CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208647Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208647
Supporting document/s:	SD-1
Applicant's letter date:	August 28, 2015
CDER stamp date:	August 28, 2015
Product:	Rosuvastatin Calcium (b) (4) capsules
Indication:	Hypertriglyceridemia
Applicant:	Sun Pharma Advanced Research Company
Review Division:	DMEP
Reviewer:	Stephanie Leuenroth-Quinn
Supervisor/Team Leader:	C. Lee Elmore
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Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

The Applicant (Sun Pharma Advanced Research Company, Ltd.) submitted 505 (b)(2) NDA 208647 for the immediate release product, rosuvastatin capsules. This product is a hard gelatin capsule filled with rosuvastatin containing (b) (4) to be used to facilitate dosing in patients who may have difficulty with swallowing tablets. Rosuvastatin capsules may be swallowed intact, sprinkled onto soft food or the contents administered via a nasogastric tube. The Applicant is relying on the Agency's prior findings of safety and efficacy for the listed drug, Crestor, and focused on the bioequivalence of rosuvastatin capsules to this listed drug.

1.2 Brief Discussion of Nonclinical Findings

The Applicant conducted a 14-Day dose range finding (non-GLP) rat toxicology study as well as a pivotal GLP-compliant 30-Day bridging rat toxicology study with the listed drug, Crestor (approved under NDA 21366), as comparator. Comparison of the toxicity profiles between the rosuvastatin test article (rosuvastatin (b) (4)) and Crestor identified similar target organs of toxicity including the liver, stomach and skeletal muscle. Liver toxicities were ≤2X elevations in liver enzymes (ALT, AST and ALP), microvesiculation and single cell necrosis and skeletal muscle toxicities included elevations in CK and a low incidence of minimal skeletal muscle necrosis. No new target organ toxicities were identified for rosuvastatin (b) (4) when compared to the toxicity profile of rosuvastatin calcium (Crestor) in the rat. In the 30-Day bridging toxicology study, plasma exposures of rosuvastatin were largely comparable between rosuvastatin (b) (4) and Crestor; however, AUC exposures tended to be higher for Crestor treated animals which corresponded with more severe toxicities in these dose groups (observed in 30-Day and 14-Day studies). 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. In summary, the rat GLP-compliant bridging toxicology study demonstrated similar toxicity profiles between rosuvastatin (b) (4) and the listed drug, Crestor, when administered at equivalent doses.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The Pharm/Tox recommendation for labeling is that the accepted labeling for rosuvastatin tablets from the innovator product (Crestor) should be used for rosuvastatin capsules. This includes the pending PLLR conversion of Section 8 as well as Section 13. The only recommended deletion from the rosuvastatin capsules 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 rosuvastatin capsules. The proposed labeling relevant to nonclinical sections (consistent with Crestor's label), is as follows but may be subject to further modifications:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Rosuvastatin is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit to therapy with rosuvastatin during pregnancy. Because HMG CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, rosuvastatin may cause fetal harm when administered to pregnant women. Rosuvastatin should be discontinued as soon as pregnancy is recognized [see Contraindications (4)]. Limited published data on the use of rosuvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, there were no adverse developmental effects with oral administration of rosuvastatin during organogenesis at systemic exposures equivalent to a maximum recommended human dose (MRHD) of 40 mg/day in rats or rabbits (based on AUC and body surface area, respectively). In rats and rabbits, decreased pup/fetal survival occurred at 12 times and equivalent, respectively, to the MRHD of 40 mg/day (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Rosuvastatin crosses the placenta in rats and rabbits and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

Rosuvastatin administration did not indicate a teratogenic effect in rats at ≤ 25 mg/kg/day or in rabbits ≤ 3 mg/kg/day (doses equivalent to the MRHD of 40 mg/day based on AUC and body surface area, respectively).

In female rats given 5, 15, and 50 mg/kg/day before mating and continuing through to gestation day 7 resulted in decreased fetal body weight (female pups) and delayed ossification at 50 mg/kg/day (10 times the human exposure at the MRHD dose of 40 mg/day based on AUC).

In pregnant rats given 2, 10, and 50 mg/kg/day of rosuvastatin from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred at 50 mg/kg/day (dose equivalent to 12 times the MRHD of 40 mg/day based body surface area).

In pregnant rabbits given 0.3. 1, and 3 mg/kg/day of rosuvastatin from gestation day 6 to day 18, decreased fetal viability and maternal mortality was observed at 3 mg/kg/day (dose equivalent to the MRHD of 40 mg/day based on body surface area).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107 week carcinogenicity study in mice given 10, 60, or 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with Salmonella typhimurium and Escherichia coli, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the in vivo mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6 month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

13.2 Animal Toxicology and/or Pharmacology

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures ≤ 60 times the human exposure at 40 mg/day based on AUC) did not reveal retinal findings during treatment for up to one year.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
[147098-20-2]

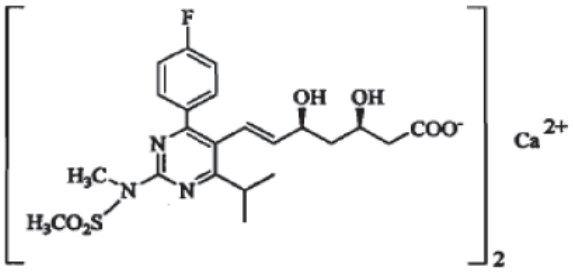
Generic Name
Rosuvastatin calcium

Code Name
Rosuvastatin calcium

Chemical Name
(3R, 5S)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt (2:1)

Molecular Formula/Molecular Weight
$C_{44}H_{54}F_2N_6O_{12}S_2 \bullet Ca$
MW = 1001.14 (salt); 963.08 (base)

Structure or Biochemical Description



Pharmacologic Class
HMG Co-A Reductase Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 21366 (rosuvastatin calcium, Crestor)

2.3 Drug Formulation

Hard gelatin capsule filled with drug containing (b) (4) (5, 10, 20, 40 mg strengths)

2.4 Comments on Novel Excipients

There are no novel excipients in the formulation.

2.5 Comments on Impurities/Degradants of Concern

All impurities are below the level of qualification per ICH guidance (0.15%).

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indications for Rosuvastatin capsules are as follows: Hypertriglyceridemia, Primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), and Homozygous familial hypercholesterolemia

The Applicant is relying on the Agency's previous findings of safety and efficacy of rosuvastatin at doses of 5 – 40 mg/day, and made the following statement: "The scientific justification for this reliance is the demonstration of bioequivalence with the listed drug in relative bioavailability studies conducted in the fasted and fed states, Studies PKD_14_128 and PKD_14_129."

Relative Bioavailability of SPARC Ltd.'s Rosuvastatin Capsules, 40 mg (Batch JKN2312) and Crestor® Tablets, 40 mg

Parameter	Least Square Means Ratio Test/Reference[1] (90% CI)[2]	
	Fasted (PKD_14_128)	Fed (PKD_14_129)
N	41[3]	45
C_{max}	97.75 (89.67 – 106.55)	111.09 (102.58 – 120.31)
AUC_{0-t}	93.40 (87.14 – 100.12)	106.80 (100.01 – 114.04)
$AUC_{0-\infty}$	93.14 (86.83 – 99.90)	106.46 (100.10 – 113.22)

Source: PKD_14_128 Report Table 4B and PKD_14_129 Report Table 14.2 – 1B
[1] Ratio of Least Square Means: calculated according to the formula: $e^{(\text{LSM Treatment (B)} - \text{LSM Treatment (A)})} \times 100$
[2] Ln-transformed data
[3] Excluding data for subject (b) (6) see Section 2.7.1.2.1.1 for justification of exclusion as an outlier

(Applicant Table)

2.7 Regulatory Background

- Crestor approved 2003 (rosuvastatin calcium)
- Written Response to Briefing Package, Feb. 21, 2014
- Pre-NDA 208647 Meeting on May 18, 2015 (T-Con)
- NDA 208647 submitted August 28, 2015

3 Studies Submitted

3.1 Studies Reviewed

Study No. BRT_14_043_TN: A 14-Day Repeated Dose Oral Dose Range Finding Toxicity Study of Rosuvastatin Calcium (b) (4) Capsules in Wistar Rat with Toxicokinetic Evaluation

Study No. BRT_14_070_TN: A 30-Day Repeated Dose Oral Toxicity Study of Rosuvastatin Calcium (b) (4) Capsules in Wistar Rats with Toxicokinetic Evaluation

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

Rosuvastatin has been previously shown to be an inhibitor of HMG-CoA reductase. This enzyme is the rate limiting enzyme involved in the conversion of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate, upstream of cholesterol production. As

a result of this inhibition, the synthesis and secretion of endogenously produced cholesterol is reduced and hepatic surface LDL Receptor expression is increased.

4.2 Secondary Pharmacology

Not conducted.

4.3 Safety Pharmacology

Not conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Not conducted.

5.2 Toxicokinetics

TK data is presented in individual toxicology study reports (Section 6 General Toxicology).

6 General Toxicology

6.1 Single-Dose Toxicity

Not conducted.

6.2 Repeat-Dose Toxicity

Study title: A 30-Day Repeated Dose Oral Toxicity Study of Rosuvastatin Calcium (b) (4) Capsules in Wistar Rats with Toxicokinetic Evaluation	
Study no.:	BRT_14_070_TN
Study report location:	SD-1
Conducting laboratory and location:	Biological Research Toxicology Sun Pharma Advanced Research Company Limited. Tandalja, Vadodara – 390 020, India
Date of study initiation:	November 12, 2014
GLP compliance:	Yes, p.15 (OECD Principles of GLP, except for TK sample analysis phase)
QA statement:	Yes, p.16
Drug, lot #, and % purity:	Rosuvastatin calcium (b) (4) capsule 40 mg, Batch No. JKN2312; Crestor rosuvastatin calcium tablets 40 mg, Batch No. CB0063

Key Study Findings

- Wistar rats were orally administered the test article (rosuvastatin calcium (b) (4) daily at doses of 0 (placebo or vehicle control), 20, 40 or 80/60 mg/kg. The highest dose of 80 mg/kg was reduced to 60 mg/kg effective on Day 12 (females) or 14 (males) due to toxicity. An additional comparator Crestor group was also dosed at 80/60 mg/kg/day. Rosuvastatin (b) (4) or Crestor tablets were (b) (4) (b) (4)
- There were several deaths in the Crestor groups between Days 13-21 in males and females. When histopathology was possible (no autolysis), findings included liver necrosis, small thymus, and stomach hyperkeratinization. Body weight loss was also observed. Additional deaths in a mid-dose female and a placebo control were likely related to gavage error.
- Clinical signs were predominantly limited to those animals found dead and included hunched back, piloerection and lethargy.
- There was a trend for body weight decrease in dosed animals versus placebo or vehicle control animals, but did not reach statistical significance in either sex. This correlated with a transient decrease in food consumption in high-dose animals (rosuvastatin (b) (4) and Crestor) predominantly in males.
- Hematology parameter changes were mild or not dose dependent with a slight increase in WBC counts in HD Crestor administered males.
- Target organs of toxicity included the following:
  Liver: Elevations in liver enzymes were noted in both sexes for the highest dose of rosuvastatin (b) (4) test article and Crestor with ALT, AST and ALP increased ≤2X. Liver weight significantly decreased in males in these two high-dose groups and histopathology correlates included liver microvesicles and single cell necrosis in both sexes.
  Stomach: Forestomach hyperkeratinization was observed in both sexes in the high-dose rosuvastatin (b) (4) and Crestor dose groups.
  Muscle: CK levels increased in both sexes at the highest dose tested and one high-dose male in the rosuvastatin (b) (4) group had minimal skeletal muscle necrosis.
- GLP Compliance: The Applicant stated the following in the study protocol: “This study will be performed in compliance with the OECD principles of GLP, as revised in 1997 by decision of the OECD council [ENV/MC/CHEM(98)17] except toxicokinetic sample analysis phase which will be conducted at (b) (4) (b) (4) had been inspected several times by regulatory agencies e.g. USFDA, EU, and ANVISA. Hence, data generated at (b) (4) is considered accurate and reliable. Test facility is certified by National GLP Compliance Monitoring Authority to conduct subacute toxicity studies as per OECD principles of GLP.”
- TK analysis was conducted on Days 1, 15 and 30. The highest dose tested for rosuvastatin test article and Crestor started at 80 mg/kg/day on Day 1 and was decreased to 60 mg/kg/day on Day 12 for females and Day 14 for males. Exposures (AUC) were increased 12X and 18X in males at this high dose in both test article and Crestor dose groups, versus Day 1. This dropped to a 2-3X increase versus Day 1 on Day 30. Although there was only 1 day of lower 60

mg/kg dosing before TK analysis on Day 15 in males (versus 3 days for females) it is unclear why exposures were so high in these groups on Day 15.

- TK comparison between equivalent doses of rosuvastatin (b) (4) and Crestor in both sexes demonstrated that Crestor has slightly higher plasma exposure than the test article. Toxicities were as expected for this drug class (liver, muscle) with higher systemic exposures leading to more extensive liver toxicity and death.
- The Applicant stated the NOAEL was 20 mg/kg for both sexes where male and female AUC_{0-t} was 709.935 and 649.168 hr*ng/mL and C_{max} 56.820 and 68.277 ng/mL, respectively on Day 30. Adverse toxicities at 60/80 and 40 mg/kg included elevated liver enzymes with liver necrosis and microvesiculation; stomach hyperkeratinization; skeletal muscle necrosis; and mild decreases in body weight gain. This reviewer would agree with this NOAEL. Based on a 40 mg maximum recommended human dose (b) (4) the safety margin based on body surface area would be 5X.

Methods

Doses: Rosuvastatin: 0, 20, 40, 80* mg/kg (*reduced to 60 mg/kg)
Crestor: 0, 80* mg/kg (*reduced to 60 mg/kg)

Group	Test Substance	Dose (mg/kg/day)	Concentration (mg/mL)	Number of animals (Animal ID)	
				Male	Female
G1	Vehicle control (PEG (b) (4)	0	0	10 (101 - 110)	10 (151 - 160)
G2	Placebo of Rosuvastatin	0	0	10 (201 - 210)	10 (251 - 260)
G3	Rosuvastatin	20	2.0	10 (301 - 310)	10 (351 - 360)
G4	Rosuvastatin	40	4.0	10 (401 - 410)	10 (451 - 460)
G5	Rosuvastatin	80*	8.0	10 (501 - 510)	10 (551 - 560)
G6	Reference Item (Crestor)	80*	8.0	10 (601 - 610)	10 (651 - 660)
G1 Reversal	Vehicle control (PEG (b) (4)	0	0	10 (111 – 120)	10 (161 – 170)
G2 Reversal	Placebo of Rosuvastatin	0	0	10 (211 – 220)	10 (261 – 270)
G5 Reversal	Rosuvastatin	80*	8.0	10 (511 – 520)	10 (561 – 570)
G6 Reversal	Reference Item (Crestor)	80*	8.0	10 (611 – 620)	10 (661 – 670)
Total				**100**	**100**

*Dose reduced from 80 mg/kg/day to 60 mg/kg/day as per Study Plan Amendment 01, on Day 14 (males) and Day 12 (females). (Applicant Table)
Placebo of rosuvastatin (b) (4) was Batch No. JKN4350.

Frequency of dosing: Once daily for 30 days; followed by a 14 day treatment-free recovery period

Route of administration: Oral gavage

Dose volume: 10 mL/kg except for Groups 5 and 6 (dosing, recovery and TK) which was 7.5 mL/kg to achieve the reduced dose

Formulation/Vehicle: Polyethylene glycol (PEG (b) (4) was used to (b) (4) test, placebo and reference items.

Species/Strain: Wistar rat (b) (4)

Number/Sex/Group: 10/sex/group

Age: 6 - 8 weeks old at dosing initiation

Weight: Stated the following: "After randomization body weight variation of animals was minimal and did not exceeded ±20 % of the mean weight for each sex." Week 1 weights were reported in summary tables. Body weights were not reported at arrival.

Satellite groups: 6/sex/group for TK

Toxicokinetic Satellite Groups					
G2TK	Placebo of Rosuvastatin	0	0	6 (221 - 226)	6 (271 - 276)
G3TK	Rosuvastatin	20	2.0	6 (311 - 316)	6 (361 – 366)
G4TK	Rosuvastatin	40	4.0	6 (411 - 416)	6 (461 - 466)
G5TK	Rosuvastatin	80*	8.0*	6 (521 - 526)	6 (571 - 576)
G6TK	Reference Item (Crestor)	80*	8.0*	6 (621 - 626)	6 (671 - 676)
Total				**30**	**30**

*Dose reduced from 80 mg/kg/day to 60 mg/kg/day as per Study Plan Amendment 01.

Unique study design:	Assessment of sensory function tests
Deviation from study protocol:	None reported. (p. 42)

Observations	
Mortality:	Assessed twice daily during the dosing and recovery periods
Clinical signs:	Cage side observations were assessed twice daily during dosing and recovery periods. Detailed observations were performed before initiation of dosing and then once weekly for main study animals.
Body weights:	Animals were weighed on Day 1 of dosing and at least once weekly during the dosing period. During the recovery period, body weights were recorded on Day 1 of recovery, at the initiation of the second week and on Day 44.
Feed consumption:	Recorded weekly per cage during the dosing period for main study animals. During the recovery period, feed weight was recorded on Day 1 and then at least once weekly. Expressed as mean weekly food consumption (g/animal/week).
Ophthalmoscopy:	Performed on all main study animals before dosing initiation, and towards the end of the dosing period in control (G1 and G2) and high-dose groups (G5, G6). Examinations were performed with a hand held ophthalmoscope.
Sensory Functions:	Towards the end of the dosing period, tests to assess the sensory reactivity to different stimuli were performed on control and high-dose groups (G1, G2, G5, G6). These included startle response, touch response, response to nociceptive stimuli and righting reflex.
Hematology:	Blood was collected at termination (Day 31) and also at the end of the recovery period (Day 45). The following parameters were analyzed: erythrocyte count (RBC), Hemoglobin (Hb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Platelet Volume (MPV), Cell Hemoglobin Concentration Mean (CHCM), Leukocyte Count (WBC), Differential Leukocyte Count, Platelet Count (PLT), Reticulocyte Count, and Prothrombin time (seconds)
Clinical chemistry:	Blood was collected at termination (Day 31) and also at the end of the recovery period (Day 45). The following parameters were analyzed: Albumin/Globulin (A/G), Alanine Amino Transferase (ALT), Albumin (ALB), Alkaline Phosphatase (ALK-P), Aspartate Amino Transferase (AST), Calcium (Ca), Cholesterol (Chol), Creatinine (Creat), Creatinine Kinase (CK), Globulin (Glob), Glucose (Glu), Inorganic Phosphorus (PHOS), Total Bilirubin (T.Bil), Total Protein (TP), Triglycerides (TRIG), Urea, Potassium (K), Sodium (Na), and Chloride (CL)

<table>
<tr><td>Urinalysis:</td><td>Animals were kept in metabolic cages for a minimum of 16 hours to collect urine. Physical observations included clarity and color; chemical observations evaluated by reagent strip included specific gravity, glucose, bilirubin, ketone, blood, pH, protein, urobilinogen, nitrate and leukocytes; microscopic observations included pus cells, casts, epithelial cells, red blood cells, crystals and sperm</td></tr>
<tr><td>Gross pathology:</td><td>Animals were fasted overnight before necropsy. Carcasses were observed externally for abnormalities and cranial, thoracic and visceral cavities were opened and examined macroscopically.</td></tr>
<tr><td>Organ weights:</td><td>The following organs were weighed at necropsy (paired organs were weighed together): adrenals, kidneys, thymus, brain, liver, testes, heart, spleen, epididymis, ovaries with fallopian tubes, uterus with cervix, and lungs with main stem bronchi</td></tr>
<tr><td>Histopathology:</td><td>Tissues and organs were fixed in 10% neutral buffered formalin except for the testes and epididymis which were fixed in modified Davidson’s fixative before transfer to 10% neutral buffered formalin. Bone marrow smears were prepared from the femur but were not examined. The following tissues were preserved for histopathology examination from control and high-dose animals (G1, G2, G5, G6); however based on findings in the liver and stomach, lower dose groups were evaluated for these organs (except G3 males):
<table>
<tr><td>Adrenals</td><td>Lachrymal glands</td><td>Skeletal muscle</td></tr>
<tr><td>Aorta</td><td>Larynx</td><td>Seminal vesicles</td></tr>
<tr><td>Bone (femur) with joint</td><td>Liver</td><td>Spinal cord (Cervical, Mid-Thoracic, Lumbar)</td></tr>
<tr><td>Brain</td><td>Lungs including main stem bronchi</td><td>Spleen</td></tr>
<tr><td>Cecum</td><td>Lymph nodes (Mandibular, Mesenteric, Cervical)</td><td>Skin</td></tr>
<tr><td>Colon</td><td>Mammary glands</td><td>Sternum</td></tr>
<tr><td>Duodenum</td><td>Nasal cavity</td><td>Stomach</td></tr>
<tr><td>Epididymes</td><td>Optic nerves</td><td>Testes</td></tr>
<tr><td>Esophagus</td><td>Ovaries with Fallopian tubes</td><td>Thymus</td></tr>
<tr><td>Eyes</td><td>Pancreas</td><td>Thyroids including parathyroid</td></tr>
<tr><td>Heart</td><td>Pharynx</td><td>Tongue</td></tr>
<tr><td>Harderian Gland</td><td>Pituitary</td><td>Trachea</td></tr>
<tr><td>Ileum</td><td>Prostate</td><td>Urinary bladder</td></tr>
<tr><td>Jejunum</td><td>Rectum</td><td>Uterus including cervix</td></tr>
<tr><td rowspan="2">Kidneys</td><td>Salivary glands (Submandibular, Sublingual, Parotid)</td><td>Vagina</td></tr>
<tr><td>Sciatic nerve</td><td>Zymbal Gland</td></tr>
</table>
“Histopathology of found dead animals and moribund animals, sacrificed during course of the study, will be done at the discretion of the study director/pathologist.”
(Applicant Table)</td></tr>
<tr><td>Toxicokinetics:</td><td>Blood samples were collected from TK animals (3/sex/group) on Days 1, 15 and 30 during the dosing period. Blood samples were collected at 0 (pre-dose), 1.5, 3, 8 and 24 hours post-dosing and additionally at 48 hours post-dose on Day 30. Rosuvastatin concentrations were estimated by using validated LC/MS/MS.</td></tr>
</table>

Results

Mortality

There were several deaths in Group 6 / Group 6R (Crestor) as follows:

- G6: Male No. **602**, Day 14: No microscopic findings as all organs were autolysed; Clinical signs included hunched back, piloerection and lethargy
- G6R: Male No. **616**, Day 20: Liver necrosis (single cell, minimal) and congestion; cachectic appearance, small thymus; forestomach hyperkeratinization (mild); Clinical signs included hunched back, piloerection and lethargy: BW loss between Week 2 – Week 3 (~59 g)
- G6R: Male No. **619**, Day 13: Liver necrosis (single cell, minimal) and congestion; small thymus; forestomach hyperkeratinization (mild); Clinical signs included hunched back, piloerection and lethargy: BW loss between Week 1 – Week 2 (~3 g)
- G6: Female No. **655**, Day 21: No microscopic findings as all organs were autolysed; Clinical signs included hunched back, piloerection and lethargy; BW loss between Week 1 – Week 3 (~35 g)
- G6: Female No. **660**, Day 15: No microscopic findings as all organs were autolysed; Clinical signs included hunched back, piloerection and lethargy

There were two additional animal deaths which the Applicant stated could be attributed to “wrong dosing” (Reviewer’s note: gavage error). Evidence of gavage error was noted:

- G2R (placebo control): Female No. **261**, Day 18; Dark red lung, evidence of trachea puncture; No clinical signs
- G4 (40 mg/kg rosuvastatin): Female No. **455**, Day 15: Liver necrosis (single cell, mild) and congestion (mild); fore stomach hyperkeratinization (minimal); Lungs red, possible puncture in trachea/lung; No clinical signs

The following TK animals were found dead and were not further assessed per protocol:

- G3TK (20 mg/kg rosuvastatin): Female 364 Found Dead on Day 18
- G5TK (80/60 mg/kg rosuvastatin): Male 522 Found Dead on Day 15
- G6TK (80/60 mg/kg Crestor): Male 622 Found Dead on Day 19

Clinical Signs

- Clinical signs were limited to those animals found dead during the study period and included hunched back, piloerection and lethargy.

Table 1: Clinical Signs – MALES (Number of Incidences/ Animal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
***N=**	**20**	**10**	**10**	**10**	**19**	**15**
Hunched Back	--	--	--	--	38/1	18/4
Piloerection	--	--	--	--	--	14/3
Lethargy	--	--	--	--	--	19/3

*N= combined main study and recovery animals during dosing period

Table 2: Clinical Signs - FEMALES (Number of Incidences/ Animal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
***N=**	**20**	**20**	**10**	**10**	**20**	**18**
Hunched Back	--	--	--	--	--	19/2
Piloerection	--	--	--	--	--	19/2
Lethargy	--	--	--	--	--	10/2

*N= combined main study and recovery animals during dosing period

Body Weights

- There was no significant difference in body weight or body weight gain in dosed animals versus control or placebo groups in either sex. There was a trend for decreased body weight gain with doses ≥40 mg/kg in males and at 60/80 mg/kg in females (both rosuvastatin (b) (4) and Crestor reference).
- During the 14 day recovery period, although there was no statistically significant difference in body weight gain of 60/80 mg/kg dosed animals, both sexes had higher weight gain versus vehicle control or placebo.

Table 3: Body Weight Gain (g) (Week 1 – Week 5)

Group	PEG (b) (4) G1, G1R	Placebo G2, G2R	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5, G5R	60/80 mg/kg CRESTOR G6, G6R
Males	108.65	106.44	102.76	87.2	83.37	91.07
Females	40.81	43.91	42.36	40.35	37.62	34.86

Table 4: Body Weight Gain (g) (Recovery Week 1 – Recovery Week 2/ Day 44)

Group	PEG (b) (4) G1R	Placebo G2R	60/80 mg/kg Rosuva. G5R	60/80 mg/kg CRESTOR G6R
Males	27.04	33.64	49.04	44.36
Females	9.96	7.56	11.1	14.54

Feed Consumption

- There was a transient decrease in food consumption during Week 2 of dosing in males at the highest dose (60/80 mg/kg rosuvastatin (b) (4) and Crestor). This decrease continued in Week 3 but was not statistically significant.

Table 5: MALES – Average Food Consumption (g) (Week 1 – Week 4)

Group	PEG (b) (4) G1, G1R	Placebo G2, G2R	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5, G5R	60/80 mg/kg CRESTOR G6, G6R
Week 1	144.87	142.06	142.19	147.44	140.07	138.46
Week 2	149.31	148.11	144.98	145.76	**119.58***	**106.35***
Week 3	152.89	153.54	149.92	145.77	133.23	134.81
Week 4	139.47	136.40	141.05	140.44	148.41	147.44

(*) $p<0.05$ versus vehicle control using Dunnett's test

Table 6: FEMALES – Average Food Consumption (g) (Week 1 – Week 4)

Group	PEG (b) (4) G1, G1R	Placebo G2, G2R	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5, G5R	60/80 mg/kg CRESTOR G6, G6R
Week 1	98.76	98.15	102.29	105.61	94.36	97.02
Week 2	100.62	99.59	101.82	109.81	106.89	95.41
Week 3	99.67	100.25	104.16	105.69	104.55	102.60
Week 4	99.18	101.30	106.57	107.25	102.81	108.11

Ophthalmoscopy

No abnormal ophthalmology findings were reported at pre-dose or at the termination of dosing for the control groups (G1, G2) or high dose rosuvastatin and Crestor dose groups (G5, G6).

Sensory Function Tests
No abnormal findings were reported at the termination of dosing for the control groups (G1, G2) or high dose rosuvastatin and Crestor dose groups (G5, G6). Parameters evaluated included startle response, touch response, nociceptive stimuli response, and righting reflex.

ECG

Not conducted.

Hematology

Dosing Phase:

- Group 6 (Crestor) males had a slight elevation in WBCs (~1.3X).
- There were slight and non-dose dependent increases in CHCM (Cell Hemoglobin Concentration Mean) in males.
- When compared to PEG (b) (4) vehicle control, all other female dose groups had a decrease in PT (prothrombin time). As there was no difference to placebo control, this finding is not likely biologically relevant.

Recovery Phase:

- Reticulocyte counts slightly increased in males following recovery in rosuvastatin dosed animals.

Table 7: MALES – Hematology (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**10**	**10**	**9**
WBC (10^3/µL)	7.225	7.262	7.410	8.418	7.016	**9.086***
CHCM (g/dL)	35.07	34.92	35.07	**35.69***	35.48	**35.80***
PLT (10^3/µL)	925.9	905.7	958.8	926.0	1043.8	986.4
Neutrophil (%)	15.86	20.20	16.05	**21.80***	17.54	17.62
PT (sec)	8.94	8.82	**8.51***	**8.46***	8.60	8.83

(*) $p<0.05$ versus vehicle control using Dunnett's test

Table 8: FEMALES – Hematology (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**9**	**10**	**8**
WBC (10^3/µL)	4.769	5.198	4.809	5.889	5.314	5.659
CHCM (g/dL)	35.71	35.30	35.40	35.40	35.55	35.79
PLT (10^3/µL)	881.3	980.8	919.4	927.7	910.3	1036.8
Neutrophil (%)	14.67	15.92	15.96	15.99	13.21	14.79
PT (sec)	9.21	**7.58***	**7.75***	**7.51***	**7.87***	**7.95***

(*) p<0.05 versus vehicle control using Dunnett's test

Table 9: MALES – Hematology (Recovery)

Group	PEG (b) (4) G1R	Placebo G2R	60/80 mg/kg Rosuva. G5R	60/80 mg/kg CRESTOR G6R
N =	**10**	**10**	**10**	**8**
PLT (10^3/µL)	884.0	881.0	952.3	972.8
Reticulocyte (%)	2.148	2.563	**2.988***	**3.223***

(*) p<0.05 versus vehicle control using Dunnett's test

Table 10: FEMALES – Hematology (Recovery)

Group	PEG (b) (4) G1R	Placebo G2R	60/80 mg/kg Rosuva. G5R	60/80 mg/kg CRESTOR G6R
N =	**10**	**10**	**10**	**8**
PLT (10^3/µL)	838.7	907.9	937.3	921.0
Reticulocyte (%)	2.544	2.231	2.337	2.497

Clinical Chemistry

- Liver enzymes (ALT, ALKP, AST) increased similarly in animals dosed with 60/80 mg/kg rosuvastatin test article or Crestor reference in both sexes. AST increased at all doses in males (<2X compared to PEG (b) (4) vehicle control). In general these increases were ≤2X when compared to either PEG (b) (4) or placebo control.
- CK (creatinine kinase) increased significantly (<2X) in males at doses ≥40 mg/kg rosuvastatin and in females only at the highest dose tested (60/80 mg/kg).
- Glucose decreased mildly in males at doses ≥40 mg/kg rosuvastatin and in females only at the highest dose tested (60/80 mg/kg) which only reached statistical significance for Crestor.
- TG decreased at all rosuvastatin doses only in females.

- Total protein and globulin both decreased in males at the highest rosuvastatin dose (test article and Crestor) resulting in an increase in A/G ratio.
- These clinical chemistry changes were reversible.

Table 11: MALES – Clinical Chemistry (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	10	10	10	10	10	9
ALT (U/L)	27.7	28.1	34.0	36.8	**41.1***	**44.3***
ALKP (U/L)	265.9	307.9	320.0	**337.0***	329.7	**374.3***
AST (U/L)	101.6	87.7	**152.8***	**189.6***	**191.7***	**205.6***
Chol (mg/dL)	92.0	108.2	**111.8***	104.3	90.4	96.1
CK (U/L)	676.7	472.4	902.4	**1244.3***	**1050.9***	**1049.2***
GLU (mg/dL)	104.6	115.1	106.3	**83.0***	**82.5***	**82.8***
TRIG (mg/dL)	46.2	**61.9***	41.9	44.3	38.7	42.0
Ca (mg/dL)	10.997	**11.671***	10.904	10.638	**10.368***	**10.061***
T.Prot (g/dL)	7.006	7.322	7.031	7.068	**6.289***	**6.529***
T.Bili (mg/dL)	0.139	0.173	**0.373***	**0.413***	0.133	0.204
Globulin (g/dL)	3.239	3.476	3.209	3.209	**2.676***	**2.806***
A/G	1.163	1.106	1.197	1.206	**1.354***	**1.331***

(*) p<0.05 versus vehicle control using Dunnett's test

Table 12: FEMALES – Clinical Chemistry (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	10	10	10	9	10	8
ALT (U/L)	24.2	20.9	24.0	23.7	**29.2***	**30.3***
ALKP (U/L)	108.5	124.0	129.1	122.6	132.8	**199.1***
AST (U/L)	105.3	100.7	106.6	104.4	**131.9***	**145.5***
Chol (mg/dL)	77.6	76.3	96.4	**101.2***	**104.7***	88.4
CK (U/L)	678.9	898.9	761.5	763.3	**1043.1***	**940.5***
GLU (mg/dL)	93.0	97.1	90.3	91.6	83.2	**79.4***
TRIG (mg/dL)	56.7	52.7	**32.7***	**38.7***	**36.3***	**29.5***
Ca (mg/dL)	11.198	11.345	11.165	11.398	11.298	11.166
T.Prot (g/dL)	7.053	7.225	7.334	7.407	7.370	7.193
T.Bili (mg/dL)	0.213	0.230	0.222	0.214	0.217	0.199
Globulin (g/dL)	3.000	3.096	3.107	3.171	3.143	2.991
A/G	1.355	1.336	1.365	1.340	1.346	1.408

(*) p<0.05 versus vehicle control using Dunnett's test

Table 13: MALES – Clinical Chemistry (Recovery)

Group	PEG (b) (4) G1R	Placebo G2R	60/80 mg/kg Rosuva. G5R	60/80 mg/kg CRESTOR G6R
N =	**10**	**10**	**10**	**8**
Phos (mg/dL)	8.318	8.001	**8.901***	8.053
CL (mmol/L)	104.22	104.78	105.11	**106.28***

(*) p<0.05 versus vehicle control using Dunnett's test

Table 14: FEMALES – Clinical Chemistry (Recovery)

Group	PEG (b) (4) G1R	Placebo G2R	60/80 mg/kg Rosuva. G5R	60/80 mg/kg CRESTOR G6R
N =	**10**	**10**	**10**	**8**
ALKP (U/L)	84.0	92.6	**113.9***	108.5
CK (U/L)	596.8	535.7	555.5	756.2
Phos (mg/dL)	6.663	6.538	6.799	6.919
T.Bili (mg/dL)	0.241	0.223	**0.174***	**0.162***

(*) p<0.05 versus vehicle control using Dunnett's test

Urinalysis

- There were no significant changes in urinalysis parameters; however, the incidence of nitrite increased slightly at the highest rosuvastatin dose tested in females but was likely in the normal range of variability.

Table 15: FEMALE - Urinalysis (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**9**	**10**	**8**
Protein (trace)	0	0	2	2	3	2
Nitrite (positive)	1	1	1	1	3	4

Table 16: FEMALE - Urinalysis (Recovery)

Group	PEG (b) (4) G1	Placebo G2	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**9**	**10**	**10**
Protein (trace/ 1+)	0	1	1	1
Nitrite (positive)	5	1	0	2

Gross Pathology

Gross pathology findings were limited to animals found dead and included cachectic appearance, red/dark lung (possible puncture), small thymus, and autolysis of organs.

Table 17: Gross Pathology – Terminal Animals

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
(M/F) N =	**10/10**	**10/10**	**10/10**	**10/10**	**10/10**	**10/10**
Cachectic Appearance						0/1
Organs Autolysed						1/2
Red lung (possible puncture)				0/1		

Table 18: Gross Pathology – Recovery Animals (Male/Female)

Group	PEG (b) (4) G1	Placebo G2	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
(M/F) N =	**10/10**	**10/10**	**10/10**	**10/10**
Cachectic Appearance				1/0
Froth (nostrils)		0/1		
Small Thymus				2/0
COD unknown				2/0
Kidney – soft/ fluid filled		0/1		
Dark lung (possible puncture)		0/1		

COD = Cause of Death

Organ Weights

- Liver: There were decreased absolute liver weights in males of all rosuvastatin dose groups (≤16%). Females had a slight increase in relative liver weight in rosuvastatin (b) (4) dose groups ≥40 mg/kg (~1.1X).

- Adrenals: Absolute adrenal weights decreased slightly in males at the highest rosuvastatin dose tested. In rodents this could be attributed to decreased cholesterol production, but clinical chemistry did not indicate a significant reduction of cholesterol in this study in any rosuvastatin dose group.
- Testes: Testes relative weight increased slightly at rosuvastatin doses ≥40 mg/kg when compared to vehicle control (~1.2X).
- These mild changes in organ weights were reversible.

Table 19: MALES - Organ Weights (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**10**	**10**	**9**
Mean BW (g)	**303.52**	**303.19**	**288.19**	**280.88**	**272.31**	**288.56**
Liver (g)	9.823	9.529	**8.543***	**8.345***	**8.279***	**8.733***
% BW	3.237	3.142	2.961	2.971	3.087	3.028
Adrenals (g)	0.079	0.083	0.069	0.077	**0.061***	**0.066***
% BW	0.026	0.027	0.024	0.028	0.023	0.023
Brain (g)	1.857	1.864	1.841	1.912	1.850	1.846
% BW	0.614	0.619	0.642	**0.683***	**0.692***	0.642
Testes (g)	3.259	3.329	3.209	3.600	3.348	3.568
%BW	1.076	1.100	1.116	**1.285***	**1.255***	**1.237***

(*) p<0.05 versus vehicle control using Dunnett's test; Note: Numbers have been rounded by reviewer.

Table 20: FEMALES - Organ Weights (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**9**	**10**	**8**
Mean BW (g)	**188.98**	**183.76**	**187.69**	**179.09**	**185.79**	**179.38**
Liver (g)	6.083	6.146	6.489	6.392	6.704	6.205
% BW	3.222	3.343	3.460	**3.578***	**3.611***	3.470
Adrenals (g)	0.077	0.076	0.073	0.075	0.073	0.072
% BW	0.041	0.041	0.039	0.042	0.040	0.040

(*) p<0.05 versus vehicle control using Dunnett's test; Note: Numbers have been rounded by reviewer.

Table 21: MALES - Organ Weights (Recovery)

Group	PEG (b) (4) G1	Placebo G2	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**10**	**10**	**8**
Mean BW (g)	**323.48**	**326.31**	**334.65**	**321.09**
Liver (g)	9.213	9.645	10.114	9.517
% BW	2.849	2.951	3.028	2.965
Lungs + bronchi (g)	1.823	1.667	1.710	**2.284***
% BW	0.566	0.513	0.514	0.713
Adrenals (g)	0.080	0.077	0.070	0.074
% BW	0.025	0.024	0.021	0.023
Kidneys (g)	2.001	2.077	2.261	2.096
% BW	0.618	0.636	**0.679***	0.653

(*) p<0.05 versus vehicle control using Dunnett's test; Note: Numbers have been rounded by reviewer.

Table 22: FEMALES - Organ Weights (Recovery)

Group	PEG (b) (4) G1	Placebo G2	60/80 mg/kg Rosuva. G5	60/80 mg/kg CRESTOR G6
N =	**10**	**9**	**10**	**10**
Mean BW (g)	**196.78**	**199.43**	**192.85**	**197.38**
Liver (g)	6.301	5.999	6.082	6.579
% BW	3.196	3.012	3.156	3.351
Lungs + bronchi (g)	1.516	1.483	1.546	1.489
% BW	0.770	0.747	0.803	0.761
Adrenals (g)	0.071	0.079	0.077	0.076
% BW	0.036	0.039	0.040	0.039

Note: Numbers have been rounded by reviewer.

Histopathology

Adequate Battery: Yes

Peer Review: Noted only for liver and stomach in all groups except G3 males and kidney was peer reviewed in G1, G2, G5 and G6.

Histological Findings

- *Liver*: Cytoplasmic microvesiculation and single cell necrosis was observed in males at rosuvastatin doses ≥40 mg/kg and in females at the highest dose tested (60/80 mg/kg). The incidence was comparable between high-dose rosuvastatin

(b) (4) and Crestor. Minimal microvesiculation tended to persist following the 14-Day recovery period in animals of both sexes.

- *Stomach*: Minimal to mild forestomach hyperkeratosis was observed at the highest dose tested in both sexes and also at 40 mg/kg rosuvastatin (b) (4) in females.
- *Muscle*: One HD rosuvastatin (b) (4) male had a finding of skeletal muscle necrosis (No. 506). This same animal had a high CK value of 1528 U/L.
- *Lung*: Individual animals at the highest rosuvastatin doses in both sexes had mild lung infiltration of WBCs.

Table 23: MALES - Histopathology (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**9**
Liver						
Microves., cytoplas. +	0	0	0	4	4	3
Microves., cytoplas. ++	0	0	0	0	2	6
Necrosis, single cell +	0	0	0	1	5	6
Lung + Bronchi						
Infiltration, PMN +	0	0	-	-	1	1
Stomach						
Hyperkerat. forestom. +	0	0	-	0	4	4
Hyperkerat. forestom. ++	0	0	-	0	1	1
Skeletal Muscle						
Necrosis +	0	0	-	-	1	0

(+) Minimal (++) Mild (-) Not analyzed

Table 24: FEMALES - Histopathology (Terminal)

Group	PEG (b) (4) G1	Placebo G2	20 mg/kg Rosuva. G3	40 mg/kg Rosuva. G4	60/80 mg/kg Rosuva. G5	60/80 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**8**
Liver						
Microves., cytoplas. +	0	0	0	0	2	1
Microves., cytoplas. ++	0	0	0	0	3	2
Necrosis, single cell +	0	0	0	0	2	2
Necrosis, single cell ++	0	0	0	1*	0	0
Congestion	0	0	0	1*	0	0
Lung + Bronchi						
Infiltration, monocyte +	0	0	-	-	2	1
Histiocytes, alveolar +	0	1	-	-	0	2
Stomach						
Hyperkerat. forestom. +	0	0	0	2	4	4
Hyperkerat. forestom. ++	0	0	0	0	0	1

(+) Minimal (++) Mild (-) Not analyzed (*) Found Dead animal

Table 25: MALES - Histopathology (Recovery)

Group	PEG (b) (4) G1	60/80 mg/kg Rosuva. G5	60/80 mg/kg Crestor G6
N =	**10**	**10**	**10**
Liver			
Infiltration, Mono. +	0	0	0
Microves., cytoplas. +	0	3	2
Necrosis, single cell +	0	0	2*
Congestion ++	0	0	2*
Stomach			
Hyperkerat. forestom. ++	0	0	2*

(+) Minimal (++) Mild (-) Not analyzed (*) Found Dead animal

Table 26: FEMALES - Histopathology (Recovery)

Group	PEG (b) (4) G1	60/80 mg/kg Rosuva. G5	60/80 mg/kg Crestor G6
N =	**10**	**10**	**10**
Liver			
Infiltration, Mono. +	1	2	2
Microves., cytoplas. +	0	1	1

(+) Minimal (++) Mild (-) Not analyzed

Table 27: Terminal Histopathology

Phase: Terminal

Tissues and Observation		Groups											
		G1		G2		G3		G4		G5		G5	
Dose (mg/kg/day)		0, Vehicle control (PEG (b) (4)		0, Placebo of Rosuvastatin		20		40		60		60, Reference Item (Crestor)	
						Rosuvastatin							
Number of animals in dose group		10		10		10		10		10		10	
		M	F	M	F	M	F	M	F	M	F	M	F
Number of animals examined		10	10	10	10	10	10	10	10	10	10	9	8
Liver													
WNL		2	5	4	7	10	9	5	7	3	4	0	3
Infiltration, MNC	+	3	1	3	0	0	1	1	2	3	1	0	1
Vacuolation, cytoplasmic, diffuse	+	6	4	5	3	0	0	0	0	0	0	0	0
Microvesicle, cytoplasmic, periportal	+	0	0	0	0	0	0	4	0	4	2	3	1
	++	0	0	0	0	0	0	0	0	2	3	6	2
Necrosis, single cell	+	0	0	0	0	0	0	1	0	5	2	6	2
	++	0	0	0	0	0	0	0	1*	0	0	0	0
Congestion	++	0	0	0	0	0	0	0	1*	0	0	0	0
Stomach													
WNL		10	10	10	10	NA	10	10	8	5	6	4	3
Hyperkeratinization, fore stomach	+	0	0	0	0		0	0	2	4	4	4	4
	++	0	0	0	0		0	0	0	1	0	1	1

(Applicant Table)

Table 28: Recovery Histopathology

Phase: Reversal

Tissues and Observation		Groups					
		G1R		G5R		G6R	
Dose (mg/kg/day)		0, Vehicle control (PEG (b) (4)		60, Rosuvastatin		60, Reference Item (Crestor)	
Number of animals in dose group		10		10		10	
		M	F	M	F	M	F
Number of animals examined		10	10	10	10	10	10
Liver							
WNL		10	9	7	8	6	8
Infiltration, MNC	+	0	1	0	2	0	2
Microvesicle, cytoplasmic, periportal	+	0	0	3	1	2	1
Necrosis, single cell	+	0	0	0	0	2*	0
Congestion	++	0	0	0	0	2*	0
Stomach							
WNL		10	10	10	10	8	10
Hyperkeratinization, fore stomach	++	0	0	0	0	2*	0

Key: WNL- Within Normal Limit, MNC- Mono Nuclear Cell, +- Minimum, ++- Mild, P- Present, NA- Not Applicable, *In found dead animal

(Applicant Table)

Special Evaluation

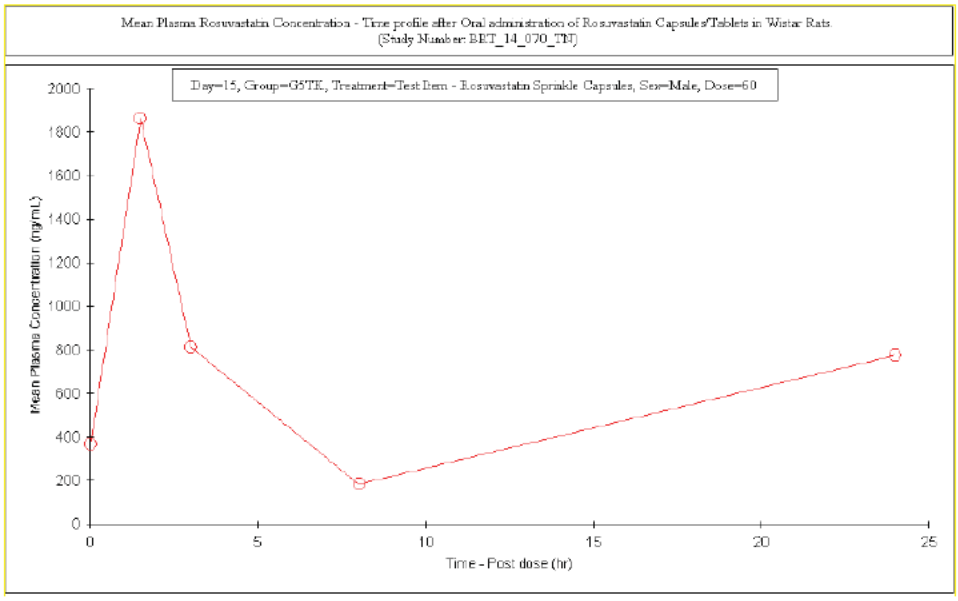
N/A

Toxicokinetics

- C_{max} was lower in rosuvastatin test article (G5TK) animals than for the same dose of Crestor reference drug (G6TK). On Day 30, the C_{max} of rosuvastatin test article was approximately 38% lower in females and approximately 5% lower in males.
- AUC_{0-t} was lower in rosuvastatin test article (G5TK) animals than for the same dose of Crestor reference drug (G6TK). On Day 30, the AUC_{0-t} of rosuvastatin test article was approximately 29% lower in females and approximately 9% lower in males.
- AUC_{0-inf} was lower in rosuvastatin test article (G5TK) animals than for the same dose of Crestor reference drug (G6TK). On Day 30, the AUC_{0-inf} of rosuvastatin test article was approximately 27% lower in females and approximately 8% lower in males.
- Exposures (C_{max} and AUC) increased with dose in both sexes.
- Exposures (C_{max} and AUC) tended to increase with dosing from Day 1 to Day 30 in both sexes for rosuvastatin. Exposures of Crestor (G6TK) also increased from Day 1 to Day 30.
- On Day 15, AUC_{0-t} and Cmax was increased from Day 1 in males in Groups 5TK and 6TK (high dose rosuvastatin (b) (4) and Crestor).

Reviewer's Note: Day 15 TK (G5TK) males had an unexplained increase in mean plasma concentration between 8 and 24 hours post-dose (Tmax was 1.5 hr.).

Figure 1: Mean Rosuvastatin Concentration (Day 15/ Group 5TK Males)



(Applicant Figure)

Reviewer's Note: TK analysis on Day 15 showed an approximate increase in AUC_{0-t} of 12X and 18X for males in the highest dose groups of rosuvastatin (b) (4) and Crestor, respectively. The high-dose was decreased to 60 mg/kg beginning on Day 12 for females and Day 14 for males (one day before TK analysis). This extensive increase was not observed on Day 30 where exposures were increased from Day 1 by 2-3X in high-dose males. This observed increase as measured on Day 15 may have been due to accumulation from 80 mg/kg/day in males in both of these high-dose groups. Dosing was decreased to 60 mg/kg on Day 14 for males (only 1 day before TK analysis), and the previous 14-Day toxicology study demonstrated a more than dose

proportional increase in exposure with increasing dose along with higher exposure in Crestor treated animals.

Table 29: Increase in AUC_{0-t} (ng.hr/mL) Following Repeat Dosing

Sex	TK Analysis	60/80 mg/kg Rosuvastatin	60/80 mg/kg CRESTOR
MALE	Day 1 → Day 15	11.6X	17.8X
	Day 1 → Day 30	2.4X	2.7X
FEMALE	Day 1 → Day 15	1.1X	1.5X
	Day 1 → Day 30	1.4X	1.2X

The 80 mg/kg/day dose was decreased to 60 mg/kg/day effective on Day 12 for females and Day 14 for males.

Table 30: Increase in C_{max} (ng/mL) Following Repeat Dosing

Sex	TK Analysis	60/80 mg/kg Rosuvastatin	60/80 mg/kg CRESTOR
MALE	Day 1 → Day 15	29X	22X
	Day 1 → Day 30	4X	4X
FEMALE	Day 1 → Day 15	2X	2X
	Day 1 → Day 30	2X	2X

The 80 mg/kg/day dose was decreased to 60 mg/kg/day effective on Day 12 for females and Day 14 for males.

The Applicant noted that the elimination phase was not properly characterized for the following groups (less than three concentrations were available after C_{max}):

- Group 4TK (40 mg/kg) Females on Day 1
- Group 3TK (20 mg/kg) Males on Day 15
- Group 3TK (20 mg/kg) Males and Females on Day 30
- Group 4TK (40 mg/kg) Females on Day 30
- Group 6TK (80 mg/kg Crestor) Males Day 15

Table 31: PK Profile (Days 1, 15 and 30)

Number of animals	3/tp		3/tp		3/tp		3/tp	
	M	F	M	F	M	F	M	F
Group, Dosage	G3TK, 20 mg/kg/day		G4TK, 40 mg/kg/day		G5TK, 80 mg/kg/day		G6TK, 80 mg/kg/day	
Day 1								
C_{max} (ng/mL)	26.320	45.967	54.987	84.780	65.413	129.983	74.920	180.207
AUC_{0-t} (hr*ng/mL)	140.283	463.483	778.054	1014.593	1197.256	1728.765	1156.778	2731.158
AUC_{0-inf} (hr*ng/mL)	*	535.358	*	*	*	1926.463	1301.150	*
T_{max} (hr)	3.00	1.50	8.00	3.00	8.00	1.50	1.50	8.00
Day 15								
C_{max} (ng/mL)	38.463	60.720	209.733	240.283	1865.377	291.783	1610.677	305.523
AUC_{0-t} (hr*ng/mL)	533.873	770.860	2280.672	1465.971	13876.831	1943.132	20617.898	4015.123
AUC_{0-inf} (hr*ng/mL)	*	935.363	2652.372	1649.498	*	2098.874	*	4639.936
T_{max} (hr)	3.00	1.50	1.50	1.50	1.50	1.50	3.00	1.50
Day 30								
C_{max} (ng/mL)	56.820	68.277	233.650	138.927	264.983	220.283	278.927	354.313
AUC_{0-t} (hr*ng/mL)	709.935	649.168	2411.964	1355.544	2845.074	2408.928	3136.893	3383.720
AUC_{0-inf} (hr*ng/mL)	*	*	2488.099	*	2997.286	2537.264	3268.624	3455.460
T_{max} (hr)	3.00	3.00	3.00	3.00	1.50	1.50	1.50	1.50

All the values for parameters mentioned above were 0 for G2TK animals on all days. tp: Time Point, *: Values not estimable

(Applicant Table)

Table 32: $T_{1/2}$ (hours) Values

	Male				Female			
	G3TK	G4TK	G5TK	G6TK	G3TK	G4TK	G5TK	G6TK
	20 mg/kg Rosuva.	40 mg/kg Rosuva.	80 mg/kg Rosuva.	80 mg/kg Crestor	20 mg/kg Rosuva.	40 mg/kg Rosuva.	80 mg/kg Rosuva.	80 mg/kg Crestor
Day 1	--	--	--	7.978	8.771	--	7.546	--
Day 15	--	8.927	--	--	10.558	7.749	6.541	8.810
Day 30	--	10.274	10.899	9.738	--	--	10.252	8.786

(--) Not generated; Rosuva. = Rosuvastatin (b) (4) (test article)

In summary, exposures at equivalent doses of rosuvastatin were slightly lower for the rosuvastatin test article than for the reference product Crestor, in both sexes (AUC_{0-t} was ~29% lower in females and ~9% lower in males on Day 30). $T_{1/2}$ was similar with slightly longer half-life of rosuvastatin (b) (4) than Crestor at comparable doses.

Dosing Solution Analysis

All rosuvastatin suspensions were within the specification limits.

Study title: A 14-Day Repeated Dose Oral Dose Range Finding Toxicity Study of Rosuvastatin Calcium (b) (4) Capsules in Wistar Rat with Toxicokinetic Evaluation	
Study no.:	BRT_14_043_TN
Study report location:	SD-1
Conducting laboratory and location:	Biological Research Toxicology Sun Pharma Advanced Research Company Limited Tandalja, Vadodara – 390 020, India
Date of study initiation:	7/11/14
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Rosuvastatin Calcium (b) (4) Capsules, Batch No. JKN2312

Key Study Findings

- This study was conducted to establish a NOAEL and target organ toxicity for the pivotal, GLP-compliant 30-Day bridging toxicology study with Crestor reference.
- Deaths were observed at the highest dose tested in both rosuvastatin (b) (4) and Crestor dose groups (100 mg/kg)
- Target organ toxicities included the liver, kidney, spleen/thymus/bone marrow and reproductive organs predominantly in the highest rosuvastatin dose groups tested (rosuvastatin (b) (4) and Crestor). Toxicities and deaths were more prevalent in the male Crestor group likely because plasma exposures (AUC) were approximately 4X higher than in the high-dose rosuvastatin (b) (4) dose group.
- TK analysis showed increased dose with exposure, higher plasma exposures in males versus females, increased exposures following repeat dosing (Day 14 versus Day 1), and higher rosuvastatin plasma exposure in 100 mg/kg treated Crestor males than 100 mg/kg rosuvastatin (b) (4) (test article) treated males.
- The NOAEL proposed by the Applicant was the mid-dose group, 50 mg/kg rosuvastatin, for 14 days. Toxicities at higher doses included decreased body weight gain; liver vacuolation, single cell necrosis, and karyomegaly; kidney glomerular atrophy and tubule dilatation/ degeneration; thymus and spleen congestion or lymphoid depletion; and testes tubule degeneration. This reviewer would agree with this assessment of the NOAEL. The AUC_{0-t} values at the NOAEL are 3996.377 and 1708.249 ng.hr/ml for males and females, respectively, on Day 14.

Methods	
Doses:	0 (vehicle), 0 (placebo), 25, 50, 100 mg/kg plus 100 mg/kg Crestor

Group and Test item	Dose (mg/kg/day)	Concentration (mg/mL)	Number of animals (Animal ID)	
			Male	Female
G1, Vehicle control (PEG (b) (4)	0	0	10 (101 – 110)	10 (151 – 160)
G2, Placebo of Rosuvastatin	0	0	10 (201 – 210)	10 (251 – 260)
G3, Rosuvastatin	25	2.5	10 (301 – 310)	10 (351 – 360)
G4, Rosuvastatin	50	5.0	10 (401 – 410)	10 (451 – 460)
G5, Rosuvastatin	100	10	10 (501 – 510)	10 (551 – 560)
G6, Reference Item (Crestor)	100	10	10 (601 – 610)	10 (651 – 660)
G2TK, Placebo of Rosuvastatin	0	0	6 (211 – 216)	6 (261 – 266)
G3TK, Rosuvastatin	25	2.5	6 (311 – 316)	6 (361 – 366)
G4TK, Rosuvastatin	50	5	6 (411 – 416)	6 (461 – 466)
G5TK, Rosuvastatin	100	10	6 (511 – 516)	6 (561 – 566)
G6TK, Reference Item (Crestor)	100	10	6 (611 – 616)	6 (661 – 666)
Total			90	90

(Applicant Table)

Frequency of dosing:	Daily for 14 days
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Polyethylene Glycol (PEG)
Species/Strain:	Wistar rats (b) (4)
Number/Sex/Group:	10/sex/group
Age:	5-7 weeks (receipt); 6-8 weeks (dosing)
Weight:	Not stated
Satellite groups:	TK animals 6/sex/group
Unique study design:	None
Deviation from study protocol:	None reported.

Observations	
Mortality:	Assessed twice daily during the dosing period
Clinical signs:	Monitored once weekly
Body weights:	Monitored once weekly
Feed consumption:	Monitored once weekly
Ophthalmoscopy:	N/A
Hematology:	Blood was collected at termination (Day 15). The following parameters were analyzed: erythrocyte count (RBC), Hemoglobin (Hb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Platelet Volume (MPV), Cell Hemoglobin Concentration Mean (CHCM), Leukocyte Count

<table>
<tr><td></td><td>(WBC), Differential Leukocyte Count, Platelet Count (PLT), Reticulocyte Count, and Prothrombin time (seconds)</td></tr>
<tr><td>Clinical chemistry:</td><td>Blood was collected at termination (Day 15). The following parameters were analyzed: Albumin/Globulin (A/G), Alanine Amino Transferase (ALT), Albumin (ALB), Alkaline Phosphatase (ALK-P), Aspartate Amino Transferase (AST), Calcium (Ca), Cholesterol (Chol), Creatinine (Creat), Creatinine Kinase (CK), Globulin (Glob), Glucose (Glu), Inorganic Phosphorus (PHOS), Total Bilirubin (T.Bil), Total Protein (TP), Triglycerides (TRIG), Urea, Potassium (K), Sodium (Na), and Chloride (CL)</td></tr>
<tr><td>Urinalysis:</td><td>Animals were kept in metabolic cages overnight to collect urine. The following were analyzed: appearance/ clarity, color, specific gravity, glucose, bilirubin, ketone, blood, pH, protein, urobilinogen, nitrate and leukocytes; microscopic observations included pus cells, casts, epithelial cells, red blood cells, crystals and sperm</td></tr>
<tr><td>Gross pathology:</td><td>Animals were fasted overnight before necropsy. Carcasses were observed externally for abnormalities and cranial, thoracic and visceral cavities were opened and examined macroscopically.</td></tr>
<tr><td>Organ weights:</td><td>The following organs were weighed at necropsy (paired organs were weighed together): adrenals, kidneys, thymus, brain, liver, testes, heart, spleen, epididymis, ovaries with fallopian tubes</td></tr>
<tr><td>Histopathology:</td><td>Tissues and organs were fixed in 10% neutral buffered formalin except for the testes and epididymis which were fixed in modified Davidson’s fixative before transfer to 10% neutral buffered formalin. The following tissues were preserved for histopathology examination from control and high-dose animals (G1, G2, G5, G6) and extended in a step-down manner to evaluate findings in lower dose groups:
<table>
<tr><td>Adrenals</td><td>Larynx</td><td>Seminal vesicles</td></tr>
<tr><td>Aorta</td><td>Liver</td><td>Spinal cord (Cervical, Mid-Thoracic, Lumbar)</td></tr>
<tr><td>Bone (femur) with joint</td><td>Lungs including main stem bronchi</td><td>Spleen</td></tr>
<tr><td>Brain</td><td>Lymph nodes (Mandibular, Mesenteric, Cervical)</td><td>Skin</td></tr>
<tr><td>Cecum</td><td>Mammary glands</td><td>Sternum</td></tr>
<tr><td>Colon</td><td>Nasal cavity</td><td>Stomach</td></tr>
<tr><td>Duodenum</td><td>Optic nerves</td><td>Testes</td></tr>
<tr><td>Epididymes</td><td>Ovaries with Fallopian tubes</td><td>Thymus</td></tr>
<tr><td>Esophagus</td><td>Pancreas</td><td>Thyroids including parathyroid</td></tr>
<tr><td>Eyes</td><td>Pharynx</td><td>Tongue</td></tr>
<tr><td>Heart</td><td>Pituitary</td><td>Trachea</td></tr>
<tr><td>Harderian Gland</td><td>Prostate</td><td>Urinary bladder</td></tr>
<tr><td>Ileum</td><td>Rectum</td><td>Uterus including cervix</td></tr>
<tr><td>Jejunum</td><td>Salivary glands (Submandibular, Sublingual, Parotid)</td><td>Vagina</td></tr>
<tr><td>Kidneys</td><td>Sciatic nerve</td><td>Zymbal Gland</td></tr>
<tr><td>Lachrymal glands</td><td>Skeletal muscle</td><td>Gross lesion/ Any other</td></tr>
</table>
Histopathology of found dead animals during course of the study was done at the discretion of the study director/pathologist.

(Applicant Table)</td></tr>
</table>

Toxicokinetics:	Blood samples were collected from TK animals on Days 1 and 14 during the dosing period. Blood samples were collected at 0 (pre-dose), 1.5, 3, 8 and 24 hours post-dosing and additionally at 48 hours post-dose on Day 14. Rosuvastatin concentrations were analyzed using LC/MS/MS method.

Results

Mortality

The following animals were found dead at doses of 100 mg/kg (Crestor (G6) and rosuvastatin test article (G5)):
G5 Female (No. 553): Day 10
G5 Female (No. 556): Day 15 (post-blood collection)
G5 Female (No. 557): Day 15 (post-blood collection)

G6 Male (No. 606): Day 12
G6 Male (No. 601): Day 13
G6 Male (No. 609): Day 13
G6 Male (No. 602): Day 15
G6 Male (No. 605): Day 15
G6 Male (No. 607): Day 15 (post-blood collection)
G6 Female (No. 657): Day 9
G6 Female (No. 652): Day 10
G6 Female (No. 651): Day 15
G6 Female (No. 659): Day 15
G6TK Female: Day 13

Table 33: Mortality (%)

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**10**
Males	0	0	0	0	0	60%
Females	0	0	0	0	30%	40%

Clinical Signs

There were no reported clinical signs.

Body Weights

- In the highest dose rosuvastatin groups (G5 and G6), there was a decrease in both absolute and percent body weight gain which only reached statistical significance in the Crestor dose group.

Table 34: Mean Absolute Body Weight (g) - Day 14

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	10	10	10	10	10	7
Males	258.84	255.93	256.82	261.54	247.53	**185.27***
Females	183.19	177.79	173.54	180.30	175.66	**159.80***

(*) p < 0.05 versus vehicle control using Dunnett's Test

Table 35: Percent Body Weight Change - Day 14

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	10	10	10	10	9	8
Males	42.50	33.91	37.47	38.85	33.63	**0.89***
Females	21.75	20.37	17.16	21.28	18.32	**6.61***

(*) p < 0.05 versus vehicle control using Dunnett's Test

Feed Consumption

- There was a statistically significant reduction in food consumption in G6 (Crestor) males. Reduced food consumption (non-significant) was also observed in G5 males (rosuvastatin (b) (4) 100 mg/kg) and Crestor dosed females.

Table 36: Summary of Food Consumption (g/animal/week) - Day 14

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	5	5	5	5	5	5
Males	123.23	118.47	117.68	122.27	113.91	**60.88***
Females	82.29	82.37	81.25	84.22	83.41	70.37

(*) p < 0.05 versus vehicle control using Dunnett's Test

Ophthalmoscopy

N/A

ECG

N/A

Hematology

- Changes in hematology parameters were limited to the highest dose tested (100 mg/kg) for both Crestor and the rosuvastatin test article predominantly in males.
- Slight increases in RBC parameters including Hgb, Hct, MCHC and CHCM were observed in males.
- A significant increase in neutrophils and a decrease in lymphocytes were observed in high-dose Crestor males. Slight increases in monocytes and basophils were also observed.
- Reticulocytes significantly decreased in Crestor dosed males.

Table 37: MALES: Hematology – Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**5**
RBC (10^6/µL)	8.057	8.193	8.176	8.127	**8.578***	**9.598***
HGB (g/dL)	15.50	15.82	15.73	15.71	16.29	**18.56***
HCT (%)	46.97	47.90	47.95	47.68	48.29	**53.02***
MCV (fL)	58.28	58.54	58.63	58.69	56.35	**55.24***
MCHC (g/dL)	33.03	33.03	32.82	32.94	**33.76***	**35.02***
CHCM (g/dL)	34.48	34.45	34.54	34.64	**35.05***	**36.42***
MPV (fL)	7.72	7.99	7.96	8.20*	**8.41***	**8.42***
Neutrophil (%)	18.11	17.34	15.38	15.75	18.38	**53.70***
Lymphocyte (%)	78.95	79.10	81.90	81.50	78.51	**39.86***
Monocyte (%)	1.94	2.25	1.70	1.73	1.94	**4.66***
Basophil (%)	0.30	0.31	0.35	0.32	0.42	**0.56***
Reticulocyte (%)	3.619	3.292	3.707	3.925	3.336	**0.884***

(*) $p < 0.05$ versus vehicle control using Dunnett's Test

Table 38: FEMALES: Hematology – Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**9**	**6**
WBC (10^3/µL)	4.879	5.361	6.116	5.866	**6.657***	**6.962***
MPV (fL)	7.58	7.80	7.91	**8.09***	**8.23***	**8.15***
Eosinophil (%)	1.39	**0.97***	**0.69***	**0.79***	**0.83***	1.02

(*) $p < 0.05$ versus vehicle control using Dunnett's Test

Clinical Chemistry

- Liver enzymes increased after 14 days of dosing in Crestor treated males only. ALT increased 7X, ALP increased 2X and AST increased 5X, versus vehicle control. Additional changes in Crestor treated males included increased urea (2X), decreased total protein and globulin and decreased sodium and chloride.
- In high-dose rosuvastatin test article dosed animals, there were slight increases in phosphorus and decreased total protein and globulin in males.
- Females in all rosuvastatin dose groups had decreased triglycerides when compared to vehicle control (≤60%) but not to placebo control.

Table 39: MALES: Clinical Chemistry – Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	10	10	10	10	10	5
ALT (U/L)	36.5	28.4	36.2	34.7	46.5	**239.6***
ALKP (U/L)	494.3	404.5	457.5	469.3	649.4	**859.6***
AST (U/L)	123.2	101.2	139.0	146.3	198.1	**661.8***
Chol (mg/dL)	78.4	75.7	93.6	95.5	97.5	99.6
ALB (g/dL)	3.778	3.691	3.735	3.671	3.732	**3.398***
Urea (mg/dL)	36.1	31.7	33.5	35.9	33.1	**62.2***
Phos (mg/dL)	8.709	9.274	9.352	8.972	**9.838***	**7.110***
Ca (mg/dL)	11.010	10.904	10.746	10.500	**10.908***	**10.116***
T.Prot (g/dL)	6.446	6.233	6.194	**6.061***	**5.942***	**5.248***
T.Bili (mg/dL)	0.094	0.083	0.104	0.114	**0.148***	**0.208***
Globulin (g/dL)	2.668	2.542	**2.459***	**2.390***	**2.210***	**1.850***
A/G	1.420	1.456	1.524	**1.541***	**1.701***	**1.846***
Na	142.50	143.52	**145.27***	143.71	143.27	**137.94***
Cl	103.37	105.15	**106.47***	**105.77***	104.44	**100.34***

(*) $p < 0.05$ versus vehicle control using Dunnett's Test

Table 40: FEMALES: Clinical Chemistry – Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	10	10	10	10	9	6
TRIG (mg/dL)	72.7	**44.5***	**39.0***	**39.0***	**34.2***	**29.2***
Phos (mg/dL)	6.199	**7.460***	**7.663***	**8.061***	**8.409***	**7.858***
T.Bili (mg/dL)	0.133	0.130	0.151	0.157	**0.174***	0.142
Na	142.12	141.31	143.20	143.82	143.21	**138.83***
K	5.250	5.013	4.910	5.621	**5.951***	5.022
Cl	105.41	105.24	106.68	**107.66***	106.46	**102.43***

(*) $p < 0.05$ versus vehicle control using Dunnett's Test

Urinalysis

- There was a slight increase in specific gravity in Crestor treated males (G6).
- In general, Crestor dosed males had higher levels of protein, leukocytes and RBCs when compared to controls.
- There was a slight decrease in pH in rosuvastatin G4 and G5 females as compared to vehicle control (G1).

Table 41: MALES – Urinalysis Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**7**
Sp. Gravity	1.0105	1.0140	1.0150	1.0170	1.0145	**1.0229***
Protein 1+	4	0	0	2	0	1
Protein 2+	0	0	0	0	0	1
Protein 3+	0	0	0	0	0	5
Leukocytes 1+	0	0	0	0	0	2
Leukocytes 3+	0	0	0	0	0	3
Pus cells/field Min.	0	0	0	0	0	4
Pus cells/field Mild	0	0	0	0	0	2
RBC/field Min.	0	0	0	0	0	4

1+: Small, 2+: Moderate, 3+: Moderate; (*) p<0.05 using Dunnett's test

Table 42: FEMALES – Urinalysis Day 15

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**9**	**6**
pH	7.55	6.95	7.25	**6.80***	**6.67***	7.00

(*) p < 0.05 versus vehicle control using Dunnett's Test

Gross Pathology

- One 100 mg/kg dosed Crestor male (Group 6) was found with a small thymus and spleen.

Table 43: MALES - Gross Pathology

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**10**
Found Dead	-	-	-	-	-	5
Spleen/Thymus small	-	-	-	-	-	1
Autolysis	-	-	-	-	-	3

Table 44: FEMALES - Gross Pathology

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**10**
Found Dead	-	-	-	-	3	4
Autolysis	-	-	-	-	3	3

Organ Weights

- In males, there were statistically significant decreases in absolute weights of the liver, heart, spleen, brain, thymus, testes and epididymides in Crestor dosed animals (G6) as compared to vehicle control (G1). This correlated to the significant decrease in total body weight.
- In males, there were significant changes in relative organs weights (%) in the Crestor dose group (G6) as follows: increased relative kidney and adrenal weights and decreased relative spleen and thymus weights.
- In females, there was a statistically significant decrease in thymus weight (absolute and relative) in all rosuvastatin treated groups as well as in the placebo group. There was a trend of increased liver weight in high dose rosuvastatin groups and a slight increase in relative kidney weight in all rosuvastatin treated groups.

Table 45: MALES – Organ Weights

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**10**	**5**
BW (g)	**229.68**	**228.74**	**228.63**	**234.60**	**217.97**	**169.32***
Kidneys (g)	1.989	1.929	1.948	1.927	1.870	1.829
% BW	0.868	0.844	0.852	0.822	0.858	**1.110***
Spleen (g)	0.489	0.514	0.475	0.517	0.512	**0.218***
% BW	0.213	0.225	0.207	0.221	0.235	**0.124***
Thymus (g)	0.537	0.539	0.532	0.559	0.508	**0.238***
% BW	0.235	0.235	0.234	0.239	0.234	**0.130***
Adrenals (g)	0.072	0.066	0.065	0.064	0.061	0.065
% BW	0.031	0.029	0.029	0.027	0.028	**0.040***

(*) p<0.05 using Dunnett's test versus control; Numbers have been rounded by reviewer.

Table 46: FEMALES – Organ Weights

Group	PEG (b) (4) G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**10**	**10**	**7**	**6**
BW (g)	**165.42**	**159.85**	**156.93**	**161.00**	**158.66**	**155.63**
Liver (g)	5.404	5.506	5.213	5.370	5.744	6.023
% BW	3.268	3.446	3.322	3.334	3.628	**3.872***
Kidneys (g)	1.300	1.349	1.357	1.376	1.381	1.386
% BW	0.786	0.844	**0.866***	**0.855***	**0.872***	**0.894***
Thymus (g)	0.509	**0.421***	**0.422***	**0.416***	**0.406***	**0.395***
% BW	0.308	0.264	0.269	**0.260***	**0.257***	**0.251***

(*) p<0.05 using Dunnett's test versus control; Numbers have been rounded by reviewer.

Histopathology

Adequate Battery Yes

Peer Review No

Histological Findings

- Liver: Cytoplasmic vacuolation, single cell necrosis and karyomegaly were observed in both sexes at the highest rosuvastatin dose tested (100 mg/kg test article and Crestor) following 14 days of administration. Additionally, males in the 50 mg/kg rosuvastatin dose group also had minimal cytoplasmic vacuolation.

- Kidney: The kidney cortex was affected in both sexes at the highest dose of rosuvastatin (100 mg/kg test article and Crestor) with findings of glomerular atrophy, tubule degeneration, tubule dilatation and leukocyte infiltration.
- Spleen/ Thymus/ Immune System: Spleen congestion and thymus lymphoid depletion were only observed in high-dose Crestor groups of both sexes. Additional findings of congestion (thyroid, pituitary) and lymphoid depletion of the mandibular lymph nodes were also observed in Crestor dosed animals.
- Bone Marrow: High-dose Crestor had 6/7 males and 1/7 females with a finding of bone marrow (femur) hemorrhage.
- Reproductive Organs: Tubule degeneration of the testes was observed in high-dose rosuvastatin males (100 mg/kg test article and Crestor) and 1/7 females in the Crestor group had mild hemorrhage of the ovaries.

Table 47: MALES - Histopathology

Group	PEG [(b) (4)] G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**-**	**-**	**10**	**7**
Spleen						
Congestion +	0	0	-	-	0	1
Congestion ++	0	0	-	-	0	4
Thymus						
Depletion, Lymphoid +	0	0	-	-	0	3
Depletion, Lymphoid ++	0	0	-	-	0	2
Salivary Glands						
Depletion, gland.+	0	0	-	-	0	4
Mandibular LN						
Depletion, lymphoid+	0	0	-	-	0	4
Liver						
Vacuolation, cyto peri+	0	0	-	2	5	1
Vacuolation, cyto peri++	0	0	-	0	3	0
Necrosis, single cell+	0	0	-	0	3	3
Necrosis, single cell++	0	0	-	0	0	2
Karyomegaly+	0	0	-	0	0	1
Thyroid						
Congestion+	0	0	-	-	0	2
Pituitary						
Congestion+	0	0	-	-	0	3
Kidney, Cortex						
Infiltration, MNC+	0	0	-	0	2	0
Atrophy, glom.+	0	0	-	0	3	4
Atrophy, glom.++	0	0	-	0	2	2
Dilatation, tubule+	1	0	-	0	4	5
Dilatation, tubule++	0	0	-	0	0	1
Degen., tubules+	0	0	-	0	2	0
Degen., tubules++	0	0	-	0	0	3
Degen., tubules+++	0	0	-	0	0	2
Kidneys, Medulla						
Dilatation, tubule+	0	0	-	0	0	1
Testes						
Degeneration, tubule+	0	0	-	-	1	1
Degeneration, tubule++	0	0	-	-	0	2
Harderian Glands						
Pigmentation, brown+	1	4	-	-	0	3
Pigmentation, brown++	0	0	-	-	0	3
Bone (femur)						
Hemorrhage, BM+	1	0	-	-	0	6

cyto = cytoplasmic; peri. = periportal; degen. = degeneration; glom. = glomerular; BM = bone marrow; MNC = mononuclear cell; + = minimal, ++ = mild, +++ = moderate

Table 48: FEMALES - Histopathology

Group	PEG [(b) (4)] G1	Placebo G2	25 mg/kg Rosuva. G3	50 mg/kg Rosuva. G4	100 mg/kg Rosuva. G5	100 mg/kg Crestor G6
N =	**10**	**10**	**-**	**-**	**7**	**7**
Spleen						
Congestion +	0	0	-	-	0	2
Thymus						
Depletion, Lymphoid +	0	0	-	-	0	1
Depletion, Lymphoid ++	0	0	-	-	0	1
Congestion+	0	0	-	-	2	0
Salivary Glands						
Depletion, gland.+	0	0	-	-	0	1
Liver						
Vacuolation, cyto peri+	0	2	-	0	4	3
Necrosis, single cell+	0	0	-	0	1	0
Necrosis, single cell++	0	0	-	0	0	1
Karyomegaly+	0	0	-	0	3	1
Pituitary						
Congestion+	0	0	-	-	0	1
Kidney, Cortex						
Infiltration, MNC+	0	2	-	0	2	0
Atrophy, glom.+	0	0	-	0	4	2
Atrophy, glom.++	0	0	-	0	0	1
Dilatation, tubule+	0	0	-	0	3	2
Degen., tubules+	0	0	-	0	0	2
Degen., tubules++	0	0	-	0	1	1
Ovaries						
Hemorrhage++	0	0	-	-	0	1
Harderian Glands						
Pigmentation, brown+	0	1	-	-	0	5
Pigmentation, brown++	0	0	-	-	0	1
Bone (femur)						
Hemorrhage, BM+	0	0	-	-	0	1

cyto = cytoplasmic; peri. = periportal; degen. = degenerated; glom. = glomerular; BM = bone marrow; MNC = mononuclear cell; + = minimal, ++ = mild

Special Evaluation

N/A

Toxicokinetics

- Noted in study report: Due to minimal contamination in plasma samples of placebo TK group (G2TK), blood samples were recollected using 6 males and 6 females at predefined time points and plasma samples were sent to PKD.
- Exposures of rosuvastatin (AUC and Cmax) increased with dose on Day 1 and Day 14 (more than dose proportional on Day 14).
- Exposures of rosuvastatin (AUC and Cmax) generally increased from Day 1 to Day 14, in both sexes, but were more prominent in males.
- Plasma exposures of rosuvastatin were higher in males than in females.
- In males, plasma AUC exposure of rosuvastatin following 100 mg/kg Crestor administration was approximately 4X higher than 100 mg/kg rosuvastatin (b) (4) on Day 14. C_{max}, T_{max} and $t_{1/2}$ in these two dose groups were similar.
- Plasma AUC exposures of rosuvastatin following 100 mg/kg Crestor or 100 mg/kg rosuvastatin (b) (4) were similar in females on Day 14 (rosuvastatin (b) (4) exposures were ~1.6X higher than for Crestor). C_{max}, T_{max} and $t_{1/2}$ in these two dose groups were similar.

Table 49: Day 14 PK Parameters

Sex	Dose Group	AUC_{0-t} (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Males	G5 TK	61,731	10,487	1.5	5.9
	G6 TK	235,688	9781	3.0	5.7
Females	G5 TK	17,633	1426	3.0	6.4
	G6 TK	10,781	998	3.0	6.1

G5 TK = 100 mg/kg rosuvastatin (b) (4) (test article)
G6TK = 100 mg/kg Crestor (reference article)

Table 50: PK Profile (Days 1 and 14)

Group and Dose (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	T_{max} (hr)
Sex: Male	**Day: 1**				**Day: 14**			
G2TK, 0	0	0	0	0	0	0	0	0
G3TK, 25	34.920	573.023	-	3.00	71.020	887.426	1407.293	1.50
G4TK, 50	58.947	805.707	889.736	1.50	418.177	3996.377	4621.398	3.00
G5TK, 100	110.267	1270.145	-	3.00	10487.147	61731.374	61962.694	1.50
G6TK, 100	105.437	1684.544	1964.154	1.50	9780.970	235687.965	236101.965	3.00
Sex: Female	**Day: 1**				**Day: 14**			
G2TK, 0	0	0	0	0	0	0	0	0
G3TK, 25	147.523	1777.638	-	3.00	103.397	1074.133	1176.468	1.50
G4TK, 50	115.443	1557.956	-	3.00	144.500	1708.249	1794.779	1.50
G5TK, 100	934.323	8813.798	-	3.00	1426.457	17632.873	17662.275	3.00
G6TK, 100	321.140	3506.249	5017.795	1.50	998.400	10781.466	10822.481	3.00

- : Value not estimable
(Applicant Table)

Dosing Solution Analysis

Stated that "Results of concentration and homogeneity analysis were within acceptance limits (b) (4)

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Not conduced.
The approved label for rosuvastatin (Crestor) under NDA 21366 states, "Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with Salmonella typhimurium and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells."

7.2 *In Vitro* Assays in Mammalian Cells

Not conducted.
The approved label for rosuvastatin (Crestor) under NDA 21366 states, "Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with Salmonella typhimurium and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells."

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Not conducted.
The approved label for rosuvastatin (Crestor) under NDA 21366 states, "Rosuvastatin was negative in the in vivo mouse micronucleus test."

7.4 Other Genetic Toxicity Studies

Not conducted.

8 Carcinogenicity

Not conducted.
The approved label for rosuvastatin (Crestor) under NDA 21366 states the following:

"In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses."

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Not conducted.
The approved label for rosuvastatin (Crestor) under NDA 21366 states the following: "In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class."

9.2 Embryonic Fetal Development

Not conducted.
The approved label for rosuvastatin (Crestor) under NDA 21366 states the following: "Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times the human exposure at 40 mg/day based on AUC)."

"Rosuvastatin was not teratogenic in rats at ≤ 25 mg/kg/day or in rabbits ≤ 3 mg/kg/day ([redacted]^(b) (4) equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively)."

9.3 Prenatal and Postnatal Development

Not conducted.

The approved label for rosuvastatin (Crestor) under NDA 21366 states the following: "In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, (b) (4) 12 times the human exposure at 40 mg/day based on body surface area.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), (b) (4) equivalent to the human exposure at 40 mg/day based on body surface area, decreased fetal viability and maternal mortality was observed."

10 Special Toxicology Studies

Not conducted.

11 Integrated Summary and Safety Evaluation

The Applicant is submitting NDA 208647, a 505(b)(2) application for rosuvastatin (b) (4) capsules. A GLP-compliant rat bridging toxicology study was conducted with the listed drug, Crestor (rosuvastatin calcium) as well as a 14-Day rat dose-range finding study. No other nonclinical studies were submitted with this application and the Applicant proposes to rely on the Agency's finding of safety and effectiveness for the U.S. approved listed drug, Crestor (rosuvastatin calcium). From a nonclinical perspective, there are three issues pertaining to the review of this application: 1) does the GLP-compliant, pivotal rat bridging toxicology study adequately show head-to-head comparability of the two rosuvastatin products for the safety profile, 2) are there any unqualified impurities that would require genetic toxicology testing per ICH guidance documents, and 3) are the excipients all previously used and within the accepted limits.

I. Nonclinical safety profile of rosuvastatin (b) (4) test article as compared to Crestor

The 30-Day rat toxicology bridging study was completed under GLP-compliance except for the toxicokinetic sample analysis phase. Doses selected were appropriate with two control groups (PEG (b) (4) vehicle control and placebo) and a 14-Day recovery period. Direct comparison of the TK and toxicity profiles of rosuvastatin (b) (4) test article and a single high-dose group of Crestor (80/60 mg/kg) was completed. Due to toxicity and animal deaths, the high dose of 80 mg/kg was reduced to 60 mg/kg beginning on Day 12 for females and Day 14 for males until the completion of the study. A 14-Day rat dose range finding study used a high-dose of 100 mg/kg rosuvastatin which also caused animal deaths beginning as early as Day 9 of dosing.

There were multiple animal deaths between Day 14 – Day 21 in the high-dose Crestor groups (male and female) only; however, it is noted that rosuvastatin plasma exposures in these groups were higher than in the high-dose rosuvastatin (b) (4) groups. Animals that did not have organ autolysis were reported to have findings including liver necrosis, forestomach hyperkeratinization and a small thymus. Additional deaths (including

placebo) were sporadic and were thought to be due to gavage error which was supported by gross pathology findings.

Target organs of toxicity in the 30-Day rat bridging toxicology study included: 1) the liver with elevated liver enzymes (AST, ALT, ALP), decreased liver weights and histopathology findings of cytoplasmic microvesicles and single cell necrosis, 2) the forestomach with a finding of hyperkeratinization, and 3) skeletal muscle as creatinine kinase was elevated and an individual male rat presented with necrosis upon histological examination. Most of these toxicities were more prevalent at the highest dose tested of rosuvastatin (80/60 mg/kg) in both sexes for both rosuvastatin (b) (4) test article and Crestor. See toxicity comparison in the table below.

Table 51: Toxicity Comparison between Rosuvastatin calcium (b) (4) and Crestor (30-Day GLP Rat Toxicology Study)

	Parameter	Male		Female	
		60 mg/kg Rosuvastatin	60 mg/kg Crestor	60 mg/kg Rosuvastatin	60 mg/kg Crestor
PK (Day 30)	AUC_{0-t} (hr.ng/mL)	2845	3137	2409	3384
	C_{max} (ng/mL)	265	279	220	354
	$T_{1/2}$ (hr)	10.9	9.7	10.3	8.8
Clinical Signs	Death	-	✓	-	✓
	↓ BW Gain	✓ (ns)	✓ (ns)	✓ (ns)	✓ (ns)
Hematology	↑ WBC	-	✓ (1.3X)	-	-
Clinical Chemistry	↑ ALT	✓ (1.5X)	✓ (1.6X)	✓ (1.2X)	✓ (1.3X)
	↑ ALP	-	✓ (1.4X)	-	✓ (1.8X)
	↑ AST	✓ (1.9X)	✓ (2.0X)	✓ (1.3X)	✓ (1.4X)
	↑ CK	✓ (1.6X)	✓ (1.6X)	✓ (1.5X)	✓ (1.4X)
	↓ Glucose	✓ (-21%)	✓ (-21%)	-	✓ (-15%)
	↓ T. Protein	✓ (-10%)	✓ (-7%)	-	-
	↓ Globulin	✓ (-17%)	✓ (-13%)	-	-
Organ Weights	↓ Liver Wt.	✓ (-16%)	✓ (-11%)	-	-
	↓ Adrenal Wt.	✓ (-23%)	✓ (-16%)	-	-
	↑ Testes Wt.	✓ (1.2X)	✓ (1.2X)	-	-
Histopath (incidence)	Liver microves.	6/10	9/9	5/10	3/8
	Liver sc necrosis	5/10	6/9	2/10	2/8
	Stomach hyper.	5/10	5/9	4/10	5/8
	Sk. M. necrosis	1/10	-	-	-
	Lung Infiltration	1/10	1/9	2/10	1/8

Note: Numerical values in parenthesis are fold increase/ percent decrease from vehicle control.
(ns) = not statistically significant; (sc) = single cell; (microves.) = microvesicles; (hyper.) = hyperkeratosis; (Sk. M.) = Skeletal Muscle
The original dose in the 30-Day rat toxicology bridging study was 80 mg/kg; however due to toxicity, this dose was reduced to 60 mg/kg on Day 12 for females and Day 14 for males.

The TK profile of rosuvastatin between the test article and Crestor were reasonably comparable on Day 30 of dosing. For 60 mg/kg dosed males, rosuvastatin plasma

exposure (AUC_{0-t}) was approximately 9% lower in the rosuvastatin [(b) (4)] dose group than for Crestor. For 60 mg/kg treated females, rosuvastatin plasma exposure was approximately 29% lower in the rosuvastatin [(b) (4)] group versus Crestor. Given the modestly higher exposures with Crestor treated animals, the toxicity profile was either comparable (e.g. same target organs of toxicity) or more severe (i.e., only Crestor treated animals were found dead as related to rosuvastatin administration), which could be reasonably expected from the higher plasma exposures. It was observed that rosuvastatin exposures increased significantly with increased dose as observed in the 14-Day dose ranging toxicity study in the rat. In this study, Crestor treated males at 100 mg/kg had a 4X increase in exposure than rosuvastatin [(b) (4)] treated males and also correlated with mortality. Despite the general differences of increased rosuvastatin plasma exposure with Crestor treated animals (predominantly in males), the toxicity profile of both products were similar in both the 14-Day dose range finding study as well as the GLP-compliant pivotal 30-Day bridging toxicology study. Higher exposures only exacerbated liver and kidney toxicities and resulted in clinical signs (lethargy, piloerection etc.) that preceded death associated with liver necrosis.

II. Impurity profile of rosuvastatin [(b) (4)] test article

The Applicant submitted data on the impurity profile of the drug product batch used in nonclinical studies (Batch No. JKN2312), which was identical to the clinical drug product used in PK studies. Per ICH Q3B(R2) for impurities in new drug products, the maximum recommended dose of 40 mg/day rosuvastatin is used for the following threshold limits: Reporting threshold is [(b) (4)]% [(b) (4)]; Identification threshold is [(b) (4)]% or [(b) (4)] mg total daily intake (TDI), whichever is lower [(b) (4)] and the qualification threshold is [(b) (4)]% or [(b) (4)] mcg TDI, whichever is lower [(b) (4)] Per these guidance limits and the impurity table below, no additional qualification on the impurities (i.e. genetic toxicology) would need to be completed for the following reasons:

- The highest unknown impurity at [(b) (4)]% would not need to be identified as it is below the identification threshold for a total daily intake of 40 mg.
- The highest impurity [(b) (4)] [(b) (4)] has been qualified in the 30-Day rat toxicology bridging study but would not need additional qualification as it is well below the qualification threshold of [(b) (4)] for a total daily intake of 40 mg.
- No structural alerts were identified.

Table 52: Assay and Impurity Results of Batch JKN2312 Drug Product, 40 mg

Parameter	Specification	Result
Assay by HPLC	(b) (4)	(b) (4)
(b) (4)		

NMT = not more than; RRT = relative retention time

(Applicant Table)

Therefore, per ICH Q3B(R2), the impurities identified do not reach the threshold for qualification (b) (4)% or (b) (4) mcg TDI) through additional in vitro genetic toxicology testing for 40 mg/day of a drug product. Additionally, the highest unknown impurity at (b) (4)% does not meet the identification threshold for a drug product (b) (4)% or (b) (4)mg TDI).

The Applicant provided additional information on the content of elemental iron for each proposed rosuvastatin capsule. The reported daily dietary recommendation for iron ranges between 8-18 mg/day depending on age and gender for adult (b) (4) (1.8X higher for (b) (4)), per the NIH Office of Dietary Supplements on Iron (2015) and the Institute of Medicine[1]. The highest reported amount of iron based on formulation would result from a 40 mg rosuvastatin dose (8 capsules of 5 mg) and (b) (4). This would be (b) (4) lower than the lowest 8 mg dietary daily recommendation in adults. In contrast, one capsule of 5 mg rosuvastatin would only contain (b) (4) lower than the daily recommended dietary intake.

(b) (4)

[1] Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc : a Report of the Panel on Micronutrients. Washington, DC: National Academy Press; 2001.

III. Excipients

There are no novel excipients used in the formulation of rosuvastatin (b) (4) drug product. All excipients as reported in the table below are within the approved limits in the IIG (Inactive Ingredient Guide).

Table 54: Excipients in Rosuvastatin Capsules

Excipients	Function	mg/capsule				IIG Limit
		5-mg capsule	10-mg capsule	20-mg capsule	40-mg capsule[1]	
Capsule contents						
Mannitol (b) (4)	(b) (4)					
Microcrystalline cellulose (b) (4)						
Crospovidone, (b) (4) (b) (4)						
Sodium citrate (b) (4)						
Hypromellose (b) (4) (b) (4)						
Polyethylene glycol 4000						
Silicon dioxide (b) (4) (b) (4)						
Magnesium oxide (b) (4)						
Ferric oxide (b) (4)						
Capsule composition[2]						
(b) (4) capsules, imprinted axially (b) (4) on cap and body in black	--	(b) (4)				
Gelatin, NF, *Ph. Eur*	--					
Water, USP, IP, *Ph. Eur*	--					
Sodium lauryl sulphate, NF, IP, *Ph. Eur.*	--					
Titanium dioxide, USP, *Ph. Eur.*, IP	--					
FD & C Blue 1	--					
FD & C Green 3	--					
FD & C Red 3	--					
FD & C Red 28	--					
FD & C Red 40	---					

[1] The batch used in nonclinical studies BRT_14_043_TN and BRT_14_070_TN, as well as clinical studies PKD_14_128, PKD_14_129, and PKD_14_291, was of this capsule strength and composition.
[2] The capsules were not administered to animals in nonclinical studies.

(Applicant Table)

Nonclinical Summary and Recommendation

The Applicant submitted NDA 208647, rosuvastatin (b) (4) capsules for the treatment of a subset of Crestor indications no longer covered under patent as follows: 1) hypertriglyceridemia, 2) primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) and, 3) homozygous familial hypercholesterolemia in adult patients. The rosuvastatin capsules are an immediate release product comprised of a hard gelatin capsule filled with rosuvastatin containing (b) (4) in strengths of 5, 10, 20 and 40 mg. This design

may be used for those patients that have difficulty swallowing an intact tablet and would benefit from the (b) (4) formulation including intake via sprinkling on soft food (e.g., apple sauce). The Applicant's rationale for a 505(b)(2) pathway relies on nonclinical bridging, clinical bioequivalence to the listed drug (Crestor) and the agency's prior determination of safety and efficacy of rosuvastatin administered once daily at doses of 5 – 40 mg.

A nonclinical 30-Day rat toxicology bridging study was conducted with the listed drug Crestor (rosuvastatin calcium) for safety comparison. There was no significant difference in the toxicity profile between rosuvastatin (b) (4) and Crestor in rats in either the GLP-compliant 30-Day bridging toxicity study or in the 14-Day (non-GLP) dose range finding study. Differences in the PK profile predominantly included an increase in plasma exposure of rosuvastatin following Crestor administration (versus rosuvastatin (b) (4) in males that increased with dose. This higher exposure in Crestor treated rats correlated with a higher incidence of death in these animals and pathology findings associated with liver and forestomach toxicity. There are no novel excipients that would require further nonclinical studies and all levels are within the accepted IIG limits. Impurities and degradants are all below the qualification threshold per ICH Guidance documents but were also present in the batch used in the pivotal 30-Day bridging rat toxicology study.

Taken together, from a nonclinical perspective the applicant has demonstrated a reasonably similar toxicity safety profile in the rat between the rosuvastatin (b) (4) formulation product and the U.S. approved product, Crestor (rosuvastatin calcium tablets).

Table 55: Safety Margins

Species	NOAEL (mg/kg) M/F	AUC_{0-t} (ng.hr/mL)	Safety Margin Based on AUC[1]	Safety Margin Based on BSA[2]
Rat 30-Day	20 mg/kg (HED = (b) (4) mg/kg)	♂: 709.9	2X	5X
		♀: 649.2	2X	
Rat 14-Day	50 mg/kg (HED = (b) (4) mg/kg)	♂: 3996	13X	12X
		♀: 1708	6X	

HED = Human Equivalent Dose
(1) AUC_{0-76} in human: (b) (4) ng.hr/ml at 40 mg/day.
(2) BSA (Body Surface Area) based on a 60 kg adult and 40 mg/day dose = (b) (4) mg/kg/day

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/s/

STEPHANIE J QUINN
05/20/2016

CALVIN L ELMORE
05/20/2016
I concur