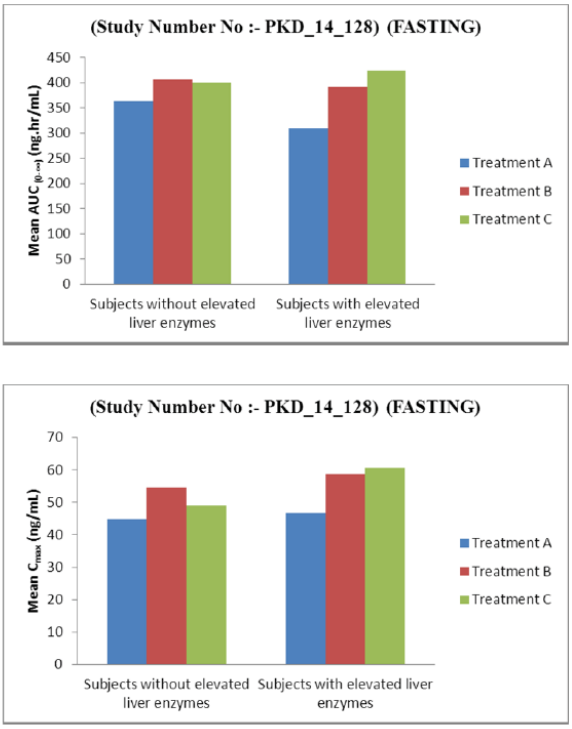
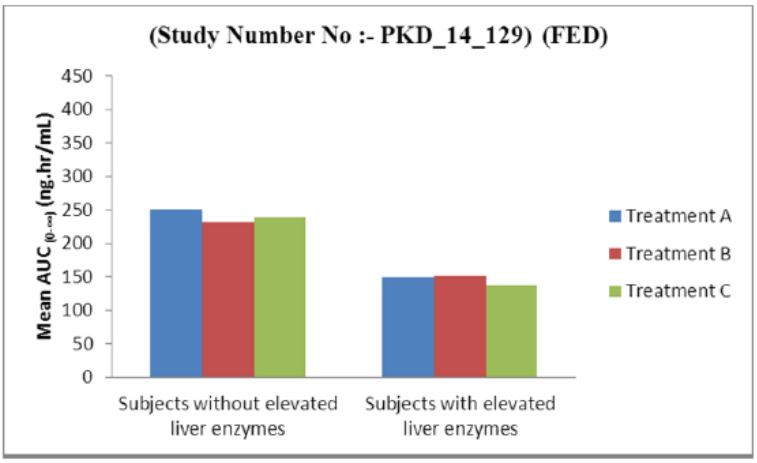


Figure 5. Graphical comparison of PK parameters between subjects with and without elevated liver enzymes (PK_14_128)
Source: Response to FDA IR; Submitted 27 November 2015; Page 16



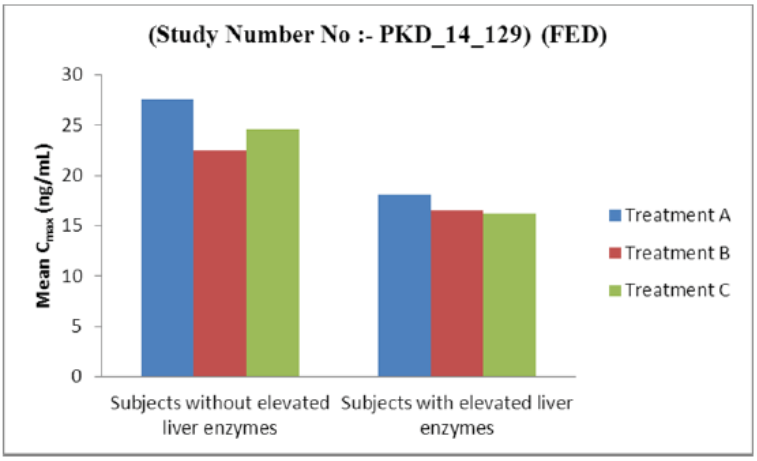


Figure 6. Graphical comparison of PK parameters between subjects with and without elevated liver enzymes (PK_14_129)
Source: Response to FDA IR; Submitted 27 November 2015; Page 16

Narratives

- Subject (b) (6): See earlier description of this patient's experience in patient discontinuation narratives. This patient's excursion in liver enzymes is not counted as a treatment-emergent event.

- Subject (b) (6): 41 year old man randomized to the following treatment sequence: RosuvaCaps 40 mg intact, Crestor 40 mg, RosuvaCaps 40 mg sprinkled. ALT and AST were within normal limits at screening: ALT 28.09 U/L; AST 25.91 U/L. Two days following treatment with RosuvaCaps 40 mg intact, ALT and AST were slightly elevated but less than 2x ULN. At the beginning of dosing Period II levels had normalized for AST and were returning to normal for ALT. Two days following treatment with Crestor, ALT was 111.40 U/L (>2x ULN normal range: 9-43 U/L) and AST 72.95 (>2x ULN normal range: 9-37 U/L). Levels were trending toward normal limits at the start of the 3rd dosing period, but were again elevated 2 days following dosing with RosuvaCaps 40 mg sprinkled (ALT 140.31 >3X ULN; AST 88.47>2x ULN).). The subject was reportedly asymptomatic and was treated with Vitamin B

complex and advised to abstain from alcohol and high protein foods. Subject returned for a follow-up visit 7 days following last dose and AST had returned to normal 34.74 U/L and ALT was trending towards normal 62.44 U/L.

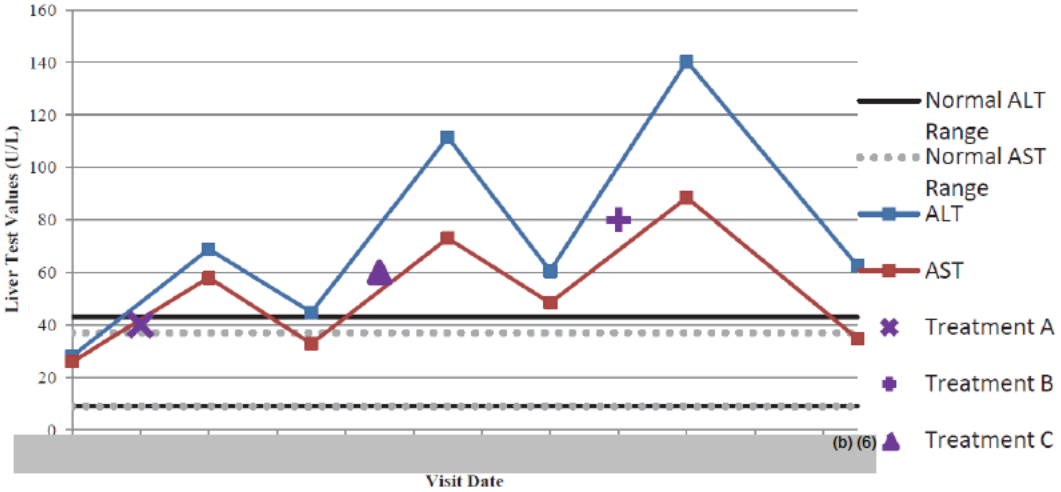


Figure 7. Laboratory values over time: Subject (b) (6) PK_14_129

- Subject (b) (6): 36 year old man randomized to the following treatment sequence: Crestor 40 mg, RosuvaCaps 40 intact, RosuvaCaps 40 mg sprinkled. ALT and AST at screening were 30.42 U/L and 33.82 U/L, respectively. Two days following dosing with Crestor 40 mg, ALT was 202.68 U/L ((>3X ULN – normal range: 9-43 U/L) and AST 226.19 U/L (>3x ULN -- normal range: 9-37 U/L). The subject was reportedly asymptomatic and was treated with Vitamin B complex and advised to abstain from alcohol and high protein foods. At Period II check in, his liver enzymes were slightly elevated but markedly improved. The subject continued in the study. Liver enzymes remained slightly elevated following dosing with RosuvaCaps 40 mg intact. The liver enzymes returned to baseline by the final dosing period and remained normal through the end of the study.

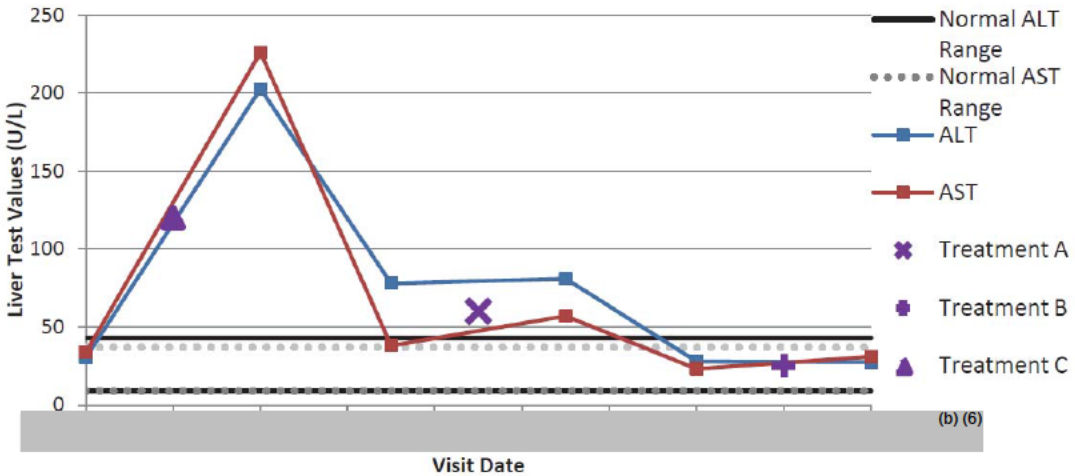


Figure 8. Laboratory values over time: Subject (b) (6) PK_14_129

- Subjec (b) (6): 29 year old man randomized to following treatment sequence: Crestor 40 mg, RosuvaCaps 40 mg sprinkled, RosuvaCaps 40 mg intact. ALT and AST at screening were 23.41 U/L and 32.4 U/L, respectively. Liver enzymes remained within normal limits after subject received single doses of Crestor 40 mg and RosuvaCaps 40 mg sprinkled. Two days following dosing with RosuvaCaps 40 mg intact, the subject's ALT was 171.40 U/L (>3X ULN – normal range: 9-43 U/L) and AST of 166.12 U/L (>3x ULN -- normal range: 9-37 U/L). The subject was asymptomatic and treated with Vitamin B complex and advised to abstain from alcohol and avoid high protein foods. Follow-up 12 days after dose of RosuvaCaps 40 mg intact, liver enzymes were within normal range

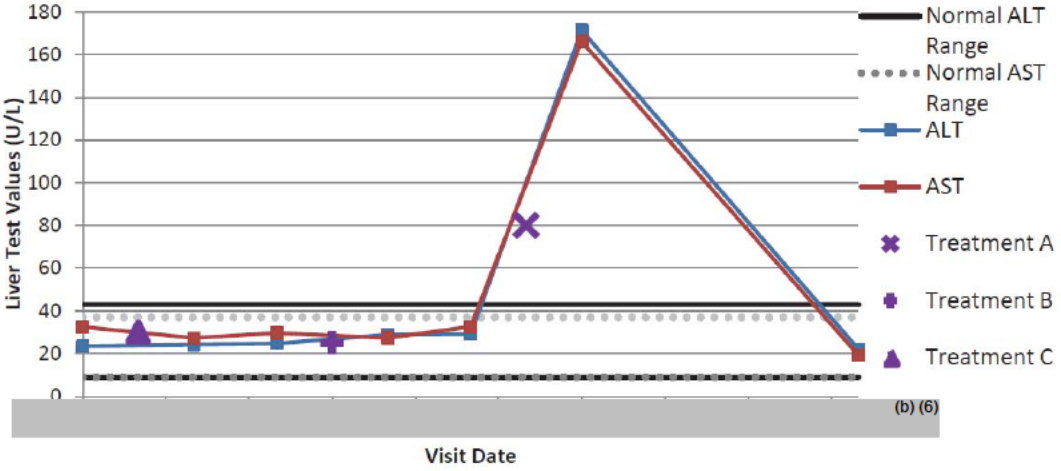


Figure 9. Laboratory values over time: Subject (b) (6) PK_14_129

- Subject (b) (6): 33 year old man randomized to following treatment sequence: Crestor 40 mg, RosuvaCaps 40 mg intact, RosuvaCaps 40 mg sprinkled. ALT of 249.93 U/L (>5X ULN -- normal range: 9-43U/L) and AST of 165.75 U/L (>3x ULN -- normal range: 9-37 U/L), were reported two days after Period I dosing with Crestor Tablets 40 mg. The subject was reportedly asymptomatic and was treated with Vitamin B complex and advised to abstain from alcohol and high protein foods. At Period II check in, his liver enzymes were slightly elevated but markedly improved. ALT (180.92 U/L) >3x ULN and elevated AST (116.42 U/L) 2 days following dosing with RosuvaCaps 40 mg as intact capsule. The subject was asymptomatic, treated with Vitamin B, and given dietary advice. The subject continued in the study, received a 3rd dose of rosuvastatin (RosuvaCaps sprinkled) and liver enzymes were within normal limits on (b) (6) (ALT 32.4 U/L; AST 29.19 U/L)

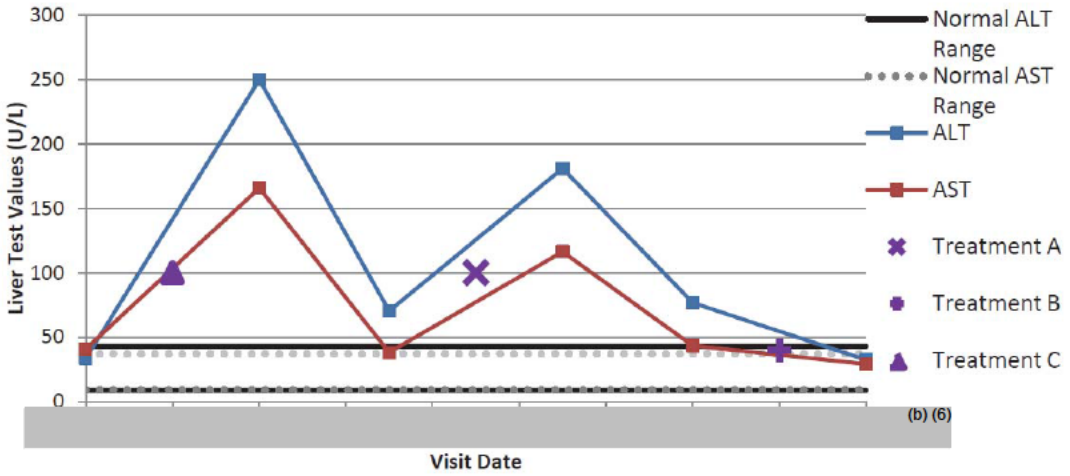


Figure 10. Laboratory values over time: Subject (b) (6) PK_14_129

Reviewer comment: Elevations in liver enzymes have been reported with statins, including rosuvastatin. In the RosuvaCaps bioequivalence studies, asymptomatic increases in liver transaminases occurred with similar frequency across all rosuvastatin formulations and resolved or improved. Review of the safety information from the two pivotal bioequivalence studies does not raise any new safety concerns.

Literature Search

The applicant submitted an Integrated Summary of Safety (ISS) and a 120-day safety update report (SUR) which included a search of the literature published between 1 July 2014 (the date of the approved Crestor® label at the version approved at the time of the Pre-NDA meeting) and 21 May 2015 for the ISS and from the ISS cut off up to 2 December 2015 for the 120-day SUR. In addition, three reviews published by The Cochrane Collaboration were assessed as were controlled trials published since April 2011 (in a search performed for the ISE).

The ISS and 120-day SUR literature searches identified a total of 215 and 150 unique citations, respectively. The output was reviewed by a medical professional (Pharm.D.). All of the titles and abstracts, the latter as available, were reviewed for information that could contribute important clinical data that describes safety-related effects that are not already in the approved label for Crestor® (July 2014 for ISS and November 2015 for 120-day SUR). According the applicant, most citations were general reviews of "statins", hyperlipidemia studies of various statins alone or in combination with other drugs or treatment modalities, discussed the anti-inflammatory effects of rosuvastatin for off labeled indications, involved use of rosuvastatin as a BCRP, OATP, or OAT3 probe in vitro, or described known safety issues (e.g., muscular or hepatic adverse effects).

Ultimately, seven publications pertaining to clinical safety were retrieved for further review to identify potential new safety information and are incorporated into this ISS and 120-day SUR. These case reports are summarized below.

- Annigeri and Mani[1] report a case of renal function impairment associated with rosuvastatin in a 54-year-old man who had previously experienced biopsy proven acute interstitial nephritis following atorvastatin therapy. He had recovery of renal function following withdrawal of the atorvastatin and steroid therapy. Six months later, he was initiated on rosuvastatin (10 mg) following acute myocardial infarction after which there was a gradual increase in SCr by 0.5 mg/dl over the baseline to a peak value of 1.8 mg/dl. SCr spontaneously returned to baseline gradually over the next 2 months after withdrawal of rosuvastatin.

Reviewer comment: The clinical significance of this case report is unclear, however, continued pharmacoviligiance for statins effect on renal function is warranted.

- Kamada et al[2] describe a case of Takotsubo cardiomyopathy, a disorder characterized by left ventricular apical ballooning with preceding emotional and/or physical stressors. This condition is also an important differential diagnosis of acute coronary syndrome. The authors report this condition was triggered by delayed-onset rhabdomyolysis (patient on rosuvastatin 2.5 mg for 4 years). The patient, a 73-year-old man presented with acute onset fatigue and difficulty walking with lower leg weakness. Medical history included dyslipidemia, diabetes, and arteriosclerosis obliterans; current medications included rosuvastatin (2.5 mg/day), glimepiride, pioglitazone, limaprost, and cilostazol on going for 4 years and miglitol ongoing for 2 years. Blood tests performed at presentation showed renal dysfunction, with a serum creatinine level of 1.4 mg/dL (baseline: 0.5 mg/dL) and markedly elevated CK level of 16,538 U/L, with 96% of the increased CK of the MM form. After admission, the withdrawal of rosuvastatin therapy and the administration of intravenous fluids improved the CK and creatinine levels.

Reviewer comment: Rhabdomyolysis is a known and labelled safety concern for the statin drug class.

- Huynh and Huot[3] report a “continuous sensation of coldness” associated with the use of rosuvastatin in a 60-year-old man with elevated LDL-C on rosuvastatin 5 mg/day. "A few months" after starting rosuvastatin, the patient began feeling cold, even during summer with surrounding temperature above 86 °F. He described the sensation as an inner sense of coldness that affected his whole body and did not respond to increase in ambient temperature or putting on more clothes. The abnormal sensation persisted for the 26 months during which he was treated with rosuvastatin. Vital signs, physical examination, including neurological examination, and hematological and biochemical parameters were normal. Rosuvastatin was stopped and within a week the feeling cold resolved. As described by the authors, the pathophysiology of this phenomenon remains unknown.

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[1] Annigeri RA and Mani RM. Acute interstitial nephritis due to statin and its class effect. Indian J Nephrol. 2015 Jan-Feb:25(1):54-56.
[2] Kamada T et al. Takotsubo cardiomyopathy with involvement of delayed-onset rhabdomyolysis and acute kidney injury after rosuvastatin treatment. Intern Med 2015; 54: 31-35
[3] Huynh NT, Huot P. BMJ Case Rep Published Online 2014 doi:10.1136/bcr-2014-205987

- Kim et al.[4] published a case report of interstitial pneumonitis associated with rosuvastatin. A 60-year-old man who was diagnosed with a transient ischemic attack was started on acetyl-L-carnitine, cilostazol, and rosuvastatin. After rosuvastatin treatment for 4 weeks, the patient presented with sudden onset fever, cough, and dyspnea. His symptoms were aggravated despite empirical antibiotic treatment. All infectious pathogens were excluded based on results of culture and polymerase chain reaction of the bronchoscopic wash specimens. Chest radiography showed diffuse ground-glass opacities in both lungs, along with several subpleural ground-glass opacity nodules; and a foamy alveolar macrophage appearance was confirmed on bronchoalveolar lavage. We suspected rosuvastatin-induced lung injury, discontinued rosuvastatin and initiated prednisolone 1 mg/kg tapered over 2weeks. After initiating steroid therapy, his symptoms and radiologic findings significantly improved.

Reviewer comment: The clinical significance of this case report is unclear, however, continued routine pharmacoviligiance for statins effect on interstitial lung disease is warranted.

- Tada et al[5] report a case of transient azoospermia in a man with who had been treated with rosuvastatin 2.5 mg for 4 weeks. While a primary infertile couple with oligoasthenospermia was preparing for an in vitro fertilization program, the male partner had been diagnosed with hypercholesterolemia in a medical check-up and prescribed four week oral administration of rosuvastatin. No motile spermatozoa were found in the ejaculated semen and urine on the day of follicular aspiration. Azoospermia was confirmed by re-examination in weeks 3 and 7. Spermatozoa appeared in the ejaculated semen following two weeks of drug withdrawal. In week 16, the sperm count and motility increased to the level where intracytoplasmic sperm injection was available.

Reviewer comment: The clinical significance of this case report is unclear, especially as there may be underlying conditions affecting fertility.

- Badri et al.[6] conducted open-label, Phase I clinical studies to characterize mechanism-based interactions with the 2D regimen of ombitasvir and paritaprevir (administered with low-dose ritonavir) used for the treatment of chronic hepatitis C virus (HCV) infection using, among other drugs, rosuvastatin as a OATP1B1/B3 and BCRP probe substrate. Coadministration of the 2D regimen increased rosuvastatin exposures: Cmax increased by 161% (from 2.33 ng/mL to 6.09 ng/mL), and AUC increased by 33% (from 23.0 ng•h/mL to 30.7 ng•h/mL). Ombitasvir and paritaprevir/ritonavir (the 2D regimen) had the following effect on the geometric mean ratios (and 90% CIs) for coadministration of rosuvastatin

[4] Kim SY et al. A case of statin-induced interstitial pneumonitis due to rosuvastatin. Tuberc Respir Dis 2015;78:281-285.
[5] Tada Y et al. Transient azoospermia following rosuvastatin medication for hypercholesterolemia. Clin Exp Obstet Gynecol 2015;42(4):545-6.
[6] Badri PS et al. Drug interactions with the direct-acting antiviral combination of ombitasvir and paritaprevir/ritonavir (2D regimen). Antimicrob Agents Ch 2015;Oct12.pii: AAC.01778-15.

with the 2D regimen versus administration of rosuvastatin alone: Cmax, 2.61 (2.01 to 3.39) and AUC, 1.33 (1.14 to 1.56). Coadministration of the 2D regimen also increased exposure to the other statin, pravastatin: Cmax increased by 43%, and AUC increased by 76%. The authors state that, based on the magnitude of these mechanism-based interactions, rosuvastatin dose should be reduced by half when coadministered with the 2D regimen. Alternatively, the rosuvastatin dose should not exceed 20 mg/day.

- Gervasoni et al. conducted a retrospective study to assess factors influencing atazanavir (ATV) trought concentrations in 273 HIV-infected patients. Concentrations of ATV exceeding the upper therapeutic threshold of 800 ng/mL are known to be associated with a high risk of experiencing ATV-related side effects. According to univariate analysis, factors significantly associated with increased ATV concentrations were ATV dosage, number of concomitant drugs, and ritonavir or statin use, with a nonsignificant trend for body mass index. According to multivariate regression analysis, the only factors independently and significantly associated with ATV concentrations were ritonavir use ($r = 0.291$, $P < 0.0001$) and concomitant rosuvastatin therapy ($r = 0.315$, $P < 0.0001$). Significant differences in ATV trough concentrations were observed between patients receiving concomitant rosuvastatin and those not receiving concomitant rosuvastatin (34 patients versus 239 patients; 817 ± 819 ng/mL versus 752 ± 806 ng/mL, respectively; $P < 0.05$). Notably, patients receiving ATV only (without ritonavir) and rosuvastatin did not have concentrations of ATV that exceed the upper therapeutic threshold of 800 ng/mL (15 patients; 524 ± 402 ng/mL). No significant differences were found in ritonavir concentrations between patients receiving or not receiving concomitant rosuvastatin (173 ± 312 ng/mL versus 228 ± 217 ng/mL; $P = 0.446$).

Reviewer comment: Further review of drug-drug interactions with protease inhibitors and statins is ongoing within DMEP.

Reviewer comment: Following review of the original reports and summaries, it is this reviewer's opinion, that these reports do not alter the overall favorable benefit/risk assessment for rosuvastatin or warrant a change in labeling at this time. Pharmacoviligiance for these concerns and others that arise in the post-marketing setting will continue to be a part of the assessment of rosuvastatin's safety profile.

AUDITS

The Division of Generic Drug Bioequivalence within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the clinical data after inspection of two clinical sites (Tandalja and Akota), Vadodara, India. The inspections of the clinical portion of the above studies were conducted during January 18-28, 2016. The audits included a thorough examination of facilities and equipment, review of study records and correspondence, and interviews and discussions with firm's staff and management on screening and eligibility, dosing, lab reports, clinical data collection, blood sample collection and storage, adverse events, medications, test article storage and accountability, and reserve samples. (b) (4)

(b) (4)

Following review of the findings, the OSIS reviewers concluded that the data from the audited studies are reliable.

CMC

Adequate support was submitted was to grant the biowaiver request for lower strengths of rosuvastatin. Furthermore, adequate dissolution data were provided in support of the use of drug granules as sprinkles on apple sauce (within 60 minutes at room temperature) and as an aqueous suspension for the nasogastric administration (within 90 minutes at room temperature, dispersed in water, and using (b) (4) (16-French) tubing).

However, recent inspection of Sun Pharmaceutical Industries Limited, Halol-Baroda 389350, Gujarat, India, site identified numerous cGMP deficiencies. The FDA issued a warning letter on 17 December 2015. At the time of this review the deficiencies have not been resolved. Therefore, the chemistry/manufacturing and controls team recommend a complete response due to manufacturing facility deficiencies.

PHARMACOLOGY/TOXICOLOGY

The pharmacology/toxicology review team recommends approval of this product. A 30-day bridging toxicity study in rats utilizing RosuvaCaps and the RLD did not show toxicological meaningful differences between RosuvaCaps and Crestor. According to the review team this study provided an adequate bridge to the Division's prior approval decision for the RLD, Crestor. All impurities were below the levels required for identification or qualification and no structural alerts were identified that would require further genetic toxicology testing. Additionally, there are no novel excipients proposed for the rosuvastatin capsules and all are within the approved limits in the Inactive Ingredient Guide. The Pharm/Tox recommendation for labeling is that the accepted labeling for rosuvastatin tablets from Crestor should be used for rosuvastatin capsules. This includes the pending Pregnancy Labeling and Lactation Rule conversion of Section 8 as well as Section 13. The only recommended deletion from the RosuvaCaps label will be the omission of the juvenile animal data listed in Section 13.2 of the updated Crestor label (pending at the time of this review). The rationale for this deletion is due to the lack of a pediatric indication or human pediatric data with RosuvaCaps. Please see Dr. Stephanie Leuenroth-Quinn's review for further details.

FINANCIAL DISCLOSURE

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

LABELING

As this application will be granted a complete response, no approved labeling will be attached to this action. However, during the review of this application, several revisions

to the label were made, including revision of relevant sections of the label to comply with the Pregnancy Labeling and Lactation Rule.

PROPRIETARY NAME

The applicant proposed to use the name Ezallor which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was determined to be acceptable.

PEDIATRIC STUDY REQUIREMENTS

The RosuvaCaps application was reviewed by the PeRC PREA subcommittee on 18 November 2015 and was granted a full waiver for pediatric studies for the sought after treatment indications because studies are impossible or highly impractical.

RECOMMENDATION

No deficiencies were noted in the clinical review of this product. RosuvaCaps was well tolerated and was consistent with the known safety profile of the reference listed drug, Crestor. However, due to issues with the manufacturing facility for this product, this reviewer recommends a complete response and defers to the CMC review team for input on how the applicant may address deficiencies in the NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY D ROBERTS
05/26/2016

JAMES P SMITH
05/27/2016

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	208647
Applicant	Sun Pharma Global FZE
Date Submission Received	28 August 2015
PDUFA Goal Date	28 June 2016
Proprietary Name / Established (USAN) names	EZALLOR (rosuvastatin)
Dosage forms / Strength	Capsule / 5, 10, 20, and 40 mg (free-acid)
Proposed Indication	1. Adjunctive therapy to diet for the treatment of adult patients with **hypertriglyceridemia;** 2. Adjunct to diet for the treatment of patients with **primary dysbetalipoproteinemia** (Type III Hyperlipoproteinemia) 3. Adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with **homozygous familial hypercholesterolemia**
Recommended:	Complete response

Material Reviewed/Consulted & Primary Reviewer(s)		
Clinical Pharmacology Review	23 May 2016	Shalini Wickramaratne Senarath Yapa, PhD
Medical Officer Review	26 May 2016	Mary Roberts, MD
Pharmacology/Toxicology Review	20 May 2016	Stephanie J. Leuenroth-Quinn, PhD
OPQ Review	18 May 2016	Suong Tran, PhD (Application Technical Lead)
DPMH Consult Review	20 Jun 2016	Carol H. Kasten, MD
OSIS Memo	26 Apr 2016	Sripal R. Mada, PhD
OSE/DMEPA Label & Labeling Review #1	17 Dec 2015	Ariane O. Conrad, PharmD, BCACP, CDE
OSE/DMEPA Label & Labeling Review #2	10 Feb 2016	Ariane O. Conrad, PharmD, BCACP, CDE
OSE/DMEPA Proprietary Name Review	21 Dec 2015	Leeza Rahimi, PharmD

OPQ: Office of Pharmaceutical Quality; DPMH: Division of Pediatric and Maternal Health; OSIS: Office of Study Integrity and Surveillance; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis

1. INTRODUCTION

This is a 505(b)(2) application for a new dosage form of rosuvastatin (oral capsule), which relies on the Agency's findings of safety and efficacy for NDA 21366, Crestor (rosuvastatin calcium) tablets, which was approved in 2003. Currently, rosuvastatin is only available as a tablet. The applicant believes that this product, which comprises a hard-gelatin capsule filled with drug-containing (b) (4), will facilitate dosing in subjects who may find it difficult to swallow a tablet. They state that rosuvastatin capsules may be swallowed intact, the contents may be sprinkled onto a soft food, or the capsule contents can be administered via a nasogastric (NG) tube. The proposed indications are identical to those currently approved for Crestor but are not covered under patent/exclusivity.

This memo, which also serves as a cross-disciplinary team leader memo, briefly summarizes the reviews of each discipline. At this time, the only deficiency that the reviewers have identified that would preclude approval comes from the manufacturing inspection recommendation; numerous cGMP deficiencies are unresolved at the site of the proposed drug product manufacturer.

2. BACKGROUND

Pre-submission interactions with the applicant included written responses (21 February 2014) to a pre-IND meeting request and a pre-NDA teleconference (18 May 2015; minutes dated 15 June 2015). In the pre-IND responses, the Division confirmed the need for a comparative bridging toxicity study and the acceptability of two bioavailability studies (one study under fasting conditions and one under fed conditions, each being a single-dose study comparing rosuvastatin capsules 40 mg – intact vs. sprinkled on applesauce – with Crestor 40 mg). The Division agreed that if rosuvastatin capsules and Crestor were shown to be bioequivalent (BE) in all dosing conditions, additional clinical studies would not be required prior to submission. In these meetings, questions related to biowaiver requests, dissolution testing, and the adequacy of nasogastric tube in-use studies were addressed as well.

3. CMC

The quality review for this application was conducted by a multidisciplinary team; Dr. Suong Tran was the application technical lead. See the integrated review for details. Overall, the recommendation from the Office of Pharmaceutical Quality (OPQ) is for a complete response (see below).

Drug Substance

DMF (b) (4) was referenced for all CMC information on the drug substance (rosuvastatin calcium). The DMF was found adequate to support this NDA.

Drug Product

This application proposes a new formulation of rosuvastatin. The product is a gelatin capsule containing immediate-release drug granules. The proposed dosage strengths (5, 10, 20, and 40 mg rosuvastatin free-acid) differ by the amount of granules per capsule and the capsule shell size. The (b) (4) size is stated to be (b) (4) microns to meet FDA's guidelines on this type of dosage form. The drug product specification includes attributes standard for the dosage form. The excipients contributing to the capsule formulation of the drug product were reviewed and found adequate; all are satisfactorily controlled. The reviewers found that the limits on degradants meet the applicable ICH identification and qualification threshold for the maximum daily dose, (b) (4) (b) (4)

Based on the submitted stability data, the reviewers accepted the requested 24-months expiry period, packaged either in 30- or 90-count bottles or in blister-pack form.

Biopharmaceutics

The 40-mg batch (JKN2312) used in the pivotal BE studies has the same formulation, except for capsule printing, as the commercial product. The biopharmaceutics reviewer found that the different strengths of 5, 10, 20, and 40 mg are (b) (4) with sufficiently similar dissolution profiles; therefore, the biowaiver request for the lower strengths (5, 10, and 20 mg) was found acceptable

provided that the BA/BE results were found acceptable for the 40 mg strength (see Clinical Pharmacology).

In addition, the biopharmaceutics review found that adequate dissolution data were provided in support for the use of drug granules as sprinkles on apple sauce (within 60 minutes at room temp) and as an aqueous suspension for NG administration (within 90 minutes at room temperature, dispersed in water, and using (b) (4) 16-French tubing). The data provided in support of the dissolution test method were adequate.

Facilities Review/Inspection

The history of the drug substance manufacturing facility was reviewed and found to be acceptable.

Two manufacturing facilities related to the drug product were identified; one was found acceptable, the other was not. (b) (4)

(b) (4)

I concur with the conclusions reached by the OPQ reviewers that the deficiencies related to the drug product manufacturing facility preclude approval at this time; however, there appear to be no additional outstanding issues related to CMC.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Leuenroth-Quinn reviewed this application from the pharm/tox perspective. The applicant conducted a 14-day dose range finding (non-GLP) rat toxicology study and a pivotal GLP-compliant 30-day bridging rat toxicology study using the listed drug, Crestor, as the comparator. Dr. Leuenroth-Quinn found similar target organs of toxicity (including liver, stomach, skeletal muscle) between rosuvastatin (b) (4) and Crestor; no new target organ toxicities were identified. All impurities were below the levels required for identification or qualification, and no structural alerts were identified that would require further genetic toxicology testing. Last, there were no novel excipients identified. I concur with the conclusions reached by Dr. Leuenroth-Quinn that there are not outstanding pharm/tox issues that preclude approval.

5. CLINICAL PHARMACOLOGY

Dr. Shalini Yapa reviewed this application for clinical pharmacology and recommends approval. Two pivotal studies were conducted to assess the BE between rosuvastatin 40 mg capsules and Crestor 40 mg tablets.

Study PKD_14_128 (hereafter Study 128) was a randomized, open-label, three-treatment, three-period, six-sequence, single-dose, crossover relative bioavailability study under fasting conditions. This study demonstrated BE of rosuvastatin 40 mg capsules (intact) vs. Crestor 40 mg tablets; rosuvastatin 40 mg capsules (sprinkling contents of on applesauce) vs. Crestor 40 mg tablets; and rosuvastatin 40 mg capsules (sprinkling contents on applesauce) vs. rosuvastatin 40 mg capsules (intact).

Study PKD_14_129 (hereafter Study 129) had a similar design as Study 128 but was conducted under fed conditions. This study demonstrated BE, under fed conditions, for the same comparisons listed above for Study 128.

The highlights of these studies are summarized in the table below, excerpted from Dr. Yapa's review.

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)

One subject (b) (6) in Study 128 was identified as an outlier (markedly lower C_{max} and AUC after receiving an intact rosuvastatin 40 mg capsule compared with both sprinkled rosuvastatin 40 mg capsule and Crestor 40 mg tablet), and the reason remains unknown. Inclusion of this single subject's data leads to a failure to demonstrate BE for comparisons that involve the intact rosuvastatin capsule. The sponsor performed a redosing study (PKD_14_291) to evaluate and verify and anomalous response of this subject; this study included Subjec (b) (6) as well as 2 control subjects and 2 standby control subjects who had participated in Study 128. Based on the results of this redosing study, in which the PK estimates for Subject (b) (6) were similar to the control subjects, the clinical pharmacology reviewer concluded that this subject could be considered an outlier and excluded from the analysis of

pivotal Study 128; she makes note that this was discussed and agreed with the Office of Clinical Pharmacology senior leadership team.

Dr. Yapa noted that BE was not demonstrated between the intact vs. sprinkled rosuvastatin 40 mg under fed conditions as a result of the C_{max} comparison (see Study 129, B vs. A, in the table above). She comments that this difference "is unlikely to result in any clinical significance." The same comparison demonstrated BE under fasting conditions (Study 128).

I concur with the conclusions reached by Dr. Yapa that there are no outstanding clinical pharmacology issues that preclude approval.

6. CLINICAL MICROBIOLOGY

Not applicable. Microbiology considerations were reviewed by OPQ and found acceptable.

7. CLINICAL/STATISTICAL-EFFICACY

Not applicable. See Clinical Pharmacology.

8. SAFETY

Dr. Mary Roberts reviewed the clinical data for safety in this application; see her review for details. There were no serious adverse events or deaths in either study. Although there were AEs reported related to elevated transaminases, these occurred in all groups with similar frequency, including Crestor 40 mg, as shown in the following table of pooled events from the two pivotal BE studies. In Study 128, there were no treatment-emergent elevations in ALT >3xULN and only one patient with an elevation in AST >3xULN. In Study 129, there were 4 subjects with ALT >3xULN, all of whom were asymptomatic (2 followed Crestor; 1 followed rosuvastatin capsules intact; 1 followed rosuvastatin capsules sprinkled on applesauce).

Table 9. Treatment emergent adverse events – pivotal BE studies pooled

Adverse Event	n (%)		
	Rosuvastatin Capsules, 40 mg		Crestor® Tablets, 40 mg
	Intact	Sprinkled	
N	**92**	**92**	**90**
Investigations			
Alanine aminotransferase increased	5 (5.4)	5 (5.4)	5 (5.5)
Aspartate aminotransferase increased	3 (3.3)	4 (4.3)	4 (4.4)
White blood cell count increased	0	1 (1.1)	0
Neutrophil count increased	0	1 (1.1)	0
Lymphocyte count decreased	0	1 (1.1)	0
Gastrointestinal Disorders			
Vomiting	1 (1.1)	2 (2.2)	0
Abdominal pain	0	1 (1.1)	0

Source: Studies PKD_14_128 and PKD_14_129 Clinical Reports

Dr. Roberts explored PK data among subjects with and without elevated liver enzymes and found that those who had elevated liver enzymes did not consistently have higher rosuvastatin exposure.

Dr. Roberts commented that "[e]levations in liver enzymes have been reported with statins, including rosuvastatin. In the RosuvaCaps bioequivalence studies, asymptomatic increases in liver transaminases occurred with similar frequency across all rosuvastatin formulations and resolved or improved. Review of the safety information from the two pivotal bioequivalence studies does not raise any new safety concerns."

Dr. Roberts noted that no deficiencies were noted in the clinical review of this product. I concur that there do not appear to be any distinct safety concerns related to this rosuvastatin formulation, and given the demonstrated BE to Crestor, it is appropriate for this application to reference FDA's previous conclusions related to the safety of Crestor.

9. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not considered necessary for this 505(b)(2) application.

10. PEDIATRICS

This application was reviewed by the PeRC PREA subcommittee on 18 November 2015. Full waivers for pediatric studies were granted for the treatment indications sought because studies would be impossible or highly practical.

11. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosures

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

Clinical Inspections

The Division of Generic Drug Bioequivalence within the Office of Study Integrity and Surveillance recommends accepting the clinical data after inspection of two clinical sites (Tandalja and Akota), Vadodara, India. The inspections of the clinical portion of Studies 128 and 129 – as well as the redosing study PKD_14_291 – were conducted 18-28 January 2016.

12. LABELING

Proprietary Name Review

The applicant has proposed the proprietary name Ezallor, which OSE/DMEPA found acceptable. This was communicated to the applicant in a letter dated 23 December 2015.

Labeling

Because this application will receive a complete response, labeling was not negotiated with the applicant. The labeling is expected to be very similar to the approved labeling for Crestor with additional Dosing & Administration information related to (1) sprinkling on applesauce and (2) administering via NG tube. See the relevant discipline reviews for labeling recommendations.

DPMH actively participated in the review of labeling related to the Pregnancy and Lactation Labeling Rule. See their consult review for details.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

The applicant has demonstrated that rosuvastatin capsules are bioequivalent to rosuvastatin calcium tablets, which are approved as Crestor. There are no clinical or nonclinical deficiencies that would

preclude approval. However, OPQ recommends a complete response on the basis of deficiencies with regard to a manufacturing facility for the drug product. Given that there is no pressing public health need for an alternative formulation for rosuvastatin, which is one of several statins marketed in the U.S., I concur with the recommendation not to approve this application until the issues related to the manufacturing facility are resolved.

Recommended Regulatory Action

- Complete Response

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
06/22/2016