CLINICAL REVIEW

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(Proposed) Trade Name	CRESTOR®
Therapeutic Class	Lipid lowering
Applicant	AstraZeneca Pharmaceuticals LP
Priority Designation	Priority
Formulation	Oral tablets
Dosing Regimen	5, 10, 20 mg
Indication	Primary hypercholesterolemia
Intended Population	Adolescents 10-17 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Rosuvastatin at daily doses of 5 mg, 10 mg and 20 mg should be approved for use as an adjunct to diet in the pediatric population, 10-17 years of age, for the treatment of familial heterozygous hypercholesterolemia (HeFH). Based on the review of the clinical data, the safety and the effectiveness of rosuvastatin have been demonstrated in this population.

1.2 Risk Benefit Assessment

The benefits of rosuvastatin outweigh its risks in this pediatric population with HeFH.

Risks associated with rosuvastatin
There were no deaths and no cases of rhabdomyolysis in this trial. The most common muscle related adverse events (AEs) observed with rosuvastatin therapy were muscle aches, followed by myopathy, muscle cramps and spasms, and musculoskeletal pain. During the double-blind phase, elevated serum creatine phosphokinase (CK) greater than 10 times the upper limit of normal (> 10 *x* ULN) was observed more frequently in the rosuvastatin-treated groups compared to the placebo-treated subjects. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK > 10 *x* ULN**,** compared to 0 of 46 children on placebo. Most of the CK elevations normalized by the end of the trial while the subjects were still on study drug. None of the subjects with muscle-related events prematurely discontinued from the trial.

None of the subjects met the criteria for Hy's Law[1], or had any hepatic adverse events. While there were elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) during the trial, most occurred during the double-blind phase, and were <3 *x* ULN. Three AST elevations exceeded 3 *x* ULN, along with increased CK> 10 *x* ULN, and all 3 subjects were in the rosuvastatin groups. In 2 of these 3 cases, the source of the AST elevations was more likely muscle given the less pronounced increase in ALT, as well as the CK elevation. The third subject's AST and ALT were both elevated about 3 *x* ULN, which may indicate liver and muscle involvement.

Urine protein: creatinine ratios were measured in this trial, given the concern for proteinuria observed in the approval trials in adults at 80 mg doses of rosuvastatin (FDA 2003). In the PLUTO trial, 4 pediatric subjects (2.3%) had increased protein: creatinine ratios >0.2. Four subjects had increases in serum creatinine >25% from baseline on 2 or more visits, 1 subject

[1] Hy's Law: The drug shown by more frequent of aminotransferases (ATs) increases 3 *x* ULN than the (non-hepatotoxic) control. Some subjects with ATs> 3 *x* ULN also show elevation of serum total bilirubin (TBL)> 2 *x* ULN, without initial findings of cholestasis (serum alkaline phosphatase [ALP] activity >2 *x* ULN). No other reason can be found to explain the combination of increased AT and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

while on 5 mg rosuvastatin, 2 subjects while on 20 mg, and 1 subject while on 10 mg and then 20 mg. However, the increased serum creatinine remained within normal limits despite the >25% increase.

Risk compared to other statins
Generally, the risks associated with rosuvastatin are comparable to other statins. Statins have been associated with myopathy and rarely, rhabdomyolysis. They also modestly increase hepatic aminotransferases, but rarely lead to severe hepatic injury, hepatitis or liver failure. These increases often resolve with continued statin therapy.

Benefits of rosuvastatin
In the Pediatric Lipid Reduction Trial with Rosuvastatin (PLUTO), subjects with HeFH, treated with 5 mg, 10 mg, and 20 mg rosuvastatin had reductions in low density lipoprotein (LDL-C) of approximately 38%, 44%, 50%, respectively, compared to placebo. Atorvastatin, simvastatin, lovastatin, fluvastatin, and pravastatin have also demonstrated efficacy in the treatment of children and adolescents with HeFH. The highest approved doses were tested in clinical trials and resulted in mean LDL-C reductions of 41% for simvastatin (de Jongh and Ose et al. 2002), 40% for atorvastatin (McCrindle and Ose et al 2003), 34% for fluvastatin (van der Graaf and Mierman et al 2006), 27% for lovastatin (Stein and Illingworth 1999), and 24% for pravastatin (Weigman and Hutten et al. 2004).While the LDL-C reductions with atorvastatin, simvastatin and fluvastatin appear to be comparable to rosuvastatin, the subjects were treated with the highest approved doses of those other statins to reach goal.

Risk: benefit of rosuvastatin
The risks and benefits of rosuvastatin are comparable to other statins, and its availability would provide another option in the armamentarium of drugs already available for treating HeFH. The balance of risk to benefit is acceptable.

1.3 Recommendations for Postmarketing Risk Management Activities

Postmarketing risk management is addressed by labeling.

1.4 Recommendations for other Post Marketing Study Commitments

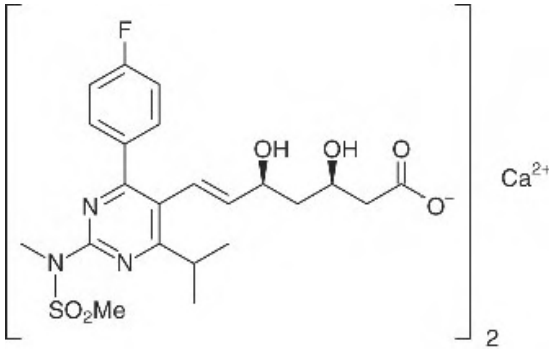
No postmarketing study commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

CRESTOR (rosuvastatin calcium) is a 3-hydroxy-3-methylglutarylcoenzyme A (HMG Co-A) reductase inhibitor. It is a synthetic lipid-lowering agent for oral administration.

Figure 1: Rosuvastatin molecular formula



It is bis[(E)-7-[4(4-fluorophenyl)-6-isopropyl-2[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)3,5-dihydroxyhept-6-enoic acid] calcium salt. Its empirical formula is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and molecular weight is 1001.14.

Rosuvastatin is available in tablet form containing 5 mg, 10 mg, 20 mg and 40 mg of the active ingredient, rosuvastatin calcium. The excipients are: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

The clinical formulations of rosuvastatin tablets used in this pediatric trial (4522IL/0086) were the same as those used in the adult rosuvastatin studies.

2.2 Tables of Currently Available Treatments for Proposed Indication

Table 1: Currently available statin treatment for children and adolescents with HeFH

Drug	Sponsor (Approval year)	Age (years)	Indication
ZOCOR (Simvastatin)	Merck (2002)	10-17	As an adjunct to diet to reduce total-C, LDL-C, and Apo-B levels in boys and postmenarchal girls with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and: • there is a positive family history of
MEVACOR (Lovastatin)	Merck and Co. (2002)		
LIPITOR (Atorvastatin)	Pfizer (2002)		
PRAVACHOL (Pravastatin)	Bristol-Myers Squibb (2002)	≥ 8	

Drug	Sponsor (Approval year)	Age (years)	Indication
LESCOL XL, LESCOL (Fluvastatin)	Novartis (2006)	10-16	• premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric subject

2.3 Availability of Proposed Active Ingredient in the United States

CRESTOR (rosuvastatin calcium), at doses up to 40 mg/day, was approved in the United States in August 2003 for adult patients with primary hypercholesterolemia and mixed dyslipidemia, as an adjunct to diet for the treatment of patients with hypertriglyceridemia and as an adjunct to apheresis and other lipid lowering treatments in patients with homozygous familial hypercholesterolemia. It was first marketed in the Netherlands in November 2002 and Canada in February 2003. Rosuvastatin is approved in over 90 countries with an estimated 4 million plus patient-years of postmarketing experience.

The major safety concern for statins as a class is muscle toxicity with the most serious complication being rhabdomyolysis. Since its approval there have been several key labeling changes due to postmarketing experience (Table 2).

Table 2: Key labeling changes to the rosuvastatin label

Date	Section	Subsection	Additions and Revisions
03/27/09	ADVERSE REACTIONS	Postmarketing experience	'hepatic failure'
01/23/09			Patient Package Insert (PPI) for CRESTOR
11/06/08	INDICATION		A new indication for CRESTOR to treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipoproteinemia) as an adjunct to diet.
11/08/07			A new indication for CRESTOR as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels
07/23/07	CLINICAL PHARMACOLOGY	Drug-drug interactions	Lopinavir/Ritonavir: Coadministration of CRESTOR and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers wasassociated with an approximately 2-fold and 5-fold increase in rosuvastatin steady- state AUC(0-24) and Cmax respectively. This increase is considered to be clinically significant. Interactions between CRESTOR and other protease inhibitors have not been examined.(See PRECAUTIONS, Drug Interactions, WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION.)

Date	Section	Subsection	Additions and Revisions
	WARNINGS	Myopathy/ Rhabdomyolysis	to the paragraph that begins with "Consequently" the following change was made to the first sentence of number four to read: 4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies, cyclosporine, or lopinavir/ritonavir (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION).
	PRECAUTIONS	Drug interactions	Lopinavir/Ritonavir: Coadministration of CRESTOR and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state AUC(0-24) and Cmax respectively. These increases should be considered when initiating and titrating CRESTOR in patients with HIV taking lopinavir/ritonavir (see DOSAGEAND ADMINISTRATION).
	ADVERSE REACTIONS	Postmarketing experience	memory loss
	DOSAGE AND ADMINISTRATION	Dosage in Patients Taking Cyclosporine	Dosage in Patients Taking Cyclosporine or Combination of Lopinavir and Ritonavir In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). In patients with HIV taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions).
03/02/05	CLINICAL PHARMACOLOGY	Special Populations, Race	After the first sentence, the paragraph was changed to read: However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and Cmax) in Asian subjects when compared with a Caucasian control group. (See WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)
	CLINICAL PHARMACOLOGY	Drug-Drug Interactions	Warfarin subsection, the warfarin dose was changed from "20 mg" to "25 mg."

Date	Section	Subsection	Additions and Revisions
	WARNINGS	Myopathy/ Rhabdomyolysis	the second paragraph, after the third sentence, was changed to read: In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency To the paragraph that begins with "Consequently" the following changes and renumbered were made: 1. "inadequately treated" was inserted before the word "hypothyroidism." Additionally, a new item number 3 was inserted in the list to read: 3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION). 6. "dehydration" was added after the word "hypotension" to the list of examples.
	PRECAUTIONS	General	The third paragraph was changed to read: The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/ Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.)
		Pregnancy	third paragraph, the phrase "In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day" was changed to ". . . 2, 10, 50 mg/kg/day"
	ADVERSE REACTIONS	Clinical Adverse Experiences, Laboratory Abnormalities	To the second paragraph, "creatinine" was changed to "creatine." A new "Postmarketing Experience: In addition to the events reported above, as with other drugs in this class, the following event has been reported during postmarketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice.

Date	Section	Subsection	Additions and Revisions
	DOSAGE AND ADMINISTRATION	Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb	the paragraph after the third sentence was changed and a second, bolded paragraph was added as follows: However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. **The 40 mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.**
		Dosage in Asian Patients (a new subsection)	Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).
	HOW SUPPLIED		The section has been changed to reflect debossing changes made to the 5, 10, 20, and 40 mg tablets. The debossing now consists of the word "CRESTOR" and the mg strength of the tablet on one side of the tablet; the other side of the tablet is blank

2.4 Important Safety Issues With Consideration to Related Drugs

Statins have been associated with elevated liver transaminases. Asymptomatic elevated liver transaminase >3 *x* ULN occur in <1% of patients on low and intermediate doses of statins and 2 to 3% at high doses (McKenney and Davidson et al. 2006). The mechanism of action of the statin mediated liver enzyme elevation has not been elucidated; however, modest elevations do not appear to signal risk for significant liver injury, even with continued statin treatment.

Statins have also been associated with muscle aches, pain, weakness and rarely, rhabdomyolysis. In 21 clinical trials, with 180,000 person-years follow-up in statin or placebo treated subjects, myopathy (muscle symptoms with CK> 10 *x* ULN) occurred in 5 subjects per 100,000 person-years and rhabdomyolysis in 1.6 subjects per 100,000 person-years (placebo-corrected) (McKenney and Davidson et al. 2006). During clinical trials with rosuvastatin, 1.0% and 0.4% of the subjects treated with 80mg/day developed myopathy and rhabdomyolysis, respectively, so the 80mg/day dose was not approved.

As mentioned in the previous section, proteinuria was detected in 12% of the subjects treated with 80mg/day of rosuvastatin (this dose was subsequently not approved) (Jones and Davidson et al. 2003). The frequency of proteinuria with lower doses of rosuvastatin (5-40 mg), atorvastatin, pravastatin, and simvastatin was the same as placebo (Jones and Davidson et al 2003). Proteinuria may occur with all statins, but may be more likely with more potent statins (Bays 2006). In 2005 the Agency concluded that proteinuria in subjects on statin therapy was not associated with renal impairment or renal failure (FDA 2009b).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

April 26, 2001
AstraZeneca requests issuance of a FDA Written Request (WR) for a pediatric study for rosuvastatin to obtain pediatric exclusivity. AstraZeneca also requests a waiver for the pediatric population of less than 10 years of age for all indications and a 2 year deferral for ages 10 – 17 years. (IND 56,385; Serial No. 206; Serial No. changed from 206 to 205 per FDA).

June 1, 2001
FDA grants a waiver for pediatric studies for children less than 10 years old and a two-year deferral for pediatric subjects aged 10 to 17 years for rosuvastatin calcium for hypercholesterolemia. However, at this time the FDA denies the issuance of pediatric WR for rosuvastatin until after the New Drug Application (NDA) approval and the availability of additional information on the safety and efficacy of rosuvastatin calcium in adults.

September 17, 2001
AstraZeneca requests FDA to reconsider the decision not to issue a WR for pediatric studies on rosuvastatin calcium. (IND 56,385; Serial No. 0252)

October 22, 2001
FDA responds that it is unable to issue a WR at this time due to insufficient information on the safety and efficacy of rosuvastatin. (Official Correspondence faxed to IND 56,385)

August 13, 2003
FDA approves rosuvastatin for use in adults.

December 4, 2003
AstraZeneca submits a Proposed Pediatric Study Request (PPSR) and requests FDA to issue a WR for a pediatric study for rosuvastatin to obtain pediatric exclusivity as referenced in the NDA approval letter dated 12 August 2003. (IND 56,385; Serial No.0439)

March 11, 2004
AstraZeneca submitted a request to withdraw the PPSR submitted on 4 December 2003, on the recommendation of the Agency (Serial No 0439) due to a Citizen Petition.[2] (IND 56,385; Serial No. 0449)

May 3, 2004
AstraZeneca and FDA teleconference to discuss the PPSR submitted on December 4, 2003 to IND 56,385; Serial No. 0439. FDA recommends the following pediatric study design:

- Study will have approximately 150-200 patients with 100 evaluable on rosuvastatin at the end of 1 year.
- Phase I: Randomized, parallel, double-blind, placebo controlled study with 5, 10, 20 mg of rosuvastatin.
- Phase II: Re-Randomized, double-blind, active control with a 2:1 randomization to rosuvastatin.
    - Start dose 5mg of rosuvastatin; titrate to goal with a max dose of 20 mg rosuvastatin
    - Start dose of 10 mg of atorvastatin; titrate to goal with a maximum dose of 20 mg atorvastatin
- No additional lipid lowering agents will be given if patient does not reach his/her goal.
- Design is similar to other pediatric studies done in the past.
- Study subject make up:
    - 30% minimum of each gender
    - 10% at each Tanner Stage ≥2
    - 10% of subjects <14
- Safety
    - Proteinuria
    - Growth and sexual development
    - Endocrine function
    - Testosterone and estradiol, no progesterone

May 24, 2004
AstraZeneca requests an extension to the original two-year deferral for pediatric subjects ages 10 – 17 years of age granted by FDA on 1 June 2001 (IND 56,385) to adjust for the post-approval discussion timelines with the Division on the appropriate pediatric study details and initiation. (IND 56,385; Serial No. 0467)

[2] A Citizen petition was submitted to the FDA on March 4, 2004 requesting the immediate removal of CRESTOR from the market before the occurrence of additional cases of rhabdomyolysis and kidney failure or damage. The Agency recommended AstraZeneca withdraw the PPSR.

May 26, 2004
FDA provides official minutes to AstraZeneca for the teleconference held on 3 May 2004 to discuss the pediatric study design. The Agency recommends that AstraZeneca not submit a PPSR until the Citizen Petition is resolved. The FDA recommends the following study design: Enroll 150 – 200 pts, > 100 evaluable subjects on rosuvastatin at 1 year. The trial should be divided into two phases:

1. Short term efficacy phase – 6-week parallel group, placebo controlled, double-blind study at rosuvastatin doses of 5, 10, 20 mg
2. Long term efficacy and safety phase (treatment to goal) – Re-randomization into a 42-week double-blind, study to compare rosuvastatin (5, 10, 20 mg) to an active control (atorvastatin 10 and 20 mg) in a 2:1 ratio. Start at the lowest approved dose (i.e., rosuvastatin 5mg and atorvastatin 10mg) and titrate to goal at 6-week intervals. The maximal possible dose should be rosuvastatin 20 mg or atorvastatin 20 mg.
    a. Additional requests for safety information include:
        i. Serum transaminase, creatinine kinase and urine protein at 6 weeks intervals.
        ii. Growth and sexual maturation - stadiometry and Tanner staging, at baseline, 24 and 48 weeks.
        iii. Effects on endocrine function - testosterone (boys), estradiol (girls), DHEAS, morning cortisol, FSH, LH at baseline, 24 and 48 weeks *(AstraZeneca questioned issues regarding Estradiol results and birth control pills)*
        iv. The Agency wants AstraZeneca to define the entry criteria of cardiovascular disease (CVD) risk factors: elevated BP, physical inactivity. Reasonable distribution of gender and Tanner stage:
            1. 30% each gender at each Tanner stage
            2. 10% at each Tanner stage (II – V)
            3. 30% under 14 years of age

June 22, 2004
FDA grants an extension to the original two-year deferral (1 June 2001) of pediatric studies for subjects 10 – 17 years of age until 29 March 2009.

October 20, 2004
FDA requests that AstraZeneca submits the required pediatric assessments as per the Pediatric Research Equity Act (PREA) by 3 December 2004. FDA further states that the rosuvastatin NDA, dated June 26, 2001, was submitted without pediatric studies and that AstraZeneca was not granted a waiver or deferral of pediatric studies under the regulations in effect at the time the application was submitted.
October 27, 2004

AstraZeneca and FDA teleconferenced regarding the Division's letter to NDA 21-366 requesting AstraZeneca either submit pediatric assessments for rosuvastatin calcium to the NDA or request waivers and deferrals as required by the US PREA. The FDA explained that this was a generic

"rule not addressed letter" sent to all companies with recent approvals who had no description in the US NDA approval letter regarding deferrals/waivers granted by the Division. AstraZeneca references official FDA correspondence to IND 56,385 dated June 1, 2001 in which FDA granted a waiver/deferral and an FDA correspondence dated June 22, 2004 in which FDA granted an extension to the initial waiver/deferral until March 29, 2009

June 14, 2005
AstraZeneca requests further clarification on recommendations for a pediatric study design provided by the Division on 26 May 2004 before submitting a PPSR. (IND 56,385; Serial No. 0516)

July 20, 2005
AstraZeneca and FDA teleconference in response to the request for guidance submitted by AstraZeneca on 14 June 2005 (IND 56,385; Serial No. 0516) regarding the design of a pediatric study for the PPSR.

August 2, 2005
AstraZeneca requests guidance from the Division regarding the design of a proposed pediatric study prior to the submission of a PPSR. (IND 56,385; Serial No. 0523)
October 19, 2005
FDA responds to AstraZeneca's 2 August 2005 request providing recommendations regarding the design of the proposed pediatric study (PLUTO):

- The effect of rosuvastatin therapy on protein excretion in the pediatric population should be part of the PPSR. Such a study would require sensitive measurement of baseline and follow-up urine protein excretion, either using 24-hour urine collections or multiple timed overnight urine collections. These measurements should be performed in all treatment groups, including placebo, during the double-blind treatment period.
- Include a 3-month double-blind treatment period that can be followed by an open-label extension period wherein all subjects will be treated to LDL-C goals with rosuvastatin calcium.
- Submit information to support feasibility of such a study taking into account the total number of subjects per treatment group and the individual variability in urine protein excretion in this subject population.

November 17, 2005
AstraZeneca submits a PPSR to request an assurance of a FDA WR to obtain pediatric exclusivity. (IND 56,385; Serial No. 0541)

January 31, 2006
AstraZeneca proposes a delivery date of 31 December 2009 for the final study report for the Pediatric WR to the CRESTOR® NDA 21-366. (IND 56,385; Serial No. 0551)

February 23, 2006
FDA responds in a letter to AstraZeneca that all post-marketing studies acknowledged in the August 12, 2003 NDA approval letter have been completed.

March 7, 2006
FDA issues a Formal WR with pediatric information on rosuvastatin calcium to be submitted on or before December 31, 2009.

May 16, 2006
AstraZeneca submits the Pediatric Protocol for Pediatric Exclusivity: Study D3561C00087 - phase IIIb, efficacy, and safety study of rosuvastatin in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH): a 12-week, double-blind, randomized, multicenter, placebo-controlled study with a 40-week, open-label, follow-up period (PLUTO: Pediatric Lipid-redUction Trial of rOsuvastatin). (IND 56,386; Serial No. 0565)

May 17, 2006
AstraZeneca informs the FDA of its acceptance of the pediatric study proposal as presented in the FDA WR dated March 7, 2006.

June 15, 2006
AstraZeneca requests an extension of deferral for a pediatric indication for rosuvastatin from March 29, 2009 (granted on 22 June 2004) until December 29, 2009 so that the dates for the WR and the NDA deferral coincide. (IND 56,385; Serial No. 0568)

September 6, 2006
FDA responds to 15 June 2006 correspondence (IND 56,385; Serial No. 0568) regarding deferral of pediatric studies in subjects 10 to 17 years of age for CRESTOR® until 31 December 2009. The deferred pediatric studies required under Section 2 of PREA are considered required post-marketing study commitments and was inadvertently omitted from the 23 February 2006 letter informing AstraZeneca all of post-marketing studies acknowledged in the 12 August 2003 NDA approval letter had been completed. At the time of the 2003 NDA approval, commitment to produce a rosuvastatin sNDA for a pediatric indication was not placed in the approval letter because FDA's Pediatric Rule was under review in the US court system. On October 17, 2002, the court ruled that FDA did not have the authority to issue a Pediatric Rule and had barred FDA from enforcing it. The status of this pediatric post-marketing study shall be reported annually according to 21 CFR314.81 and the commitment would be listed as:

- Deferred pediatric study under PREA for the treatment of Heterozygous Familial Hypercholesterolemia (HeFH) in pediatric subjects ages 10 to 17
- Final Report Submission by 31 December 2009

October 12, 2006
AstraZeneca and FDA teleconference to discuss PLUTO, specifically, the exclusion criterion: "Boys and girls with height < 3rd percentile for age and sex or height-weight ratio >97th percentile for age and sex should also be excluded" and the inclusion criterion: "children with

LDL-C >160 mg/dl would be eligible if they have 2 or more of several listed CV risk factors, including severe obesity". FDA agrees that the WR was inconsistent and confusing. The FDA does not want to exclude obese children from PLUTO. Therefore, the exclusion criterion for height-weight ratio >97th percentile can/should be deleted. AstraZeneca will clarify the inconsistency with a protocol amendment.

January 25, 2007
AstraZeneca submits a Protocol Amendment (IND 56,385; Serial No. 0593) for PLUTO which provides for the following changes:

- Removal of Appendix M Optional Carotid Ultrasound sub-study
- Administrative changes

June 4, 2008
AstraZeneca submits a pre-sNDA Briefing Document outlining the development of rosuvastatin for the pediatric population and the intended sNDA. AstraZeneca anticipated submitting a single sNDA to the FDA to:

- Respond to the Written Request
- Support an indication of the effects of CRESTOR in pediatric subjects 10 to 17 years of age with familial hypercholesterolemia
- Fulfill the Phase IV commitment for a pediatric study. AstraZeneca also intends to seek changes to selected portions of the rosuvastatin label in accord with the results of the PLUTO study. (IND 56,385; Serial No. 0670)
-

June 25, 2008
AstraZeneca submits a Statistical Analysis Plan for PLUTO. (IND 56,385; Serial No. 0676)

August 13, 2008 FDA provides responses to questions included in the pre-sNDA Briefing Document for the PLUTO sNDA submission (4 June 2008; Serial No. 0670)

- The Agency agrees that PLUTO as a single pivotal study is sufficient for filing and indication related to the effects of rosuvastatin in pediatric subjects
- CRFs for any subjects who died, experienced an SAE, discontinued treatment due to an AE or withdrew consent should be provided
- Subject narratives on all SAEs, regardless of determination of drug relation, and AEs of special interest, including but not limited to: muscle events, proteinuria, and hepatic events should be submitted.
- The submission appears to meet the requirements to reach a regulatory decision regarding approval for pediatric efficacy indication and 6 months patent exclusivity but this is a review issue.
- The Agency reserves the right to request additional safety data and review PSUR data regarding adult subjects treated with rosuvastatin before approval is granted.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

This trial was performed in accordance with the ethical principles that originated in the Declaration of Helsinki.

3.1 Submission Quality and Integrity

There were hyperlinks provided throughout the study report, which made it reasonably easy to find the information needed for the review. There were requests for additional information, primarily for further analyses of cases because the information provided was either inadequate or not organized well, or the structure of the datasets prevented effective data querying. There were no late major amendments that extended the review clock.

Generally, the sponsor's submission was satisfactory and allowed for an adequate review.

3.2 Compliance with Good Clinical Practices

There were 2 major protocol violations and 26 major protocol deviations (the majority being treatment non-compliance). These 28 subjects were excluded from the intent-to-treat (ITT)[3] population to create the per-protocol (PP)[4] population. Twenty seven percent (n=8) of these major protocol deviations occurred at the Norway site; however these protocol violations did not compromise the integrity of the trial so these subjects remained in the trial. These analysis subsets are further discussed in Section 6.1.3.

The trial complied with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

3.3 Financial Disclosures

AstraZeneca attests that all investigators have certified that they have not entered into any financial arrangements with AstraZeneca. A review of the submitted records showed no significant payments. Certification is provided for the investigators indicating that they have no financial arrangement.

[3] Intent-to-treat (ITT): The primary analysis set for all efficacy analyses included all randomized subjects who took study medication and had a baseline and at least 1 post-baseline LDL-C measurement).
[4] Per-Protocol (PP): The PP analysis set was a subset of the ITT analysis set and excluded data from patients with major protocol violations or deviations that would likely affect the efficacy outcomes

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no proposed chemistry, manufacturing and controls labeling changes in this submission. The applicant was granted a categorical exclusion from the requirements to prepare an Environmental Assessment because granting the new indication rosuvastatin will not substantially increase the use of the drug and the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No juvenile animal studies were requested or performed, so no new nonclinical data were submitted with this sNDA. The nonclinical data for rosuvastatin were reviewed for the 2003 approval of NDA 21-366. The non-clinical safety findings relevant to clinical use were:

Liver toxicity with rosuvastatin exposure was observed across animal species in studies with 1 to 7 *x* the human exposure based on the human dose of 80 mg/day, 2 to 16 *x* human exposure based on the human dose of 40 mg/day, 5 to 35 *x* human exposure based on the human dose of 20 mg/day, and 11 to 78 *x* human exposure based on the human dose of 10 mg/day. Liver toxicity appeared to be reversible.

Muscle toxicity was observed in pregnant rabbits at lethal rosuvastatin doses (≥ 3 mg/kg). It was estimated that 5 mg/kg in male rabbits and 3 mg/kg in female rabbits was 0.5, 1, 3, and 5 *x* human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively.

Renal toxicity was observed in rats and dogs at exposures 39 to 46 *x* human exposure at 80 mg/day, in monkeys at exposure levels comparable to human exposure at 80 mg/day, and in pregnant rabbits at the lethal dose.

Testicular giant cell formation was observed in dogs at 46 *x* human exposure at human dose of 80 mg/day after one month treatment. Vacuolation of seminiferous tubular epithelium was observed in monkeys after six months treatment at about 2, 4, 8, and 18 *x* human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. In an oral 104-week carcinogenicity study in rats, the incidence of uterine stromal polyps was significantly increased in females at 11, 23, 53, and 116 *x* human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively. In a 107-week carcinogenicity study in mice, incidence of hepatocellular adenoma/carcinoma was observed at 10, 21, 48, and 107 *x* human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Rosuvastatin selectively and competitively inhibits HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol. Rosuvastatin has been shown to have high uptake and selectivity in the liver, the target organ for cholesterol lowering. Rosuvastatin produces its lipid-modifying effects in two ways: it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL, and it inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

4.4.2 Pharmacodynamics

Refer to Section 6 for details on the pharmacodynamics (i.e., lipid parameters) of rosuvastatin.

4.4.3 Pharmacokinetics

In the Pharmacokinetics of Rosuvastatin in Children and Adolescents with HeFH trial (Trial number:4522IL/0086), 18 subjects were studied in an open-label, nonrandomized, parallel group trial. After single administrations of rosuvastatin from 10 to 40 to 80 mg in children and adolescents with HeFH, systemic exposure increased with rosuvastatin dose. Subjects who received multiple doses of rosuvastatin 80 mg had a maximum concentration (C_{max}) and area under the curve from time zero to 24 hours ($AUC_{(0-24)}$) of approximately 19% and 49% greater than the corresponding values after single-dose administrations. There were no important time-dependent changes observed between the pharmacokinetics on Day 7 and Day 1. Rosuvastatin was well tolerated in doses up to 80 mg for up to 7 days in this subject population.

The pharmacokinetic profile in the pediatric population was similar to the pharmacokinetic profile in the adult population.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3: Rosuvastatin clinical studies

Study number	Study title
4522IL/0086	Pharmacokinetics of Rosuvastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolemia

Study number	Study title
PLUTO D3561C00087 (4522IL/0087)	Adolescents with Heterozygous Familial Hypercholesterolemia A phase IIIb, efficacy, and safety study of rosuvastatin in children and adolescents 10 to 17 years of age with HeFH: a 12-week, double-blind, randomized, multi-center, placebo-controlled study with a 40-week, open-label, follow-up period PLUTO: Pediatric Lipid-redUction Trial of rOsuvastatin

5.2 Review Strategy

Reviewers from the various disciplines conducted independent reviews, but collaborated on areas requiring clarity. The clinical review involved evaluating the study protocol as well as re-analyzing the raw data in areas of special interest, such as the adverse events. Please refer to the statistical review conducted by Joy Mele, M.S.

5.3 Discussion of Individual Studies

This supplemental new drug application (sNDA) is based on the PLUTO D3561C00087 trial. See section 6.0 for a detailed discussion of this trial.

6 Review of Efficacy

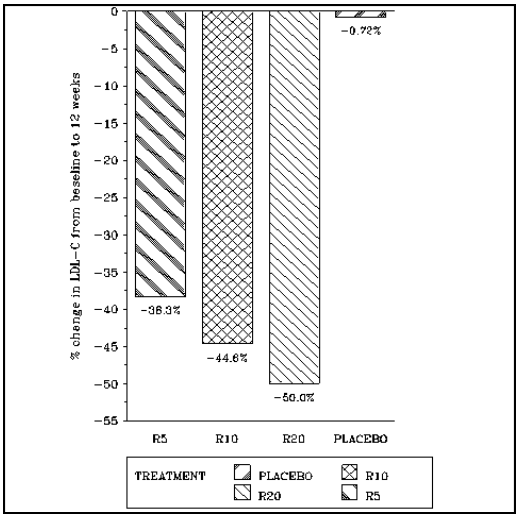
Efficacy Summary
The PLUTO trial demonstrated the effectiveness of rosuvastatin to treat pediatric subjects aged 10 to 17 years with HeFH.

The population studied in this trial reflected the general distribution of HeFH in the population, and the doses selected were appropriate for the efficacy assessments. The 12-week double-blind period was adequate to show efficacy as the full effect of rosuvastatin treatment has been measured at 6 weeks in adults (Marais and Raal et al. 2008). In the 40-week open-label phase, the doses (5 mg to 20 mg) were adjusted at specified intervals as tolerated during the course of the trial to obtain additional efficacy and safety assessments.

One hundred seventy six randomized subjects were treated with placebo, rosuvastatin 5 mg, 10 mg or 20 mg for 12 weeks, before entering a 40-week open-label phase where all subjects were treated with rosuvastatin and titrated to meet the LDL-C goal < 110 mg/dL. Ninety-three percent of the 176 randomized subjects completed the double-blind phase, with statistically significant lowering of LDL-C, total cholesterol (total-C), non-HDL-C and ApoB for each dose of rosuvastatin compared to placebo. The percent LDL-C change ranged from -38% to -50% (Figure 2). About 41% of patients on doses of 10 mg and 20 mg achieved an LDL-C less than 110 mg/dL after 12 weeks of therapy, which was maintained through the open-label phase. During the open-label phase, 71% of the patients were titrated to 20 mg in an attempt to lower LDL-C below 110 mg/dL.

Treatment effects did not significantly differ by age, sex, baseline LDL-C or Tanner stage.

Figure 2: LDL-C least squares mean percent change from baseline to Week 12



From applicant CSR D3561C00087 Figure 5
$p<0.001$ vs. placebo for all doses

6.1 Indication

The sponsor is seeking an indication for rosuvastatin as an adjunct to diet to reduce total-C, LDL-C, and ApoB levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥ 190 mg/dL or

b. LDL-C remains ≥ 160 mg/dL and:

- there is a positive family history of premature cardiovascular disease or
- two or more other cardiovascular disease (CVD) risk factors are present in the pediatric subject

6.1.1 Methods

The PLUTO trial included a 6-week, dietary lead-in/drug washout phase, a 12-week, double-blind, randomized treatment phase, and a 40-week, open-label, titration-to-goal treatment phase.

Randomized double-blind phase
At the end of the dietary lead-in phase (Week 0, Visit 3), eligible subjects were randomly assigned to double-blind treatment with rosuvastatin 5 mg, 10 mg, 20 mg, or placebo, orally once

daily for 12 weeks. Subjects were instructed to continue to follow dietary guidelines and received dietary counseling at each study visit. Two hundred twenty two male and female subjects aged 10 to 17 years with HeFH were enrolled into the study to ensure that at least 150 subjects completed the double-blind phase and 100 subjects completed the 52-week study.

The trial sites were located in the United States, Canada, Norway, Spain, and the Netherlands. Enrollment in the trial was actively managed to achieve a reasonable demographic distribution of subjects by age, sex, and Tanner stage. This distribution included at least 10% for each Tanner stage II through V (at least 1 year post-menarche) and 30% of subjects younger than 14 years of age. After the target demographic distributions were met, subjects were randomized and enrollment discontinued.

Open-label phase
At the end of the 12-week double-blind, randomized treatment phase (Week 12), lipid profiles and safety assessments were performed, and subjects entered the 40-week, open-label, titration-to-goal phase. During this phase, all subjects received rosuvastatin. The starting open-label dose of rosuvastatin was based on whether the randomized dose achieved the LDL-C goal of <110 mg/dL at the end of the double-blind phase. Subjects randomized to rosuvastatin 10 mg or 20 mg who had not reached the LDL-C goal at Week 12 were continued on that dose at the start of the open-label phase. All other subjects (including those in the placebo group), started the open-label on 5 mg rosuvastatin. During the open-label phase, the rosuvastatin dose could be up-titrated at 6-week intervals to the next highest dose (maximum daily dose of 20 mg) to achieve the LDL-C target goal of <110 mg/dL.

Table 4: Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
1) Male or female children and adolescents, 10 to 17 years old, Tanner stages II to V, at least 1 year postmenarche (females) with HeFH and at least 1 of the following criteria: a. Fasting LDL-C ≥190 mg/dL 6 weeks into the dietary lead in period or b. Fasting LDL-C >160 mg/dL 6 weeks into the dietary lead in period and either of the following: i. Family history of premature CVD or ii. Two or more other CVD risk factors (HDL-C <35 mg/dL, hypertension, cigarette smoking, severe obesity, diabetes mellitus, physical inactivity) present after vigorous attempts were made to control these risk factors during 6 weeks of dietary lead-in.	Any of the following were regarded as a criterion for exclusion from the study: 1) History of statin-induced myopathy or serious hypersensitivity reaction to other statins, including rosuvastatin 2) Fasting TG ≥250 mg/dL at Visit 2 3) Fasting serum glucose of >180 mg/dL or HbA1c >9% at Visit 1 or subjects with a history of diabetic ketoacidosis within the past 1 year 4) Uncontrolled hypothyroidism defined as TSH >1.5 *x* ULN at Visit 1 (Week -6) or patients whose TRT was initiated or modified within the last 3 months 5) Use of specified disallowed concomitant medications 6) History of alcohol abuse and/or drug abuse 7) Current active liver disease or hepatic dysfunction (excluding Gilbert's disease) as defined by elevations of 1.5 *x* ULN for any age in any of the following liver functions tests: ALT, AST, or bilirubin at Visit 1 8) CK≥3 *x* ULN (unless explained by exercise) at Visit 1

Inclusion Criteria	Exclusion Criteria
2) Negative serum pregnancy test prior to randomization and thereafter in females. Female patients must adhere to a pregnancy prevention method during the trial 3) Willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws, and compliance with study treatment regimen	9) Estimated GFR <50 mL/min at Visit 1 10) ≥2+ proteinuria on urine dipstick at Visit 1 or Visit 2 11) Stage 2 hypertension, SBP/DBP > 5 mmHg > 99th percentile for age, sex, and height 12) History of solid organ transplantation 13) Patients previously screened for this study and/or patients randomized to treatment who subsequently withdrew consent 14) Participation in another investigational drug study <4 weeks before enrollment into the dietary lead-in period 15) Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study 16) Documented history of malignancy with the exception of basal or squamous cell carcinoma of the skin 17) Patients who are Tanner stage I 18) Boys >12 years of age with testicular volume <3 mL 19) Patients with height <3rd percentile for age and sex

FeFH was defined as documented genetic defect in LDL receptor or ApoB by DNA analysis or documented evidence of FeFH in an adult first-degree relative not receiving statin therapy (LDLC >190 mg/dL) or receiving statin treatment LDL-C >95 mg/dL; in a first degree child relative <18 years not receiving a statin (LDL C >160 mg/dL) or receiving statin treatment (LDL-C >80 mg/dL).
CVD was defined as onset of clinical atherosclerotic disease before age 55 in males or age 65 in females.
HbA1c Glycosylated hemoglobin; TSH Thyroid Stimulating Hormone; TRT thyroid replacement therapy; SBP Systolic blood pressure; DBP Diastolic blood pressure; GFR Glomerular filtration rate

6.1.2 Demographics

The demographic distributions were similar across the treatment groups (Table 5). Approximately 95% of the randomized subjects were Caucasian, 1.7% were Black, 2.8% were Asian, and 0.6% were an other race. Fifty-five percent were male. About 5.6% were 10-11 year olds, 24.3% were 12-13 year olds, 42.9% were 14-15 year olds and 27.1% were 16-17 year olds. The overall mean age was 14.3 years, and the mean ages of randomized males and females were 13.9 and 14.8 years, respectively. The age difference between males and females was expected based on the inclusion criterion that females were required to be at least 1 year post-menarche.

Approximately 17% of the subjects were Tanner II, 18% Tanner III, 40% Tanner IV and 25% Tanner V at study entry. Mean height, weight, and BMI by age and sex were similar across the treatment groups and were within normal ranges.

Table 5: Baseline demographics of all randomized treated subjects

	Rosuvastatin				Placebo
	5 mg	**10 mg**	**20 mg**	**Total**	
N	**42**	**44**	**44**	**176**	**46**
Age					
Mean (SD)	14.1 (1.9)	14.4(1.5)	14.2 (1.8)	14.3 (1.7)	14.3 (1.7)
Range	10.0-17.0	11.0 – 17.0	11.0-17.0	10.0-17.0	10.0 – 17.0
Gender					
Female	38%	43%	50%	45%	48%
Race					
Caucasian	95%	95%	93%	95%	89%
Tanner Stage					
II	14%	16%	20%	17%	17%
III	33%	9%	11%	18%	17%
IV	26%	45%	43%	40%	43%
V	26%	30%	25%	25%	22%

Adapted from statistical evaluation and review Table 3.1.2
SD Standard deviation

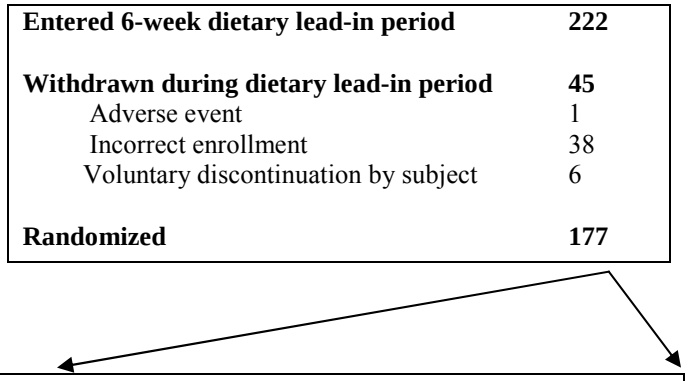
<u>Reviewer comment</u>: This population reflects the predominantly Caucasian distribution of HeFH in the general population, as there is a higher prevalence of this disease in certain populations with Finnish, Lebanese, Ashkenazi Jewish, Afrikaner, or French Canadian origins (Marks and Thorogood et al. 2003).

6.1.3 Subject Disposition

Two hundred twenty two subjects were recruited into the trial. Forty-five (20.3%) subjects did not progress to the double-blind phase; 38 (84%) of these failed to meet inclusion or exclusion criteria after the lead-in period. One hundred seventy seven subjects entered the double-blind phase. One subject completed the 12-week, double-blind treatment phase but chose not to continue in the trial. Since this subject had not started the open-label phase, the subject was counted as discontinuing from the double-blind period even though the subject actually completed that phase.

One hundred seventy four subjects completed the 12-week, double-blind phase and 173 of these entered the open-label phase. Nine subjects discontinued from the open-label phase; therefore, a total of 164 subjects completed the trial. The details for discontinuation are summarized in Figure 3.

Figure 3: Subject Disposition



	Rosuvastatin			Placebo
	5 mg	10 mg	20 mg	
Randomized, n	**42**	**44**	**45**	**46**
Not treated	0	0	1	0
Received drug	**42**	**44**	**44**	**46**
Discontinued during 12-week, double-blind period[a], n (%)	**1 (2.4)**	**0**	**0**	**1 (2.2)**
Adverse event	1 (2.4)	0	0	1 (2.2)
Completed 12-week, double-blind period, n (%)	**41 (97.6)**	**44 (100)[b]**	**44 (100)**	**45 (97.8)**
	All subjects (rosuvastatin 5 mg, 10 mg, or 20 mg)			
Subjects entering open-label period	**173[b]**			
Discontinued during 40-week, open-label period[a], n (%)	9 (5.2)			
Adverse event	4 (2.3)			
Protocol non-compliance or deviation	1 (0.6)			
Subject withdrew consent	3 (1.7)			
Other	1 (0.6)			
Completed 40-week, open-label period, n (%)	**164 (94.8)**			

Adapted from applicant CSR D3561C00087 Figure 2
[a] Reasons for withdrawal for individual subjects
[b] One subject (rosuvastatin 10 mg) completed the 12-week, double-blind treatment phase but chose not to continue study participation thereafter. This subject is counted as discontinuing from the double-blind phase but the subject actually completed randomized treatment. Therefore, 174 subjects completed the 12-week, double-blind phase and 173 of these entered the open-label phase.

Description of trial population analysis sets

Intention to treat (ITT) analysis set: The primary analysis set for all efficacy analyses included all randomized subjects who took study medication and had a baseline LDL-C and at least 1 post-baseline LDL-C measurement. All efficacy outcome variables were analyzed by the last

observation carried forward (LOCF) method. The LOCF was defined as the last non-missing post baseline LDL-C value carried forward. Only 1 subject was excluded from the randomized group to create the ITT analysis set (Table 6).

Per protocol (PP) analysis set: The PP analysis set was a subset of the ITT analysis set and excluded data from patients with major protocol violations or deviations that would likely affect the efficacy outcomes. Major protocol violations included not meeting inclusion criteria number-one in Table 4, as well as a fasting TG ≥250 mg/dL at Visit 2, uncontrolled hypothyroidism at Visit 1, and the use of specified disallowed concomitant medications during the dietary lead-in period. A major violation excluded the subject's data from the PP analysis set.

A major deviation excluded the subject's data from the time when the deviation occurred. Major deviations included non-compliance with study treatment, misrandomizations, misallocations, concomitant therapy, thyroid replacement therapy and unblinding. Minor violations or deviations alone did not lead to the exclusion of a subject's data from the PP analysis set. Twenty-eight subjects were excluded for the randomized subjects to create the PP analysis set (Table 6).

Table 6: Subject analysis sets

Analysis set, n (%)	**Treatment assigned during double-blind period**					**Total screened**
	Rosuvastatin				**Placebo**	
	5 mg	**10 mg**	**20 mg**	**Total**		
N	**42**	**44**	**45**	**131**	**46**	**222**
Randomized subjects	42 (100)	44 (100)	45 (100)	131 (100)	46 (100)	177 (79.7)
ITT analysis set	42 (100)	44 (100)	44 (97.8)	130 (99.2)	46 (100)	176 (79.3)
PP analysis set	37 (88.1)	37 (84.1)	39 (86.7)	113 (86.3)	36 (78.3)	149 (67.1)

Adapted from applicant CSR D3561C00087 Table 11
ITT Intention-to-treat
PP Per-protocol.

Reviewer comments: The efficacy endpoints were measured in the ITT population. It is reassuring that only one randomized subject was excluded from this analysis set.

Twenty-eight randomized subjects were excluded to create the PP analysis set. Two (21.4) of the 28 subjects were excluded due to major protocol violations, 1 subject treated with 10 mg rosuvastatin, and the other subject treated with placebo. Twenty-six (78.6%) of the 28 subjects were excluded due to major protocol deviations, 5 subjects each treated with 5 mg and 20 mg rosuvastatin, 6 subjects treated with 10 mg rosuvastatin, and 10 subjects on placebo (Table 7). Of the 26 major deviations, the majority (22 [84.6%]) were treatment non-compliance (Table 7). Most of these deviations (8 [27%]) occurred at the Norway site, and of these 8 subjects, 5 subjects were randomized to the placebo group, 2 subjects to the 20 mg and 1 subject to the 5 mg group.

Table 7: Number (%) of randomized subjects with major protocol violations or deviations leading to exclusion of the randomized subjects (PP analysis set)

Protocol violation or deviation	**Rosuvastatin**			**Placebo**	**Total randomized**
	5 mg	**10 mg**	**20 mg**		
N	**42**	**44**	**45**	**46**	**177**
Major protocol violation	**0**	**1 (2.3)**	**0**	**1 (2.2)**	**2 (1.1)**
Did not meet lipid entry criteria	0	1 (2.3)	0	0	1 (0.6)
Use of disallowed medication at baseline	0	0	0	1 (2.2)	1 (0.6)
Major protocol deviation	**5 (11.9)**	**6 (13.6)**	**5 (11.1)**	**10 (21.7)**	**26 (14.7)**
Treatment non-compliance	5 (11.9)	4 (9.1)	4 (8.9)	9 (19.6)	22 (12.4)
Misrandomization	0	2 (4.5)	1 (2.2)	1 (2.2)	4 (2.2)
Use of disallowed concomitant medication during double-blind treatment	0	0	0	1 (2.2)	1 (0.6)
Unblinding	0	0	0	1 (2.2)	

Adapted from applicant CSR D3561C00087 Table 10

6.1.4 Analysis of Primary Endpoint(s)

Lipid endpoints were evaluated using an analysis of covariance model, with treatment as a fixed effect and baseline as a covariate. There were other models using other covariates, including centers that had similar results. The primary endpoint was the change in last LDL-C value from baseline for each subject. Any missing value was imputed using the LOCF LDL-C value. Only 2 subjects had their last LDL-C values imputed.

Reduction in LDL-C from baseline (Week 0) to the end of the double-blind Phase (Week 12)

The mean LDL-C baseline values were similar across the 4 treatment groups (Table 8). There were significant LDL-C reductions after 12 weeks of treatment with rosuvastatin 5 mg, 10 mg, and 20 mg compared with placebo ($p<0.001$ for all 3 rosuvastatin doses compared with placebo). The least squared (LS) mean percent LDL-C reduction was -38.3% in the rosuvastatin 5 mg group, -44.6% in the 10 mg group, and -50.0% in the 20 mg group compared to -0.7% in the placebo group. The doubling of the rosuvastatin dose led to an additional 6% mean LDL-C reduction.

Table 8: LDL-C percent change from baseline to Week 12 during the double-blind phase

LDL-C[a]	**Rosuvastatin**			**Placebo**
	5 mg	**10 mg**	**20 mg**	
Baseline[b] (Week 0)				
n	42	44	44	46
Mean (SD) (mg/dL)	237.7 (55.1)	229.1 (44.7)	237.4 (47.8)	229.0 (43.1)
Median	223.5	229.5	245.5	223.5
Range	149.0 to 394.0	154.0 to 325.0	129.0 to 399.0	168.0 to 344.0
End of double-blind phase (Week 12)				
n	42	44	44	46
Mean (SD) (mg/dL)	143.1 (31.1)	127.8 (39.9)	117.1 (33.2)	227.1 (48.8)
Median	138.0	118.0	113.5	217.5
Range	102.0 to 252.0	69.0 to 249.0	53.0 to 217.0	123.0 to 387.0
% Change from baseline to Week 12[c]				
Mean (SD)	-38.5 (11.4)	-44.4 (12.1)	-50.2 (13.3)	-0.5 (13.2)
Median	-39.5	-47.2	-51.9	0.5
Range	-66.5 to -15.5	-61.8 to -0.8	-70.0 to 1.4	-30.1 to 46.3
ANCOVA analysis				
LS mean % change from baseline	-38.3	-44.6	-50.0	-0.7
Rosuvastatin difference vs. placebo				
LS mean difference vs. placebo in % change from baseline[d]	-37.5	-43.9	-49.2	NA
LCL to UCL[e]	-42.8 to -32.3	-49.1 to -38.8	-54.4 to -44.1	NA
p-value	<0.001	<0.001	<0.001	NA

Adapted from applicant CSR D3561C00087 Table 15

[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL , in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL during the PLUTO study.

[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.

[c] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) *x* 100.

[d] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.

[e] Upper and lower bounds of the 95% 2-sided confidence interval of the LS mean difference vs. placebo. ANCOVA Analysis of covariance; LCL Lower confidence interval limit; LDL-C Low-density lipoprotein cholesterol; LS Least-squares; NA Not applicable; SD Standard deviation; UCL Upper confidence interval limit.

6.1.5 Analysis of Secondary Endpoints(s)

Percent change in LDL-C from Baseline to week 6

The LDL-C percent change after 6 weeks of double-blind treatment was significantly greater for subjects treated with rosuvastatin 5 mg, 10 mg, and 20 mg compared with placebo (Table 9). The LS mean percent LDL-C reduction was -40.1% in the rosuvastatin 5 mg group, -45.4% in the 10 mg group, and -49.8% in the 20 mg group compared with -0.8% in the placebo group (p<0.001

for all 3 rosuvastatin doses compared with placebo). These changes were similar to the changes at Week 12.

Table 9: LDL-C percent change from baseline to Week 6 during the double-blind period (LOCF, ITT analysis set)

LDL-C[a]	Rosuvastatin 5 mg N=42	Rosuvastatin 10 mg N=44	Rosuvastatin 20 mg N=44	Placebo N=46
Baseline[b]				
Mean (SD) (mg/dL)	237.7 (55.1)	229.1 (44.7)	237.4 (47.8)	229.0 (43.1)
Median	223.5	229.5	245.5	223.5
Range	149.0 to 394.0	154.0 to 325.0	129.0 to 399.0	168.0 to 344.0
% Change from baseline to Week 6[c]				
Mean (SD)	-40.3 (12.2)	-45.2 (11.1)	-50.0 (11.4)	-0.6 (13.6)
Median	-40.2	-47.4	-51.6	0.4
Range	-64.9 to -6.9	-68.1 to -0.6	-66.9 to -9.6	-32.1 to 41.6
ANCOVA analysis				
LS mean difference vs. placebo in % change from baseline[d]	-39.3	-44.6	-49.0	NA
p-value	<0.001	<0.001	<0.001	NA

Adapted from applicant CSR D3561C00087 Table 18
[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL, in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL during the PLUTO study.
[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.
[c] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) *x* 100.
[d] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.
ANCOVA Analysis of covariance; LCL Lower confidence interval limit; LS Least-sq

Percent Total-C, HDL-C, non-HDL-C, triglycerides, and Apo-B from baseline to week 6, and week 12 or the end of the trial

The results at Week 6 for secondary lipids and lipoproteins were similar to those at Week 12, so only data from baseline to Week 12 are presented. There were significantly greater mean changes from baseline to Week 6 compared to placebo for total-C, non–HDL-C, Apo-B ($p<0.001$ for all rosuvastatin doses vs. placebo). No significant differences for HDL-C were observed at Week 6 between any rosuvastatin dose and placebo. TG achieved a significant mean change from baseline with only rosuvastatin 10 mg compared to placebo at Week 6 ($p=0.035$).
There were significantly greater mean changes from baseline values at Week 12 compared to placebo for total-C (Table 10), non–HDL-C, and Apo-B ($p<0.001$ for all rosuvastatin doses vs. placebo). No significant differences were observed at Week 12 between placebo and rosuvastatin

for HDL-C. A significant mean change was achieved for TG from baseline with only rosuvastatin 10 mg compared to placebo at Week 12 (p=0.048) (Table 10).

Table 10: Analysis of change in secondary lipid parameters from baseline to Week 12 during the double-blind period (LOCF, ITT analysis set)

	Rosuvastatin			Placebo
Lipid parameter	**5 mg N=42**	**10 mg N=44**	**20 mg N=44**	**N=46**
Total-C				
Baseline[a] Mean (SD)[b] (mg/dL)	300.2 (60.2)	296.5 (48.9)	302.0 (50.1)	293.2 (50.1)
LS mean difference vs. placebo in % change from baseline[d]	-29.9	-34.2	-38.7	NA
p-value[f]	<0.001	<0.001	<0.001	NA
HDL-C				
Baseline[a] Mean (SD)[b] (mg/dL)	46.3 (11.5)	49.1 (10.3)	46.8 (13.2)	45.3 (10.5)
LS mean difference vs. placebo in % change from baseline[d]	-2.7	4.3	2.0	NA
p-value	0.392	0.173	0.517	NA
Non–HDL-C				
Baseline[a] Mean (SD)[b] (mg/dL)	254.0 (58.9)	247.4 (46.4)	255.2 (50.8)	248.0 (47.0)
LS mean difference vs. placebo in % change from baseline[d]	-35.2	-42.1	-46.6	NA
p-value	<0.001	<0.001	<0.001	NA
TG				
Baseline[a] Mean (SD)[b] (mg/dL)	81.8 (38.0)	91.5 (56.0)	89.0 (42.1)	94.9 (53.9)
LS mean difference vs. placebo in % change from baseline[d]	-4.8	-18.7	-13.2	NA
p-value	0.613	0.048	0.163	NA
Apo-B (g/L)				
Baseline[a] Mean (SD)[b]	1.5 (0.4)	1.4 (0.2)	1.4 (0.3)	1.4 (0.3)
LS mean difference vs. placebo in % change from baseline[c]	-30.0	-36.4	-39.0	NA
p-value	<0.001	<0.001	<0.001	NA

Adapted from applicant CSR D3561C00087 Table 19

[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL, in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL during the PLUTO study.

[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.

[c] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.

ANCOVA Analysis of covariance;

Percentage of subjects who reach LDL-C goal (<110mg/dL) at Week 52 or the end of the trial with any dose of rosuvastatin

At the end of the double-blind treatment phase (Week 12), 11.9% of the subjects in the 5 mg rosuvastatin group, 40.9% in the 10 mg group and 40.9% in the 20 mg group achieved the LDL-C goal <110 mg/dL. No subject in the placebo group reached that goal. In an ad hoc analysis, 33.3% of subjects in the 5 mg rosuvastatin group, 63.6% in the 10 mg group and 68.2% in the 20 mg group achieved LDL-C <130mg/dL at Week 12, compared with 1 (2.2%) subject treated with placebo.

At the end of the open-label phase (Week 52), 40.5% of subjects treated with rosuvastatin achieved the LDL-C goal of <110 mg/dL. At Week 52, 68.2% of all rosuvastatin-treated patients achieved LDL-C <130 mg/dL.

Only 44% of the 9 subjects titrated from 5 mg to a final 10 mg rosuvastatin dose reached the LDL-C goal, and only 33% of the 27 subjects titrated from 10 mg to a final 20 mg rosuvastatin dose reached the LDL-C goal. Overall, most of subjects (122 [71%]) were titrated to the 20 mg to achieve LDL-C goal; but only 39 (40%) of these 122 subjects achieved LDL-C < 110 mg/dL at the end of the trial (Table 11).

Table 11: Number (%) of subjects achieving the LDL-C treatment goal <110 mg/dL by randomized treatment and final rosuvastatin dose

Randomized group	**Rosuvastatin Final Dose (% response)**			**Total**
	5 mg	**10 mg**	**20 mg**	
Placebo	5/7 (71)	1/5 (20)	12/33 (36)	18/45 (40)
5 mg	3/6 (50)	4/9 (44)	9/26 (35)	16/41 (39)
10 mg	7/11 (65)	3/5 (60)	9/27 (33)	19/43 (44)
20 mg	2/2 (100)	6/6 (100)	9/36 (13)	17/44 (39)
Total	17/26 (63)	14/25 (56)	39/122 (32)	70/173 (40)

Adapted from the statistical review and evaluation Table 3.1.6

The closer the subject's baseline LDL-C was to the treatment goal, the more likely that subject would reach the treatment goal. Thirty seven (66%) subjects with baseline LDL-C <204 mg/dl achieved LDL-C goal of <110mg/dL, compared 22 (37%) subjects with baseline LDL-C between 204 mg/dL and 251 mg/dL, and 11 (19%) subjects with baseline LDL-C greater that 251 mg/dL (Table 12).

Table 12: Number (%) of subjects achieving the LDL-C treatment goal <110 mg/dL by baseline LDL-C

Baseline LDL-C (mg/dL)	N	Number of subjects (%)
<204	57	37 (66)
204 to 251	60	22 (37)
>251	57	11 (19)

Adapted from the statistical review and evaluation Efficacy Results Section

6.1.6 Other Endpoints

Rosuvastatin doses (5, 10, and 20 mg) did not achieve significantly greater mean changes from baseline values at Week 12 compared with placebo for ApoA-1 (Table 13).

Table 13: Analysis of change in secondary lipid parameters from baseline to Week 12 during the double-blind period (LOCF, ITT analysis set)

Lipid Parameter	Rosuvastatin 5 mg N=42	Rosuvastatin 10 mg N=43	Rosuvastatin 20 mg N=43	Placebo N=46
ApoA-1 (g/L)				
Baseline[a] Mean (SD)[b]	1.3 (0.2)	1.4 (0.3)	1.3 (0.3)	1.3 (0.2)
LS mean difference vs. placebo in % change from baseline[c]	-1.0	2.6	1.2	NA
p-value	0.666	0.260	0.591	NA

Adapted from applicant CSR D3561C00087 Table 19
[a] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.
[b] Mean baseline and Week 12 values are for all patients with these values.
[c] LS mean of the difference vs placebo; analysis of covariance with the baseline value as the covariate and treatment as a fixed effect.
NA Not applicable; SD Standard deviation

At Weeks 6 and 12 the mean changes from baseline of the ratios ApoB/ApoA-1, LDL-C/HDL-C, TC/HDL-C, non–HDL-C/HDL-C were significantly different compared to placebo ($p<0.001$ for all rosuvastatin doses vs. placebo). These changes from baseline were each in the direction of improved lipid responses for rosuvastatin.

6.1.7 Subpopulations

Seventy percent of the subjects were 14 to 17 years old and 30% were 10 to 13 years of age. The treatment interaction by age was not significant ($p=0.55$) (Table 14). The comparisons across treatment groups by age group for LDL-C percent change at Week 12 were similar to those of the entire ITT population.

Table 14: Analysis of age by treatment interaction for LDL-C percent change at week 12

Age (years)		Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Placebo
10-13	n	15	9	14	14
	Mean % change from baseline[b]	-43.0	-50.3	-50.0	-3.6
	LS mean difference vs. placebo in % change from baseline[c,d]	-39.4	-46.6	-46.4	-
14-17	n	27	35	30	
	Mean % change from baseline[b]	-36.6	-43.2	-49.9	0.5
	LS mean difference vs. placebo in % change from baseline[c,d]	-36.1	-43.7	-50.4	-
Age by treatment interaction		p=0.550			

Adapted from applicant CSR D3561C00087 Table 12.1.9.5
[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL, in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL during the PLUTO study.
[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.
[c] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) *x* 100.
[d] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.
ANCOVA Analysis of covariance

Approximately 45% of subjects in the analysis were female and 55% were male. The treatment interaction with sex was not significant (p=0.49). The comparisons across treatment groups by sex for LDL-C percent change at Week 12 were similar to those of the entire ITT population.

Table 15: Analysis of sex by treatment interaction for LDL-C reduction at week 12

Sex		Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Placebo
Male	n	26	25	22	24
	Mean % change from baseline[b]	-36.5	-44.5	-50.0	-2.5
	LS mean difference vs. placebo in % change from baseline[c,d]	-34.0	-42.0	-47.5	-
Female	n	16	19	22	22
	Mean % change from baseline[b]	-41.1	-44.7	-49.9	1.3
	LS mean difference vs. placebo in % change from baseline[c,d]	-42.4	-46.0	-51.1	-
Sex by treatment interaction		p=0.490			

Adapted from applicant CSR D3561C00087 Table 12.1.9.6
[a] The concentration of fasting LDL-C was determined by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL, in which case a β-quantification measurement of LDL-C would be used. However, there was no case in which TG levels were >400 mg/dL during the PLUTO study.
[b] Measured at the randomization visit (Week 0; Visit 3). If missing, Visit 2 was used.
[c] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) *x* 100.
[d] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.
ANCOVA Analysis of covariance

Approximately 93% of subjects in the analysis were Caucasian and 7% were non-Caucasian (Black, Asian, Other). Due to the limited number of non-Caucasians, these subjects were examined as a group. The treatment interaction by race was not significant (p=0.54). The comparisons across treatment groups by race for LDL-C percent change at Week 12 were similar to those of the entire ITT population.

Approximately 17%, 18%, 40%, and 25% of the subjects were classified as Tanner stages II, III, IV and V respectively. The treatment interaction by Tanner stage was not significant (p=0.80). The comparisons across treatment groups by Tanner stage for LDL-C percent change at week 12 were similar to those of the entire ITT population.

In the 5 mg rosuvastatin treated group, there was a -19.9% LDL-C reduction in the United States and the LDL-C percent change with 5 mg observed in the other countries ranged from -31.8% to -50.8%. There was no clear evidence of differential effect across countries (p=0.235) (Table 16).

Reviewer comment: The number of US subjects was small, so there may not be enough power to draw definitive conclusions about the findings in the 5 mg rosuvastatin group from the US compared to the other countries.

Table 16: Analysis of country by treatment interaction for LDL-C reduction at Week 12

Country	LS mean % difference vs. placebo in % change from baseline[a,b]		
	Rosuvastatin		
	5 mg N=42	10 mg N=44	20 mg N=44
United States (n)	2	4	5
	-19.9	-33.5	-34.5
Spain (n)	3	3	3
	-31.8	-26.3	-49.0
Norway (n)	6	6	5
	-50.9	-60.0	-60.0
The Netherlands (n)	18	19	17
	-35.7	-41.6	-50.9
Country by treatment interaction p=0.235			

Adapted from applicant CSR D3561C00087 Table 12.1.9.9
[a] Percent change was calculated as ([Visit value – Baseline value] / Baseline value) *x* 100.
[b] Analysis of covariance with the baseline LDL-C as the covariate and treatment as a fixed effect.
ANCOVA Analysis of covariance; LS Least-sq

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommendation for the use of rosuvastatin 5 mg, 10 mg and 20 mg to lower LDL-C in children and adolescents (10-17 years of age) is supported by the significant reduction in LDL-C, the dose response for LDL-C lowering, and the persistence of LDL-C reduction.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was significant LDL-C reduction as early as Week 6, which persisted through Week 12. Approximately 41% of the subjects treated with rosuvastatin achieved the LDL-C treatment goal of <110 mg/dl at Week 12 and 40.5% achieved this goal at Week 52. Sixty eight percent of all rosuvastatin-treated subjects achieved LDL-C <130 mg/dL at Week 52 **(**historically, clinical trials evaluating LDL-C lowering therapies in pediatric patients have focused on achieving the <130 mg/dL target).

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy analyses were conducted.

7 Review of Safety

Safety Summary

There were no deaths or cases of rhabdomyolysis in this trial. The most frequently reported treatment emergent adverse events were headache and nasopharyngitis (incidence ≥ 1.0%), and the majority of the AEs were mild to moderate in intensity (Section 7.4.1). There were 3 serious adverse events (SAEs): 1 subject experienced blurred vision while on placebo and another had appendicitis while on 10 mg. The third subject developed a vesicular skin eruption on 20 mg rosuvastatin and was discontinued from the trial (Section 7.3.2). Six subjects experienced AEs that led to discontinuation (DAEs) from the trial; 2 subjects developed nausea and 1 subject had menorrhagia while on 5 mg rosuvastatin, 1 subject developed fatigue while on 10 mg, 1 subject developed vesicular skin eruption on 20 mg, and 1 subject developed blurred vision while on placebo (Section 7.3.3). The latter 2 subjects were also classified as having SAEs.

During the 12-week double-blind phase, 74 subjects (56.9%) experienced an adverse event while on rosuvastatin: 23 (54.7%) were on 5 mg rosuvastatin, 27 (61.4%) on 10 mg and 24 (54.5%) on 20 mg. This was similar to the placebo group (27 [58.7%]). Two subjects (1.5%) had SAEs during this phase, one subject while on 5 mg rosuvastatin, and the other while on 10 mg. Only 1 (0.8%) subject had a DAE, which occurred while on 5 mg **(**Table 17).

During the 40-week open-label phase, 130 subjects (75.1%) experienced AEs: 53 (41.1%) were treated with 5 mg rosuvastatin, 59 (48.0%) with 10 mg and 82 (66.7%) with 20 mg. There appeared to be an upward trend in the number of subjects with AEs with increasing rosuvastatin dose. Although there were 2 (1.2%) subjects with SAEs during the open-label phase of the trial, 1 of these subjects was up-titrated from 10 mg to 20 mg while the event was ongoing, so is counted twice in Table 17 (once under 10 mg and once under 20 mg). Four (2.3%) subjects had DAEs, 3 of the DAEs occurred while on 5 mg and 1 DAE occurred while on 20 mg rosuvastatin (Table 17).

Table 17: Number (%) of subjects[a] with adverse events by adverse event category and treatment dose, during the 12-week double-blind and open-label phases

Adverse Event Categories[b]	**Rosuvastatin**				**Placebo**
	5 mg	**10 mg**	**20 mg**	**Total**	
12-week double-blind phase					
N	42	44	44	130	46
Deaths	0	0	0	0	0
All AE[c]	23 (54.7)	27 (61.4)	24 (54.5)	74 (56.9)	27 (58.7)
SAE	1 (2.4)	1 (2.3)	0	2 (1.5)	1 (2.2)
DAE	1 (2.4)	0	0	1 (0.8)	1 (2.2)

Adverse Event Categories [b]	Rosuvastatin				Placebo
	5 mg	10 mg	20 mg	Total	
40-week open-label phase					
N	129	123	123	173	NA
Deaths	0	0	0	0	
All AE [c]	53 (41.1)	59 (48.0)	82 (66.7)	130 (75.1)	
SAE	0	1 (0.8)	2 (1.6)	2 (1.2) [d]	
DAE	3 (2.3)	0	1 (0.8)	4 (2.3)	

Adapted from applicant CSR D3561C00087 Tables 24 and 25
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Includes only AEs that started during the double-blind treatment period, or any AE that was ongoing from the dietary lead-in period and subsequently worsened during the double-blind period.
[c] An AE may be counted more than once if a patient had multiple occurrences of the event.
[d] Subject E0027007 was summarized for both the 10- and 20 mg doses because the subject was up-titrated from 10 to 20 mg while the event was ongoing.

Safety findings classified by system are summarized below:

Musculoskeletal
The most common muscle related AEs were muscle aches, followed by myopathy[5], muscle cramps and spasms, and musculoskeletal pain. Compared with placebo, treatment with rosuvastatin was associated with increased incidence rates of CK elevations and reports of myalgia.

During the double-blind phase, there were 4 subjects with increased CK>10 *x* ULN. All 4 cases occurred in the rosuvastatin treated groups. None of the subjects that reported muscle-related adverse events or CK>10 *x* ULN prematurely discontinued due to these events. Most of the CK elevations normalized while on study drug.

Hepatic
None of the subjects experienced hepatic failure, met the criteria for Hy's Law, or had hepatic adverse events. Nine subjects treated with rosuvastatin during the double-blind phase had ALT greater than the upper limit of normal, but the frequency of these events at each treatment dose was similar to placebo.

One subject had a one time ALT increase >3 *x* ULN, on 5 mg rosuvastatin during the open-label phase. Subjects treated with rosuvastatin (7 [5.4%]) also demonstrated more frequent increases in AST than subjects treated with placebo (0), but none of the elevations >3 *x* ULN occurred on 2 consecutive visits (Section 7.4.2).
While there were elevations in AST and ALT during the trial, most were <3 *x* ULN, there were 3 AST elevations (all in rosuvastatin-treated subjects) that exceeded 3 *x* ULN. In 2 of these 3

[5] Myopathy was defined as muscle aches or weakness with elevation in CK>10 *x* ULN.

cases, the source of the AST elevations was more likely muscle given the less pronounced increase in ALT, as well as the CK elevation. The third subject's AST and ALT were both elevated about 3 *x* ULN, which may indicate liver and muscle involvement (Section 7.4.2).

Renal
None of the subjects developed renal failure during the trial. Three subjects (E0001003, E0021011 and E0043001) were classified as having mild renal impairment prior to starting the trial; 2 were subsequently randomized to 5 mg rosuvastatin, and the third to 10 mg rosuvastatin. Their creatinine clearance measurements were within normal limits throughout the trial.

Four subjects had increased serum creatinine >25% from baseline on 2 or more visits, 1 subject while on 5 mg rosuvastatin, 2 subjects while on 20 mg, and 1 subject while on 10 mg and then 20 mg. However, the increased levels remained within normal limits. Four subjects (2.3%) had increased protein: creatinine ratios >0.2 (Section 7.4.2).

Safety Summary (Pediatric Pharmacokinetic Study [4522IL/0086])
There were no deaths, SAEs or withdrawals from the pharmacokinetic trial. Eight subjects had 16 treatment-emergent adverse events. Three subjects experienced 8 AEs on the 40 mg dose, 2 subjects had 2 AEs on the 10 mg dose, and 1 subject had 1 AE after receiving the single 80 mg dose. In the multiple-dose 80 mg dose group, 2 subjects had 5 AEs. There were no early withdrawals from the trial, and no SAEs (Table 44).

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The PLUTO trial (Study D3561C00087) evaluated safety.

7.1.2 Adequacy of Data

The safety evaluations were followed as outlined in the pediatric Written Request. Most of the evaluations were adequate to detect safety signals of concern. Protein: creatinine ratios were followed beyond the end of the open-label phase for subjects with protein: creatinine > 0.20 on the last visit. However, no additional data on glomerular filtration rate (GFRs) or serum creatinine levels were assessed beyond the end of the trial.

Only subjects with CK > 10 *x* ULN completed a supplementary muscle symptoms questionnaire. It could be assumed that the rosuvastatin-treated subjects with the CK elevations had the same levels of exercise as those randomized to placebo, as well as those who did not have substantial elevations in CK. Since exercise data were not collected on all subjects it is not possible to accurately say whether CK elevations in the rosuvastatin-treated subjects were due in whole or part to exercise.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Pooling data across studies to estimate and compare the incidence of adverse events was not relevant to this submission as there was only one trial.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequate numbers of subjects were exposed to rosuvastatin, as required by the Written Request. There was adequate demographic representation by sex and age, but the subjects were predominately Caucasian (~95%). The subjects were similarly distributed by demographic characteristics across randomized treatment groups (Table 5), and duration of exposure to rosuvastatin was similar across treatment groups (Table 19).

Although 40 mg is approved in the adult population, and up to 80 mg was used in the pediatric pharmacokinetic trial, the doses administered during this trial were 5 mg, 10 mg and 20 mg. The maximum 20 mg daily dose was high enough to show a significant reduction in LDL-C but was low enough to reasonably minimize treatment-related adverse drug reactions in the pediatric population.

The 12-week duration of the double-blind period was adequate to show efficacy in the pediatric subjects with HeFH, as the full effect of rosuvastatin treatment had been measured at 6 weeks in adults (Marais and Raal et al. 2008). Also, the relatively short period of 12-weeks minimized subjects' time off therapy, if they were randomized to placebo. In the 40-week open-label phase, 5 mg, 10 mg and 20 mg rosuvastatin were adjusted at specified intervals as tolerated during the course of the trial.

7.2.2 Explorations for Dose Response

Ninety-nine percent of the 177 subjects randomly assigned to a treatment group during the double-blind treatment period received at least 1 dose of study drug (Table 18). The durations of exposure to treatment during the 12-week, randomized, double-blind period and the 40-week, open-label period are presented in Table 18.

Overall, the mean duration of exposure to any dose of rosuvastatin was 352.2 days.

During the 12-week double-blind phase, the mean duration of exposure across all the rosuvastatin treatment doses was 84.2 days and in the placebo group, 83.2 days (Table 18).

During the 40-week, open-label treatment period, the mean duration of exposure in the total rosuvastatin group was 266 days (Table 18). The duration for each dose varied due to the titration to goal design of this phase. The mean duration was 93 days on 5 mg, 86 days on 10 mg,

and 190 days on 20 mg. The mean duration of exposure to each treatment dose was adequate for the safety evaluation during both the double-blind and open-label treatment periods in this trial.

Table 18: The average duration of exposure in days to rosuvastatin and placebo in the 12-week double-blind and 40-week open-label phases of the trial

Duration of treatment (days) [a]	**Rosuvastatin**				**Placebo**
	5 mg	**10 mg**	**20 mg**	**Total**	
12-week double-blind phase					
N	42	44	44	130	46
Mean (SD)	83.9 (7.2)	84.4 (4.3)	84.3 (4.2)	84.2 (5.4)	83.2 (13.1)
Median	84	84	84	84	84
Range	45 - 103	76 - 103	70 - 97	45 - 103	1 - 96
40-week open-label phase					
N	129	123	123	173	NA
Mean (SD)	93.0 (85.2)	86.3 (64.7)	190.3 (62.7)	266.1 (41.0)	NA
Median	48	52	194	277	NA
Range	7 - 300	1 - 255	11 - 285	54 - 302	NA
Entire trial (double-blind and open-label phases)					
N	NA	NA	NA	173	NA
Mean (SD)	NA	NA	NA	352.2 (43.4)	NA
Median	NA	NA	NA	364	NA
Range	NA	NA	NA	141-390	NA

Adapted from applicant CSR D3561C00087 Tables 24

[a] For the randomized period, duration of treatment was calculated from the date of the first dose to the date of the last dose of study medication. During the open-label phase, a subject may have titrated to different doses. For each subject, the exposure to each dose was calculated by adding the number of days on each dose. Gaps of non-compliance in between these days were ignored. For those subjects who did not return bottles on the last visit, it was assumed that they took medication. For those subjects who are lost to follow-up, it was assumed that they took medication up until last day of contact.

NA Not applicable; SD Standard deviation

When analyzed by the demographic characteristics sex, ages, and race, the mean durations were similar among the sex and age subgroups (Table 19). The mean duration of exposure among non-Caucasian was less than for Caucasians, at about 78 days and 84 days, respectively.

Table 19: The average duration of exposure (days) to rosuvastatin by demographic characteristics, in the 12-week double-blind and 40-week open-label phases of the trial.

Demographic Characteristics		Treatment Duration, for All Rosuvastatin doses (days)				Placebo			
		N	Mean (SD)	Median	Range	N	Mean (SD)	Median	Range
12-week Double-blind Phase									
Sex	Male	73	84.5 (4.9)	84.0	70.0-103.0	24	80.7 (17.3)	84.0	1.0-94.0
	Female	57	83.9 (5.9)	84.0	45.0-97.0	22	85.9 (4.7)	84.0	77.0-96.0
	Total	130	84.2 (5.4)	84.0	45.0-103.0	46	83.2 (13.1)	84.0	1 - 96
Age (yrs)	10-13	38	82.8 (7.8)	84.0	45.0-103.0	14	85.4 (4.0)	84.5	79.0-91.0
	14-17	92	84.8 (3.8)	84.0	71.0-103.0	32	82.2 (15.4)	84.0	1.0-96.0
	Total	130	84.2 (5.4)	84.0	45.0-103.0	46	83.2 (13.1)	84.0	1 - 96
Race	Caucasian	123	84.5 (4.2)	84.0	70.0-103.0	42	83.0 (13.8)	84.0	1.0-96.0
	Non-Caucasian	7	78.7 (14.9)	84.0	45.0-87.0	4	83.7 (1.3)	84.0	82.0-85.0
	Total	130	84.2 (5.4)	84.0	45.0-103.0	46	83.2 (13.1)	84.0	1.0-96.0
40-Week Open-label Phase									
Sex	Male	96	267.4 (34.5)	276.0	54.0-302.0	NA	NA	NA	NA
	Female	77	264.4 (48.1)	277.0	61.0-300.0	NA	NA	NA	NA
	Total	173	266.1 (41.0)	277.0	54 - 302	NA	NA	NA	NA
Age (yrs)	10-13	51`	26.6 (41.7)	277.0	54.0-291.0	NA	NA	NA	NA
	14-17	122	265.8 (40.9)	277.0	61.0-302.0	NA	NA	NA	NA
	Total	173	266.1 (41.0)	277.0	54 - 302	NA	NA	NA	NA
Race	Caucasian	165	266.7 (39.8)	277.0	54.0-302.0	NA	NA	NA	NA
	Non-Caucasian	8			84.0-282.0	NA	NA	NA	NA
	Total	173	266.1 (41.0)	277.0	54 - 302	NA	NA	NA	NA

7.2.3 Special Animal and/or In Vitro Testing

There were no new animal or in vitro data submitted with this sNDA.

7.2.4 Routine Clinical Testing

Subjects fasted for 12 hours before each visit, and also refrained from consuming alcohol and cigarette smoking on the morning of each of the clinic visits. A safety laboratory panel was done every 4 weeks during the trial, and included:

Hematology Platelet count, hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), white blood cell (WBC) count, and WBC differential

	(neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils)
Clinical Chemistry	
Hepatic parameters	Albumin, ALT, AST, alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin (TBL), and total protein
Skeletal muscle parameter	CK
Renal parameters	Blood urea nitrogen (BUN), serum creatinine, urine protein, urine creatinine, urine protein: creatinine ratio, and estimated GFR
Other	Calcium, β-human chorionic gonadotropin (β-HCG), fasting glucose, phosphorus, potassium sodium, Thyroid stimulating hormone (TSH), and glycosylated hemoglobin (HbA1c)
Urinalysis	Visual description (color and appearance), a dipstick test specific gravity, pH, protein, glucose, ketones, bilirubin, nitrate, leukocyte esterase, and blood), and microscopy (RBC, WBC, bacteria, casts and crystals)

Other safety evaluations included:
Physical examinations, assessment of sexual maturation (including assessments of height, sexual maturation, and Tanner staging), and adverse events, which were evaluated by treatment group: Weeks 1-12 and open-label (Weeks 13-53).

Supplementary Muscle Narrative Worksheets[6] were completed when blood CK increased >10 *x* ULN, and the CK measurements were repeated within 4 to10 days or earlier, if symptoms of myopathy appeared or worsened, or if the urine became very dark. The *Supplementary Muscle Narrative Worksheets* were also completed in cases of rhabdomyolysis, myositis, myoglobin blood present, myoglobin blood increases, myoglobinuria, and myopathy.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Pediatric Pharmacokinetic Study (4522IL/0086) was conducted prior to the PLUTO trial to assess the pharmacokinetics of rosuvastatin in children and adolescents with HeFH. The trial was an open-label, non-randomized, parallel-group trial. Serial blood samples and a 24-hour urine

[6] The *Supplementary Muscle Narrative Worksheets* collected information on the CK elevations >10 *x* ULN, as well as follow-up measurements, muscle symptoms, physical activity, concomitant medications and other clinical laboratory test that were concurrently elevated.

specimen were obtained after ascending single-dose administrations of rosuvastatin 10, 40, and 80 mg in 3 groups of subjects. Subjects receiving the 80 mg dose then received rosuvastatin 80 mg once daily for 7 days after a 4 to 10 day wash-out period; serial blood samples and a 24-hour urine specimen were obtained on Day 7. Blood specimens were also collected to determine the plasma concentrations of rosuvastatin and N-desmethyl rosuvastatin at predose and after the first dose of trial treatment.

Compared to the subjects receiving a single dose of 80 mg rosuvastatin, the subjects receiving multiple doses had 19% and 49% higher C_{max} and $AUC_{(0-24)}$ respectively. Pre-dose and 24-hour trough concentrations of rosuvastatin in plasma were comparable by inspection, suggesting that steady state was achieved by Day 7. The accumulation ratio of rosuvastatin was 1.5. No important time-dependent changes were observed when comparing the pharmacokinetics on Day 7 with Day 1. The apparent oral clearance of rosuvastatin appeared independent of dose.

The maximum geometric mean (gmean) renal excretion of rosuvastatin at any dose level was 5.5%. The exposure to N-desmethyl rosuvastatin, a metabolite of rosuvastatin, did not appear to increase with multiple administrations of rosuvastatin; mean first-dose and steady-state values of C_{max} were 8.0 and 6.5 ng/mL, $AUC_{(0-t)}$ values were 45.4 and 45.7 ng.h/mL. The metabolite was rapidly formed and plasma concentrations quickly fell below the limit of quantification; it was not possible to determine $t_{1/2}$ or renal clearance of the metabolite.

Time-dependent changes in pharmacokinetics were similar on Day 7 and Day 1. Rosuvastatin was well tolerated in doses up to 80 mg for up to 7 days in this subject population. The results are summarized in Table 20.

Table 20: Plasma pharmacokinetics of rosuvastatin

Parameter	**Summary statistic**	**Rosuvastatin single-dose**			**Rosuvastatin multiple-dose**
		10 mg N = 6	**40 mg N = 6**	**80 mg N = 6**	**80 mg N = 6**
Primary endpoints					
C_{max}, ng/mL	n	6	6	6	6
	gmean (CV)	6.3 (58.1)	23.5 (79.6)	42.6 (46.8)	50.6 (43.4)
	range[a]	2.6, 12.7	7.3, 56.6	20.5, 68.3	33.3, 89.5
$AUC_{(0-24)}$, ng.h/mL	n	6	6	6	6
	gmean (CV)	48.7 (48.3)	234 (62.9)	313 (37.1)	467 (35.3)
	range[a]	21.3, 79.9	86.0, 432	177, 493	293, 723
$AUC_{(0-t)}$,[b] ng.h/mL	n	6	6	6	6
	gmean (CV)	52.2 (52.3)	288 (65.2)	361 (35.2)	467 (35.3)
	range[a]	21.3, 79.9	101, 478	225, 560	293, 723
AUC, ng.h/mL	n	3	6	6	NA

Parameter	Summary statistic	Rosuvastatin single-dose			Rosuvastatin multiple-dose
		10 mg N = 6	40 mg N = 6	80 mg N = 6	80 mg N = 6
	gmean (CV)	47.6 (71.6)	299 (63.5)	371 (35.6)	NC
	range[a]	23.9, 85.5	105, 485	230, 578	NC
Secondary endpoints					
t_{max}, h	n	6	6	6	6
	median	2.5	3.0	4.5	5.0
	range[a]	0.5, 5.0	2.0, 6.0	1.0, 5.0	3.0, 5.0
$t_{1/2}$, h	n	3	6	6	NC
	mean[a] (SD[a])	8.6 (1.4)	14.8 (4.9)	20.0 (10.7)	NC
	range[a]	7.0, 9.7	8.3, 21.0	9.9, 34.7	NC
CL/f, L/h	n	3	6	6	NA
	gmean (CV)	210 (71.5)	134 (63.5)	215 (35.7)	NC
	range[a]	117, 418	82.4, 381	138, 348	NC
CLR, L/h	n	6	6	5	6
	gmean (CV)	6.0 (40)	9.3 (17)	12.9 (28)	5.6 (30)
	range[a]	4.1, 10.0	8.0, 11.7	8.6, 18.1	3.8, 8.4
Fe, %	n	6	6	5	6
	gmean (CV)	2.9 (45)	5.5 (53)	5.2 (41)	3.3 (24)
	range[a]	1.9, 6.1	2.5, 8.8	3.0, 7.2	2.2, 4.2
X_u, mg	n	6	6	5	6
	gmean (CV)	294 (45)	2180 (53)	4150 (41)	2630 (24)
	range[a]	187, 609	1010, 3520	2400, 5740	1740, 3390

Adapted from applicant CSR Study 4522IL/0086 Table A
a These statistics are calculated on untransformed data.
b The last sampling time was 24 h for subjects in the multiple-dose group.
AUC = area under the plasma concentration-versus-time curve from time zero to infinity; $AUC_{(0-24)}$ = area under the plasma concentration-versus-time curve from time zero to 24 hours; $AUC_{(0-t)}$ = area under the plasma concentration-versus-time curve from time zero to the last quantifiable concentration; CL/f = apparent oral clearance; CLR = renal clearance; C_{max} = maximum concentration; CV = coefficient of variation;
Fe = fraction excreted in urine; gmean = geometric mean; NA = not applicable; NC = not calculated; SD = standard deviation; t1/2 = terminal elimination half-life; t_{max} = time of maximum concentration; X_u = amount excreted in urine.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Myopathy and the clinical diagnosis of elevated CK and/or myalgia are concerning adverse events that that occur with this drug class. Statin-associated myopathy is related to statin dose, and often due to drug/drug interactions that increase statin concentration. The most serious

muscle toxicity is rhabdomyolysis, in which skeletal muscle cells break down releasing myoglobin, enzymes and electrolytes from the muscle cells. This process may lead to renal failure, as myoglobin is reno-toxic. Rhabdomyolysis occurs at a rate of approximately 1/100,000 patient-years in statin-treated patients.

Rosuvastatin is approved for use in adults up to 40 mg/day. During the pre-approval clinical trials, 1.0% and 0.4% of the subjects treated with 80 mg/day developed myopathy and rhabdomyolysis, respectively, and therefore, the 80 mg/day dose was not approved (FDA 2003).

In the preapproval clinical trials, proteinuria was detected in 12% of the subjects treated with 80 mg/day of rosuvastatin. In the STELLAR[7] trial, 2 subjects on that same dose experienced acute renal failure (Jones and Davidson et al. 2003). However, these 2 subjects had pre-existing conditions that may have increased their risk for renal failure. Rosuvastatin was the first statin to be associated with the development and progression of proteinuria and hematuria in clinical trials. The effect was most pronounced at the 80 mg dose but was also evident at 40 mg. Proteinuria, with or without hematuria, was associated with increased serum creatinine in these subjects.

Proteinuria was also observed in clinical trials in patients treated with atorvastatin 10-80 mg/day, simvastatin 20-80 mg/day, and pravastatin 20-40 mg/day. However, it was not associated with decreasing renal function, and was reversible with or without dose reduction (Davidson 2004).

Other clinically relevant adverse effects associated with statin therapy include liver transaminase elevation, which is usually mild and self-limiting.

Drug specific safety concerns evaluated, include:

- Statin-related concerns, e.g., myopathy, and rhabdomyolysis
- Liver and renal function test abnormalities, including proteinuria
- Linear growth
- Sexual maturation (Tanner staging)

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this trial.

[7] The STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) trial compared rosuvastatin, atorvastatin, simvastatin and pravastatin across licensed doses for reducing LDL-C and other lipid parameters in patients with hypercholesterolemia

7.3.2 Nonfatal Serious Adverse Events

Three subjects experienced non-fatal serious adverse events: blurred vision, appendicitis and vesicular skin eruption, the former SAE occurred during the double-blind phase on placebo, and the latter 2 SAEs occurred in the open-label phase of the trial on 10- and 20 mg rosuvastatin, respectively. Table 21 summarizes the SAEs. Narratives for these subjects are also provided below.

Table 21: Subject descriptions with non-fatal SAEs

System Organ Class **Preferred Term (severity)**	**Subject number**	**Trial Phase/ treatment**	**Sex**	**Age (yrs)**	**Time to AE (days)[a]**	**Outcome**
Eye Disorders						
Blurred vision (moderate)	E0061028	Double-blind/ Placebo	M	14	1	Discontinued
Infections and Infestations						
Appendicitis (Severe)	E0027007	OL/ 10 mg and 20 mg	M	14	172	None
Skin and subcutaneous Tissue Disorders						
Vesicular skin eruption (Severe)	E0044002	OL/20 mg	M	17	171	Discontinued

Adapted from applicant CSR D3561C00087 Table 30
OL open-label
[a] Time in days from randomization

The narratives of the 3 subjects with non-fatal SAEs:

Subject E0061028 was a 14-year-old Caucasian male (randomized to placebo) with a past medical history of left eye loss due to trauma. This subject had blurred vision in the right eye on Day 1 of the first placebo dose. The event resolved after 1 day, but the subject was discontinued from the trial.

Subject E0027007 was a 14-year-old Caucasian male (randomized to rosuvastatin 5 mg) who underwent an appendectomy 4 days into the open label treatment with 10 mg rosuvastatin. The subject was up-titrated to 20 mg the day the adverse event was resolved. The patient remained in the trial.

Subject E0044002 was a 17-year-old Caucasian male (randomized to rosuvastatin 20 mg) with a history of low iron and facial acne, on concomitant therapy with multivitamins with iron and minocycline (discontinued Day 175). On Day 175, the subject developed a vesicular rash that progressed to cellulitis. The subject was hospitalized for intravenous antibiotic treatment. A biopsy showed superficial and deep perivascular dermatitis with interstitial component composed of eosinophils, irregular psoriasiform hyperplasia, and acantholysis and intraepidermal vesicles. The rash resolved 5 days after the discontinuation of rosuvastatin.

Reviewer comment: **The vesicular rash that developed while on rosuvastatin has the histologic pattern of an inflammatory process. Cutaneous reactions to medications can produce a wide range of clinical and histologic patterns. The differential diagnosis includes but is not limited to erythema multiforme, urticaria, lichenoid drug eruption and viral exanthemata. The AE warnings in some of the statin labels include skin findings ranging from urticaria to bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) (Chaffins and Cockerell 1996). The rash resolved after rosuvastatin was discontinued and this may implicate the drug as the causative agent.**

7.3.3 Dropouts and/or Discontinuations

Two subjects experienced AEs resulting in discontinuation during the double-blind phase. Subject E0045006 experienced menorrhagia while on 5 mg rosuvastatin, and subject E0061026 had blurred vision while on placebo (Table 22). Four (2.3%) of the 173 subjects that entered the 40-week open-label phase had AEs resulting in discontinuation. Subjects E0021005 and E0046004 experienced nausea, each while on 5 mg rosuvastatin. Subject E0044002 experienced vesicular skin eruption on 20 mg and subject E0021026 had fatigue while on 10 mg rosuvastatin (Table 22).

None of these subjects in either trial phase had abnormal laboratory values while in the trial. Subjects E0061028 and E0044002 were discussed in more detail in Section 7.3.2 (SAEs). The remaining subject narratives are below.

Table 22: Subjects who had an adverse event leading to discontinuation of study treatment (DAEs)

System Organ Class Preferred term	Subject number	Treatment Period, Dose	Sex	Age (yrs)	Time to Adverse event (days)	Serious adverse event
Gastrointestinal Disorders						
Nausea	E0021005	OL, 5mg	F	17	150	No
Nausea	E0046004	OL, 5 mg	F	16	167	No
General Disorders and Administration Site Conditions						
Fatigue	E0021026	OL, 10 mg	F	15	143	No
Reproductive System and Breast Disorders						
Menorrhagia	E0045006	DB, 5 mg	F	10	12	No
Eye Disorders						
Vision blurred	E0061028	DB, Placebo	M	14	1	Yes
Skin and subcutaneous Tissue Disorders						
Vesicular skin eruption	E0044002	OL, 20 mg	M	17	171	Yes

Adapted from applicant CSR D3561C00087 Table31, OL Open-label

Subject E0021026 was a 15-year-old Caucasian female (randomized to 5 mg rosuvastatin), who experienced fatigue Days 143 to 206, then Day 246 through the end of the trial (open-label phase, 10 mg rosuvastatin). The subject also had one day of myalgia on Day 84; and CK 10 *x* ULN (1,895 U/L) on Day 171, which normalized by Day 246. All other labs were within normal limits. A supplementary muscle narrative worksheet revealed the subject had engaged in increased physical activity on Day 170. Rosuvastatin was temporarily stopped during the first occurrence of fatigue, and the symptoms resolved; however after the reoccurrence of fatigue, the drug was permanently stopped and the subject discontinued from the trial.

Reviewer comment: The fatigue may have been secondarily due to muscle damage from exposure to rosuvastatin, although the fatigue occurred on days that the subject did not have myalgia or an increased CK. The fatigue resolved once the drug was temporarily discontinued, and recurred after the drug was re-started.

7.3.4 Significant Adverse Events

Musculoskeletal adverse events

Reviewer comment: For the purpose of this review, myopathy is defined as CK>10 *x* ULN with muscle aches or weakness. Rhabdomyolysis is defined as CK>10 *x* ULN, with or without muscle symptoms, and evidence of acute renal failure. Accepted diagnostic criteria for acute renal failure include an increase in the serum creatinine level of 0.5 mg/dL or a 50% increase in the creatinine level above the baseline value, a 50% decrease in GFR from baseline, or the need for medical intervention to preserve kidney function (Thadhani and Pascual et al. 1996; Albright 2001; Singri and Ahya et al. 2003).

Nineteen (10.7%) of the 177 subjects that entered the double-blind phase experienced investigator-reported musculoskeletal AEs. These events were myalgia (9 [5.0%]), creatine phosphokinase increase (4 [2.2%]), muscle spasms (3 [1.7%]), myopathy (2 [1.1%]), musculoskeletal pain (2 [1.1%]) and musculoskeletal chest pain (2 [1.1%]) (Table 23). Nine of these events occurred in 8 subjects during the double-blind phase, and 14 events occurred in 12 subjects during the open-label phase. No cases of rhabdomyolysis were reported.

During the double-blind phase, 4 (3.1%) subjects experienced myalgia, 1 subject while on 5 mg, 1 subject while on 10 mg and 2 subjects while on 20 mg. Two subjects had myopathy, 1 subject while on 10 mg and the other while on 20 mg rosuvastatin. One subject had musculoskeletal chest pain while on 5 mg and another had musculoskeletal pain while on 20 mg rosuvastatin.

During the open-label phase, 5 (2.9%) subjects experienced myalgia, 1 subject while on 5 mg, 3 subjects on 10 mg and 2 subjects on 20 mg (subject E0023001 had myalgia on 5 mg and 10 mg rosuvastatin and was counted twice). Three subjects had muscle spasms, 2 subjects while on 5 mg and 1 subject while on 10 mg rosuvastatin. Three subjects had "blood CK elevated", 1 subject on each rosuvastatin dose. One subject had had muscular weakness while on 20 mg.

Three subjects had musculoskeletal chest pain, 2 subjects while on 10 mg and 1 subject while on 20 mg; and 1 subject had musculoskeletal pain while on 5 mg rosuvastatin.

All of the muscle and musculoskeletal events ranged from mild to moderate in intensity. None of these AEs were classified as SAEs, or resulted in discontinuation from the trial. Subject E0021026 (previously discussed in Section 7.3.3) experienced myalgia but was discontinued from the trial due to fatigue.

Table 23: Number (%) of patients with investigator reported-musculoskeletal adverse events in the 12-week, double-blind period and in the 40-week, open-label period

MedDRA preferred term	**Rosuvastatin**				**Placebo**
	5 mg	**10 mg**	**20 mg**	**Total**	
12-week, double-blind period	**N=42**	**N=44**	**N=44**	**N=130**	**N=46**
Total musculoskeletal events	2 (4.8)	2 (4.6)	3 (6.8)	7 (5.4)	1 (2.2)
Myalgia	1 (2.4)	1 (2.3)	2 (4.5)	4 (3.1)	0
Myopathy	0	1 (2.3)[a]	1 (2.3)	2 (1.5)	0
Musculoskeletal chest pain	1 (2.4)	0	0	1 (0.8)	1 (2.2)
Musculoskeletal pain	0	0	1 (2.3)	1 (0.8)	0
Blood CK increased	0	0	0	0	1 (2.2)
40-week, open-label period	**N=129**	**N=123**	**N=123**	**N=173**	NA
Total musculoskeletal events	5 (3.9)	4 (3.2)	3 (2.4)	12 (6.9)	
Myalgia	1 (0.8)	3 (2.4)	2 (1.6)	5 (2.9)[b]	
Muscle spasms	2 (1.6)	1 (0.8)	0	3 (1.7)	
Blood CK increase	1 (0.8)	1 (0.8)	1 (0.8)	3 (1.7)	
Muscular weakness	0	0	1 (0.8)	1 (0.6)	
Musculoskeletal chest pain	0	2 (1.6)	1 (0.8)	3 (1.7)	
Musculoskeletal pain	1 (0.8)	0	0	1 (0.6)	

Adapted from applicant CSR D3561C00087 Table 33
[a] Subject 0021004 had myopathy that started in the double-blind phase and continued into the open-label phase
[b] Subject E0023001 had myalgia on 5 mg and 10 mg in the open-label phase and is counted twice
Subject E0021038experiencd musculoskeletal chest pain on 5 mg during the double-blind phase and 10 mg rosuvastatin in the open-label phase
Individual patients may have been summarized at more than 1 dose level for the same AE. Therefore, the numbers of a given AE in the total rosuvastatin group may not equal the sum of occurrences of the event at individual dose levels.
MedDRA Medical Dictionary for Regulatory Activities
NA Not applicable

Reviewer comment: **The number of myalgias and myopathies (Table 23) reported by the sponsor may not reflect the true number that occurred in the trial. Clinical investigators classified 2 of the subjects (E0061004 and E0021004) with increased CK> 10 *x* ULN and muscle symptoms as having myopathy. However, upon further review of the datasets and supplementary narratives, 3 additional subjects (E0023001, E0041011 and E0061011) treated with rosuvastatin met the criteria for myopathy: had increased CK > 10 *x* ULN and muscle symptoms.**

The number of adverse events termed "blood CK increased" in Table 23 is lower compared to the number of CK increases greater than the upper limit of normal. The low number was due to only some investigators classifying the event of an elevated CK as an adverse event. All subjects that experienced musculoskeletal events are summarized in Table 24. Subjects with musculoskeletal events are discussed in detail below Table 24.

Table 24: Summary of all subjects with musculoskeletal events and increased CK> 10 *x* ULN during the double-blind and open-label phases of the trial

Subject number	Study phase	Dose at onset	Sex /Age (yrs)	AE [preferred term/ investigator text]	Time to AE from random-ization	Action taken	Muscle narrative	Labs	Outcome
E0021004	RDB OL	10 mg 5 mg	M /14	Myopathy / Myopathy due to sports	87-113	None	Increased fitness exercise, complaints of muscle pain, starting day 84	CK 4,858 (13 ULN) Day 87, WNL day 113 AST, AP, TBL >ULN days 87 and 92	Muscle pain and labs recovered while on drug
E0021011	OL	5mg	F /17	Myalgia/ Muscle ache	103-106	None	No muscle narrative Recurrent nasopharyngitis throughout trial	CK WNL; no recurrence of muscle symptoms with dose increase	Recovered
E0021015	OL	5 mg	M/ 14	Muscle spasms/ Cramp in left leg	156	None	None	All CK WNL	Recovered
E0021026	RDB	5 mg	F/ 15	Myalgia / Muscle ache back (mild)	84	None		CK 232 on Day 41; 96 (WNL) Day 89	Recovered

Subject number	Study phase	Dose at onset	Sex /Age (yrs)	AE [preferred term/ investigator text]	Time to AE from random-ization	Action taken	Muscle narrative	Labs	Outcome
	OL	10 mg		Blood CK increased	171-182	Temp stopped	Increased physical activity on day 170	CK 1,895 (10 ULN) Days 171-182 AST, ALT >ULN Day 171	Recovered
				Fatigue/Fatigue	143-206 246, ongoing	D/c'd			Ongoing
E0021030	RDB	20 mg	F/ 17	Myalgia /muscle ache (mild)	9	None	Myalgia on the first day nasopharyngitis, Days 9-14 (possible viral syndrome?)	CKs WNL	Recovered
	OL	10 mg		Malaise/General malaise	228-265	Tempor arily stopped		CKs WNL, all other labs WNL	Recovered
E0021034	OL	5- mg	M/ 12	Muscle spasms/ Cramp in neck	131	None	No muscle narrative compiled	CK 392 on Day 16, otherwise WNL	Recovered
	OL	10 mg		Fatigue/Slight fatigue	194-253	None		Started after up-titration to 10 mg from 5 mg	Recovered
E0021036	OL	5 mg	M/ 13	Musculoskeletal pain / shoulder pain	129-130	None	No muscle narrative compiled	CK 428 on Day 85, otherwise WNL	Recovered
E0021038	RDB OL	5 mg 10 mg	M/ 16	Musculoskeletal chest pain / Acute pain musculo-skeletal thorax Note: Hx of asthma	17/317 (2 events lasting 1 day each)	None	No muscle narrative compiled	All CKs WNL	Recovered
E0023001	RDB OL	Placeb o 10-20 mg	F/17	Musculoskeletal chest pain/ Musculo-skeletal chest pain right side Note: Hx of asthma	71	None	Started while on placebo and continued into OL		Ongoing
	OL	5 -10 mg		Myalgia/Myalgia	211-234	None	Increased physical activity (waitressing, Day 211 – 238)	CK 4,593 (27 ULN) AST 39 Days 215 to Day 233 (WNL)	Recovered

Subject number	Study phase	Dose at onset	Sex /Age (yrs)	AE [preferred term/ investigator text]	Time to AE from random-ization	Action taken	Muscle narrative	Labs	Outcome
E0025002	RDB	10 mg	M/ 17	Myalgia/ Muscle ache	36-71	None	No muscle narrative compiled Dental procedure, treated with ibuprofen Day 128-134	CKs WNL AST, ALT >1 *x* ULN Days 128-309, WNL Day 365	Recovered
E0026006	OL	20 mg	M/ 15	Myalgia/ Muscle pain	253-266	None	No muscle narrative	CKs WNL AST 47 Day 312, then normalized	Recovered
E0026009	RDB	20 mg	M/ 14	Myalgia/ Myalgia	89-91	Temp. stopped	Weight lifting (Day 88)	CK 1,900 (5 ULN) Day 90 (generally CK > ULN from baseline to end of trial)	Recovered
	RDB	20 mg		Fatigue/Fatigue	253-295	None			Recovered
E0027001	RDB	20 mg	F/ 16	Musculoskeletal pain/ Pain right shoulder	87-88	None	No muscle narrative	CKs WNL	Recovered
E0041001	RDB	10 mg	F/16	Blood CK increased	84-98	Temp. stopped	Muscle training Day 83	CK 18,802 (110 ULN)	Recovered
E0041011	OL	20 mg	F/14	Nausea/Nausea	217	Stopped (Day 217)	Light muscle aches Muscle training, dance work-out (~Day 200)	CK 2748 (15 ULN) Day 217, then normalized	Recovered
E0043001	OL	10 mg	M/ 14	Myalgia/ Muscular pain both forearms	153-156	None	Physical activity (tennis, day 152-155)	CKs WNL	Recovered
E0044008	OL	10 mg	F/ 16	Myalgia/ Mild muscle tenderness behind right knee	361, ongoing	None	No muscle narrative	CKs WNL	Ongoing
E0061004	RDB	20 mg	M/ 16	Myopathy/ Myopathy (mod to mild)	17-21	Temp. stopped (5-days)	Tenderness in shoulders and arms due to increased weight training on Day 15	CK 5,550 (14 ULN) AST 79, ALT 138 Day 17 CK 458, AST 47, ALT 32, Day 21	Recovered

Subject number	Study phase	Dose at onset	Sex /Age (yrs)	AE [preferred term/ investigator text]	Time to AE from random-ization	Action taken	Muscle narrative	Labs	Outcome
E0061011	OL	5 mg	F/ 15	Blood CK increased/Elevated CK	127-124	Temp. stopped day 128	Plays soccer 2*x* weekly. During recent match (day 125) had calf, thigh pain which was not usual	CK 2,306 (12 ULN) Day 127 WNL Day 134	Recovered
				Myalgia/Muscle pain thighs and calves	125-126				
E0061012	OL	20 mg	M/1 6	Blood CK increased/Elevated CK	347-421	None		CK 1,112 (3 ULN) on Day 347	Recovered
E0061017	OL	10 mg	M/ 14	Blood CK increased	51-83	None	No muscle narrative compiled	CK 775 (2 ULN) day 53 to 192 day 83 (WNL) 443 day 119 to 212 day 251 (WNL)	Ongoing
				Muscle spasms / Muscle cramps in legs	311, ongoing				
E0081002	RDB	20 mg	M/ 17	Blood CK increased	13-	None	aerobic and weight-lifting gym	CK 12,610 (35 ULN) ↑ AST and ALT	Recovered

Adapted from applicant CSR D3561C00087 Table 34
D/c'd Discontinued
OL Open-label
RDB Randomized double-blind phase
Temp. Temporarily
WNL Within normal limits

Subject with asymptomatic increased CK> 100 *x* ULN:

Subject E0041001 was a 16-year-old Caucasian female (randomized to 10 mg rosuvastatin), with CK level elevated to 18,802 U/L (110 *x* ULN) on Day 84 and AST and ALT values of 274 U/L and 85 U/L, respectively, on Day 85. CK decreased to 142 in 14 days while off rosuvastatin**.** The subject had a normal serum creatinine during the trial; however, the subject's protein creatinine ratio was elevated > 0.2 at the end of the trial, and was followed for an additional 120 days (to Day 400) until it returned to normal (<0.13). The GFR increased with the CK increase >110 *x* ULN at Visit 6, but overall, it decreased from 111 U/L (Visit 3) at baseline to 99 U/L at the end of the trial. Urinary blood and myoglobin were negative. A supplementary muscle narrative worksheet indicated that the subject participated in one day of strong muscle training on Day 83. The study drug was temporarily stopped on Day 86 and resumed on Day 100 when the CK returned to normal limits. The subject completed the study as planned. The table below shows the patient's clinical labs over time (Table 25).

Table 25: Clinical laboratory values for Subject E0041001

Clinical tests		**Double-blind phase**										**Open-label phase**						**ULN**
Visit	**-6**	**3**[a]	**4**	**5**	**6**	**6.1**		**6.2**			**6.3**	**7**	**8**	**9**	**10**	**11**	**12**	
Day post random-ization	**-42**	**1**	**14**	**43**	**85**	**92**	**92***	**99**	**99***	**105***	**106**	**129**	**170**	**212**	**254**	**310**	**373**	
Treatment		**10**	**10**	**10**	**10**	Temporarily discontinued				**5**	**5**	**10**	**10**	**5**	**5**	**5**	**5**	
CK U/L	77	289[e]	109	79	18802[b]	309[e]	314[e]	94	100	84	80	142	96	51	171[e]	675[c]	231[e]	187
AST U/L	18	20	16	15	274[c]	22	25	16	19	14	14	19	18	16	19	28	21	40
ALT U/L	14	12	13	12	85	25	34	14	16	12	11	15	19	8	18	25	11	34
Urine protein		neg			neg	trace											trace	
Serum creatinine (mg/dL)	0.80	0.80	0.80	0.90	0.70		0.80	0.70				0.90	0.90	0.80	0.90	0.80	0.90	0.6-1.1
Urine protein/ creatinine ratio		0.1			0.09												0.26	<0.20
Myoglobin							ND											
GFR (ml/min/ 1.73m^2)	111	111			127									111			99	89-165

***** Outside laboratory
Trace urine protein at Visit 2
[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN
ND Not detectable
neg negative

<u>Reviewer comment</u>: The subject's peak CK elevation occurred towards the end of the double-blind phase, but was again elevated during the latter half of the open-label phase. The protein: creatinine ratio was elevated at the end of the double-blind phase and continued for 120 days after the completion of the trial. The subject's serum creatinine did not increase greater than 25% from baseline, and it remained within normal limits throughout the trial. While the GFR appeared to be declining at the end of the trial, it also remained within normal limits. No further GFR estimates were made after the final visit to assess a consistent pattern of decline in GFR and renal function.

The subject also had a negative urine myoglobin, although that does not necessarily rule out a diagnosis of rhabdomyolysis, as myoglobin levels peak and decline within 36 hours of muscle injury. The argument for rhabdomyolysis in this subject is less compelling given the renal clinical labs. Also, rosuvastatin was temporarily stopped then re-started and the subject completed the trial without requiring any medical intervention.

Subject with asymptomatic increased CK> 10 *x* ULN:

Subject E0081002 was a 17-year-old Caucasian male (randomized to 20 mg rosuvastatin) who had a CK concentration of 12,610 U/L (35 *x* ULN) on Day 13 and 1,175 U/L on Day 19. The subject's AST and ALT values were 184 U/L and 124 U/L, respectively on Day 13. The subjects CK, ALT and AST were all normal by the end of the trial. A supplementary muscle narrative worksheet indicated that the subject engaged in "aerobic and weight-lifting gym" starting sometime between Day 1 and Day 13, but did not report any musculoskeletal symptoms or any other AEs. No action was taken and the subject completed the trial.

Table 26: Creatine Kinase (mg/dL) values for subject E0081002

	Dietary lead-in period			**Double-blind period**			**Open-label period**						**ULN**
Visit	**1**	**2**	**3** [a]	**4**	**4.1**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Day post randomization			**1**	**13**	**19**								
Treatment				**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	
CK (U/L)	93		101	12610[b]	1175[d]	186	130	382 [e]	236 [e]	138	164	124	363
ALT (U/L)	22		17	124 [e]	62 [e]	29	18	23	34	28	24	28	43
AST (U/L)	20		17	184 [e]	37 [e]	22	13	20	29	24	21	25	40
Protein: creatinine ratio			0.03		0.02							0.02	<0.20
Serum creatinine	0.94		1.06	0.97		1.02	0.99	0.94	0.93	0.92	1.03	0.92	1.19
GFR(ml/min/1.73m^2)	127		127										89-165

[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN

<u>Reviewer comment:</u> The applicant could not provide a specific date on which the increased physical activity started, but it started within 13 days of the first elevation in CK (~64 *x* ULN). The subject remained asymptomatic and CK and liver transaminases normalized while on rosuvastatin without intervention. It is reassuring that none of the labs indicated renal insufficiency.

Subjects with symptomatic increased CK> 10 *x* ULN:

Subject E0021004 was a 14-year-old Caucasian male (randomized to rosuvastatin 10 mg), who developed muscle pain Day 87 post randomization. This adverse event coincided with an elevated CK concentration of 4,858 U/L (13 ULN) as well as elevated AST, alkaline phosphatase (AP), and total TBL. The subjects also had a low red blood cell count on Day 1. The CK values normalized by day 113, rebounded on days 132 and 212, but returned to normal by the end of the trial. The AST, AP and TBL were elevated on 2 consecutive visits (Days 89, 92), and then normalized. A supplementary muscle narrative worksheet revealed the subject had engaged in increased physical activity on Day 87 (coinciding with the muscle pain symptoms), which continued throughout the rest of the trial. No action was taken with regard to study drug. The subject completed the trial.

Table 27: Creatine Kinase (mg/dL) values for Subject E0021004

	Dietary lead-in period		**Double-blind period**			**Open-label period**							
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ULN**
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Day post randomization	**-39**		**1**	**15**	**43**	**87-92**	**132**	**169**	**212**	**273**	**308**	**364**	
Treatment				**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**	**5**	
CK	503[e]		135	143	223	4858[b]-963[e]	637[e]	146	378[e]	266	110	192	363
AST	33		22	23	28	69[e]	43 [e]	24	34	34	23	25	40
ALT	13		13	14	17	32-38	19	14	16	17	15	17	43
AP (U/L)	265 [e]		290 [e]			251-258 [e]						182	100-320
TBL (mg/dL)	1.2		1.3[e]			1.7[e] -1.6[e]						1.1	0.3-1.2
Protein: creatinine ratio			0.02										<0.20
GFR (ml/min/1.73m^2)	213		203			169			179			178	89-165

[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN

<u>Reviewer comment</u>: The increase in AST coincided with the elevation in CK >10 *x* ULN. The elevated AP and TBL are suggestive of an obstructive hepato-biliary process that started before the subject started the study drug. This in conjunction with the elevated AST does not meet the Hy's law criteria. It is reassuring that these hepatic effects appear to be transient.

Subject E0023001 was a 17-year-old Caucasian female (randomized to placebo) with a history of asthma, treated with ipratropium bromide throughout the trial. The subject reported right-sided musculoskeletal chest pain that started while on placebo and continued throughout the entire trial. On Day 215, while treated with rosuvastatin 10 mg, the subject's CK started to increase, peaked at 4,593 U/L (27 *x* ULN) then normalized on Day 233 (after dose increased to 20 mg on Day 219). All other labs were within normal limits. A supplementary muscle narrative worksheet revealed that the subject also had muscle pain after starting a new job waitressing on the beach (Day 211 to Day 238). No action was taken and the subject completed the trial.

Subject E0041011 was a 14-year-old Caucasian female (randomized to rosuvastatin 10 mg) who reported light muscle aches on Day 212 that coincided with CK elevated 15 *x* ULN (2,748 U/L). CK normalized by Visit 12. Protein: creatinine ratio and GFR remained within normal limits. The supplementary muscle narrative worksheet revealed that the subject engaged in ongoing muscle training and dance work-out. Rosuvastatin was temporarily stopped on Day 212, and the subject completed the trial.

Table 28: Creatine Kinase (mg/dL) values for Subject E0041011

	Dietary lead-in period			**Double-blind period**			**Open-label period**						**ULN**
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Treatment				**10**	**10**	**10**	**10**	**20**	**10**	**20**	**20**	**20**	
Day post randomization										**212**			
CK (U/L)	84		78	78	78	69	78	294 [e]	97	2748 [b]	306 [e]	87	187
AST (U/L)	17		18	18	18	16	17	19	20	45[e]	20	20	40
ALT (U/L)	12		14	10	9	11	9	14	18	8	8	9	34
Protein/ creatinine ratio			0.06			0.10						0.06	<0.20
GFR ($ml/min/1.73m^2$)	147		126			111			127			149	89-165

[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN

<u>Reviewer comment</u>: The increased physical activity and muscle pain occurred around the same time as the elevation in CK (15 *x* ULN). The AST elevation is likely due to muscle given the normal ALT and the elevation in CK.

Subject E0061004 was a 16-year-old Caucasian male (randomized to rosuvastatin 20 mg) who reported shoulder and arm muscle pain Days 17 to 21. The subject's CK concentration was 5,550 U/L (14 *x* ULN) on Day 17 and was within normal limits on Day 30. The associated AST and ALT values were 138 U/L and 79 U/L, respectively on Day 17. The supplementary muscle narrative worksheet revealed that the subject had engaged in intense weight training on Day 15. Rosuvastatin was temporarily stopped, and CK and liver function test values returned to normal and the subject completed the study.

Subject E0061011 was a 15-year-old Caucasian female (randomized to rosuvastatin 5 mg) who developed bilateral thigh and calf pain. CK was 2,306 U/L (12.3 *x* ULN), and AST 45 U/L on Day 127, and rosuvastatin was temporarily stopped. Both measurements decreased to normal by Day 134, before rosuvastatin was re-started. The only other elevated lab was a TBL of 2.2 mg/dL on Day 134 (no other TBL measurements were measured during the trial). All other labs were within normal limits. The supplementary muscle narrative worksheet revealed that the subject usually played soccer 2 times per week, and on the day prior to the trial visit (Day 126), the subject had a soccer match and experienced unusual bilateral thigh and calf pain. The muscular pain resolved after 2 days and did not recur.

Subject with symptomatic increased CK> 5 *x* ULN:

Subject E0026009 was a 14-year-old Caucasian male (randomized to 20 mg rosuvastatin) with a history of Attention Deficit Hyperactivity Disorder on methylphenidate hydrochloride. The subject experienced myalgia on Days 89-91 associated with CK 1,900 U/L (5.2 *x* ULN) on Day 90, at which time rosuvastatin was temporarily stopped. In general, the subject's CK was > ULN at baseline and throughout the trial. Serum creatinine was elevated > 25% from baseline (0.82 mg/dL) on Days 253 and Day 309, but was within normal limits by the end of the trial. Protein: creatinine ratio was within normal limits during the double-blind phase; however, it was not measured during the open-label phase of the trial. There was a decrease in the GFR at the end of the trial compared to baseline. The supplementary muscle narrative worksheet revealed that the subject had engaged in intense weight training 2 days prior to the CK measurement (Day 88). No action was taken and the subject completed the trial. Table 29 shows a timeline for the CK elevations as well as other labs of interest.

Table 29: Creatine Kinase (mg/dL) values for Subject E0026009

	Dietary lead-in phase			**Double-blind phase**			**Open-label phase**						**ULN**
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Day post randomization	**-41**	**-6**	**1**	**15**	**43**	**90**	**127**	**169**	**211**	**253**	**309**	**372**	
Treatment	**-**	**-**	**-**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**	
CK (U/L)	404 [e]		574 [e]	203	561 [e]	1900 [c]	129	254	230	734 [e]	193	415 [e]	363
ALT (U/L)	24		24	22	35	41e	25	27	25	29	24	22	43
Urine RBC												+1	
Urine protein	trace	trace	+1			+1						+1	
Serum creatinine (mg/dL)	0.84		0.82	0.83	0.91	0.93	0.92	0.96	0.93	1.04 [f]	1.06 [f]	0.97	0.5-1.0
Protein: creatinine ratio			0.06			0.07							<0.20
GFR (ml/min/1.73m2)	141		145			128			130			125	89-165

[a] Baseline: Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >5*x* ULN
[d] >2*x*ULN
[e] >1*x*ULN
[f] > 25% increase from baseline

<u>Reviewer comment</u>: In addition to the musculoskeletal effects, this subject appeared to have changes in renal function that started towards the end of the double-blind phase. However, the protein: creatinine ratio remained within normal limits during the double-blind phase. Because no measurements were taken during the open-label phase a pattern cannot be established for that phase of the trial. The GFR remained within normal limits, but had declined 14% from baseline.

Eight subjects experienced increased CK>10 *x* ULN during the 52-week trial, ranging from 10 *x* ULN to 110 *x* ULN. These 8 cases occurred in only subjects exposed to rosuvastatin and were equally divided between the double-blind phase and the open-label phase of the trial (Table 30).

During the double-blind phase, 4 (3.1%) subjects treated with rosuvastatin, 2 of each treated with 10 mg and 20 mg rosuvastatin had elevations of CK > 10 *x* ULN. Rosuvastatin was temporarily stopped in the 2 subjects on 10 mg and 20 mg. None of the subjects had elevations in CK>10 *x* ULN on follow-up CK testing.

During the open-label period, elevations in CK>10 *x* ULN at any visit occurred in 4 (2.3%) subjects treated with rosuvastatin (Table 30), 2 subjects (1.6%) while on 5 mg, 1 subject (0.8%) while on 10 mg, and 1 subject (0.8%) while on 20 mg. None of the subjects had increased CK >10 *x* ULN on follow-up CK testing the open-label period.

Table 30: Number (%) of subjects with treatment-emergent CK elevations in the 12-week double-blind period and in the 40-week open-label period

Adverse Event (Preferred term)	**Rosuvastatin**				
	5 mg	**10 mg**	**20 mg**	**Total**	**Placebo**
Double-blind phase	**(N=42)**	**(N=44)**	**(N=44)**	**(N=130)**	**(N=46)**
CK increased ≥ ULN	13 (31.0)	7 (15.9)	10 (22.7)	30 (23.1)	6 (13.0)
CK increased ≥ 10 *x* ULN	0	2 (4.5)	2 (4.5)	4 (3.1)	0
Open-label phase[a]	**(N=129)**	**(N=123)**	**(N=123)**	**(N=173)**	**NA**
CK increased ≥ ULN	27 (20.9)	26 (21.1)	29 (23.6)	40 (30.8) [a]	NA
CK increased ≥ 10 *x* ULN	2 (1.6)	1 (0.8)	1 (0.8)	4 (2.3)	NA

Adapted from applicant CSR D3561C00087 Table 36

[a] Some subjects were counted more that once during the open-label phase of the trial, as different CK elevations may have occurred for the same subject at across rosuvastatin doses.

There were over twice as many elevations in CK> 5 x ULN in the rosuvastatin treated subjects in the PLUTO trial compared to the subjects in the simvastatin pre-approval pediatric trial (FDA 2002). There did not appear to be a difference in increased CK>5 *x* ULN between rosuvastatin and atorvastatin (FDA 2001). Data were not available to sub-stratify CK levels for atorvastatin >10 *x* ULN (Table 31).

Table 31: Number (%) of pediatric subjects with CK elevations atorvastatin and simvastatin treated groups (double-blind phase only)

CK elevation	**Treatment**[a]					
	Simvastatin	**Placebo**	**Atorvastatin**	**Placebo**	**Rosuvastatin**	**Placebo**
N	106	69	140	47	131	46
CK>1 *x* ULN	NA	NA	NA	NA	30 (23.1)	6 (13.1)
CK>5 *x* ULN	2 (1.9)	1 (1.4)	5 (3.6)	1 (2.1)	5 (3.8)	0
CK>10 *x* ULN	1 (0.9)	0	NA	NA	4 (3.1)	0

NA Data not available

[a] Across all treatment groups, atorvastatin 10 mg, simvastatin 10-m, 20 mg and 40 mg and , rosuvastatin 5 mg, 10 mg and 20 mg

During the double-blind phase, CK collected every 4 weeks up to week 24 for simvastatin, Weeks 4, 8, 18 and 39 for atorvastatin and Weeks 0, 2, 6 and 12 for rosuvastatin

<u>Reviewer summary comment</u>: The subjects discussed in the narratives above experienced a combination of musculoskeletal events and or increased CK >10 *x* ULN. The applicant attributed the elevations in CK to exercise, as they coincided with a period of increased or new exercise activity. There have been several trials investigating the effect of whether exercise in combination with statins produces greater CK increase (proxy for skeletal

muscle injury) than exercise alone. In a trial in 58 healthy adult males, CK levels were up to 77% higher in the lovastatin group 48 hours after exercise compared to the placebo group (Thompson and Zmuda et al. 1997). In another trial with atorvastatin 10 mg and 80 mg, CK and muscle soreness increased following exercise in both atorvastatin treatment groups. However, there was no significant difference between the 2 treatment groups (Kearns and Bilbie et al. 2008).

During the double-blind phase of the pediatric rosuvastatin trial, the 4 subjects exposed to rosuvastatin with elevations >10 *x* ULN reported concomitant exercise. In any study, an investigator cannot fully know all the confounding factors. The process of randomization helps to balance potential confounders among treatment groups. In this trial it could be assumed that the rosuvastatin treated subjects with the CK elevations had the same levels of exercise as those randomized to placebo, as well as those who did not have substantial elevations in CK. Since exercise data were not collected on the other subjects it is difficult to say whether the CK elevations can be attributed all or in part to exercise. However, a synergistic interaction between exercise and rosuvastatin cannot be ruled out. What is clear is that only the subjects treated with rosuvastatin in the double-blind phase had increased CK>10 *x* ULN.

Musculoskeletal events (Pediatric Pharmacokinetic Study [4522IL/0086])

None of the subjects had symptoms of muscle damage. No subject had CK elevated >10 *x* ULN. Three subjects had CK elevations above the normal range: 2 subjects in the rosuvastatin 80 mg multiple-dose phase (1 subject at follow-up and 1 subject on Day 4), and 1 subject that received a single dose of rosuvastatin 40 mg (CK 3.6 *x* ULN on Day 5 attributed to excessive athletic activity).

Hepatic events

One subject had an AE of 'AST increased' during the double-blind phase (E0061004) along with concurrently elevated CK>10 *x* ULN. This subject was discussed in detail under musculoskeletal events.

During the open-label phase, 1 subject (E00006012) had an ALT increased above the upper limit of normal and 1 subject (E0025002) had an AE termed "liver test abnormal" (Table 32). No subject met the criteria for Hy's law and there were no cases of overt hepatic injury (e.g., jaundice).

Table 32: Number (%) of patients with investigator-reported hepatic adverse events in the 12-week, double-blind period and in the 40-week, open-label period

MedDRA preferred term	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Rosuvastatin Total	Placebo
12-week, double-blind phase	**N=42**	**N=44**	**N=44**	**N=130**	**N=46**
Aspartate aminotransferase increased	0	0	1 (2.3)[a]	1 (0.8)	0
40-week, open-label phase	**N=129**	**N=123**	**N=123**	**N=173**	NA
Alanine aminotransferase increased	0	0	1 (0.8)[b]	1 (0.6)	
Liver function test abnormal	1 (0.8)[c]	0	0	1 (0.6)	

Adapted from applicant CSR D3561C00087 Table 31
[a] Patient E0061004. [b] Patient E0061012. [c] Patient E0025002
MedDRA Medical Dictionary for Regulatory Activities
NA Not applicable

During the double-blind phase, 1 subject (2.3%) on 10 mg rosuvastatin and 2 subjects (4.6%) on 20 mg rosuvastatin had increased AST>3 *x* ULN on 2 consecutive visits, or at least 48 hours apart. In the open-label phase 1 (0.6%) subject on 5 mg rosuvastatin had ALT elevated >3 *x* ULN on 2 consecutive visits, or at least 48 hours apart (
Table 33). No subject met the Hy's law criteria and there were no cases of overt hepatic injury (e.g., jaundice) nor liver-related AEs.

Table 33: Number (%) of subjects with elevations in hepatic enzymes in the 12-week double-blind period and 40-week open-label period, by degree of elevation

Adverse Event	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Rosuvastatin Total	Placebo
12-week, double-blind phase	**N=42**	**N=44**	**N=44**	**N=130**	**N=46**
ALT increased ≥1 *x* ULN	2 (4.8)	2 (4.5)	4 (9.1)	9 (6.9)	5 (10.9)
ALT increased ≥3 *x* ULN	0	0	0	0	0
AST increased ≥1 *x* ULN	1 (2.4)	3 (6.8)	3 (6.8)	7 (5.4)	0
AST increased ≥3 *x* ULN	0	1 (2.3)	2 (4.6)	3 (2.3)	0
52-week, open-label phase	**N=129**	**N=123**	**N=123**	**N=173**	**NA**
ALT increased ≥1 *x* ULN	1 (0.8)	0	0	1 (0.6)	
ALT increased ≥3 *x* ULN	1 (0.8)	0	0	1 (0.6)	
AST increased ≥1 *x* ULN	1 (0.8)	0	0	1 (0.6)	
AST increased ≥3 *x* ULN	0	0	0	0	

ALT
During 12-weeks of double-blind treatment there were 2 subjects (4.8%) on rosuvastatin 5 mg, 2 subjects (4.5%) on 10 mg, 4 subjects (9.1%) on 20 mg, and 5 subjects (10.9%) on placebo that had ALT values above the reference range. There was no apparent difference in the incidence of abnormal ALTs among the treatment groups. No subject in any treatment group experienced ALT elevations >3 *x* ULN during the double-blind period (Table 33). Only 1 subject (0.8%) had an ALT >3 *x* ULN during the open-label phase while on 5 mg rosuvastatin and it was classified "liver function test abnormal".

> Subject 25002 was a 17-year-old Caucasian male (randomized to 10 mg rosuvastatin), who experienced elevated AST and ALT on Day 128 to Day 365 of the trial. The subject also experienced myalgia on Day 36 to Day 71; however, there was no increase in CK or any other labs indicative of muscle damage during that period. All other labs were within normal limits. The subject had a dental procedure which was treated with ibuprofen from Day 128 to Day 134. No action was taken and the subject completed the trial.

Table 34: Liver transaminase (U/L) values for subject E0025002

	Dietary lead-in phase			**Double-blind phase**		**Open-label phase**							**ULN**
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Day post randomization.	**-41**	**-6**	**1**	**15**	**43**	**85**	**128**	**166**	**218**	**253**	**309**	**365**	
Treatment	**-**	**-**	**-**	**10**	**10**	**10**	**5**	**5**	**5**	**5**	**5**	**5**	
ALT (U/L)	18	-	16	25	22	36	54[e]	118[b]	56[e]	102[b]	71[e]	38	43
AST (U/L)	22	-	20	29	24	27	34	59[b]	32	50e	43[b]	33	36

<u>Reviewer comment</u>: ALT is more specific for hepatocellular injury than AST, and this subject had a greater degree of elevation in ALT that AST. Also, the subject had these elevations in liver transaminases after down-titration to 5 mg from 10 mg rosuvastatin. While this may weaken the association between rosuvastatin exposure and the transaminase increases, the study drug may still have played a role. The subject also experienced several AEs during the trial including: headache, myalgia, influenza, nasopharyngitis and had a medical history of acute hepatitis in 2001.

> Subject E0081004 was a 16-year-old Caucasian male (randomized to placebo) with a medical history of hypothyroidism and congenital adrenal hyperplasia, treated with levothyroxine, fludrocortisone and hydrocortisone. The subject had an ALT of 168 U/L (4.4 *x* ULN) during a "mononucleosis-like" event during the open-label phase while on 5 mg rosuvastatin. Rosuvastatin treatment was temporarily stopped, the ALT values were normal thereafter. During the open-label phase, the subject also developed brucellosis and oropharyngeal candidiasis, for which the subject received doxycycline, rifampin, and ketoconazole.

The mean change in ALT values from baseline to the end of the double-blind treatment period (Week 12) was higher in the rosuvastatin groups (3.3 U/L, 5.2 U/L, and 4.9 U/L for the 5 mg, 10 mg, and 20 mg groups, respectively) than in the placebo group (0.9 U/L). The mean change from baseline to the end of the open-label treatment period (Week 52) was 4.6 U/L for all the rosuvastatin groups, similar to that seen in rosuvastatin-treated subjects at Week 12.

AST
During the double-blind phase, 1 subject (2.5%) on 5 mg rosuvastatin, 3 subjects (6.8%) on 10 mg, 3 subjects (6.8%) on 20 mg, and no placebo-treated subjects had AST values above the reference range (Table 33). Three subjects (E0041001, E0061004, and E0081002) treated with rosuvastatin 10 mg, 20 mg, and 20 mg, respectively, experienced elevated AST >3 *x* ULN, as well as increased CK> 10 *x* ULN. The ALT for subject E0081002 was also elevated approximately 3 *x* ULN. Subject E0061004, who also experienced an AE of myopathy, is discussed in Section 7.3.4. Subjects E0041001 and E0081002 are discussed under Section 7.4.2.

During the open-label period, 1 (0.6%) subject treated with 5 mg rosuvastatin had an AST value above the reference range.

The mean change in AST values from baseline to the end of the double-blind treatment period (Week 12) was higher in the rosuvastatin groups: Rosuvastatin 5 mg group (1.2 U/L), 10 mg group (8.4 U/L) and 20 mg group (2.2 U/L) compared to the placebo group (0.9 U/L). The mean change from baseline to the end of the open-label treatment period (Week 52) was 1.4 U/L for total rosuvastatin group.

Reviewer comment: Most of the elevations in AST and ALT during the trial occurred during the double-blind phase. Only a small proportion exceeded 3 *x* ULN and none of the subjects met the criteria for Hy's Law.

Other Hepatic Laboratory Findings
The subjects with elevations in TBL and AP in conjunction with elevations in critical labs were discussed in detail in previous sections. Changes from baseline to the end of the double-blind phase (Week 12) in TBL, AP, GGT, total protein, and albumin were similar among the treatment groups.

Hepatic events (Pediatric Pharmacokinetic Study [4522IL/0086])
None of the subjects had symptoms consistent with liver damage. Three subjects had elevations in aminotransferase above the normal range (1.1 to 4.8 *x* ULN); 1 subject treated with the multiple doses of rosuvastatin 80 mg and 2 subjects treated with single doses of rosuvastatin 40 mg had AST elevations.

The levels of AP, TBL, total protein, and albumin remained within normal limits for the subjects in this trial.

Renal events

Three subjects (E0001003, E0021011 and E0043001) were classified as having mild renal impairment due to baseline creatinine clearance less that 80 mL/minute. However, these subjects had creatinine clearances above 80 mL/minute at the beginning of the lead-in phase and during the trial. They also had negative baseline (Visit 3) dipstick urine protein and normal serum creatinine and GFR and urinary protein: creatinine ratios.

During the double-blind phase, 1 subject had an AE (urinary tract infection) related to the renal system, while on 5 mg rosuvastatin.

During the open-label phase, 7 subjects had AEs related to the renal system. Subject E0025003 had cystitis 4-times while on 5 mg, 10 mg and 20 mg rosuvastatin, and developed dysuria while on 20 mg, so this subject is counted more that once; 2 other subjects had cystitis while on 10 mg and 20 mg rosuvastatin. Three subjects (1.7%) had multiple episodes of urinary tract infections while on 5 mg, 10 mg and 20 mg rosuvastatin and 1 subject had chromaturia while on 5 mg rosuvastatin. The subject with chromaturia is discussed below.

Table 35: Number (%) of patients with treatment-emergent renal and urinary AEs in the 12-week, double-blind period and in the 40-week, open-label period

System organ class	Preferred term	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Rosuvastatin Total	Placebo
12-Week double-blind phase	**N**	**42 (%)**	**44 (%)**	**44 (%)**	**130 (%)**	**46 (%)**
Infections and infestations	Total	8 (19.0)	12 (27.3)	14 (31.8)	34 (26.2)	17 (37.0)
	Urinary tract infection	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.8)	2 (4.3)
40-Week open-label phase	**N**	**129 (%)**	**123(%)**	**123(%)**	**173 (%)**	**NA**
Infections and infestations	Total	22 (17.1)	26 (21.1)	47 (38.2)	74 (42.8)	
	Urinary tract infection	1 (0.8)	1 (0.8)	3 (2.4)	3 (1.7)	
	Cystitis	1 (0.8)	2 (1.6)	2 (1.6)	3 (1.7)[a]	
Renal and Urinary disorders	Total	1 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)	
	Chromaturia	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	
	Dysuria	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.6)[a]	

[a] Subject E0025003 had cystitis 4-times, and then developed dysuria, so this subject is counted more that once

Subject E0021038 was a 16-year-old Caucasian male (randomized to 5 mg rosuvastatin) who developed chromaturia (abnormal coloration of the urine) Day 98 to Day 106. Rosuvastatin was temporarily stopped. The subject had normal renal function at the beginning of the trial and the urinary protein: creatinine ratios and BUN were within normal limits throughout the trial (Week 52). Urinalyses were normal throughout the double-blind phase for this subject. Other adverse events included 2 days of

musculoskeletal chest pain (Day 17, Day 317) and vasovagal syncope (Day 261). The subject completed the trial. This subject was also listed in **(**Table 24**).**

Subject E0025003 was a 14-year-old Caucasian female (randomized to placebo) who experienced 4 bouts of cystitis, treated with trimethoprim between Day 93 and Day 242, and subsequently developed dysuria Day 337 which continued through the end of the trial. The subject had elevated serum creatinine on Day 119 and again on Day 204, but returned to normal by the end of the trial. Other AEs included constipation and ear pain. No action was taken and the subject completed the trial.

Serum creatinine
Over the course of the trial, there were 14 subjects with >25% elevation in serum creatinine from baseline.

During the double-blind treatment phase, 1 subject on 5 mg and 2 subjects on 20 mg rosuvastatin, and none on placebo had a >25% increase in serum creatinine from baseline (Table 36). No subject had >50% increase from baseline during the double-blind phase.

During the open-label period, 13 (7.5%) subjects treated with rosuvastatin had a serum creatinine increase >25% from baseline. One subject (0.6%) had a serum creatinine increase >50% from baseline (see subject E0021012 narrative below).

Most of the serum creatinine increases >25% above baseline were noted at only one visit and were not associated with increases in BUN, protein: creatinine ratios or other lab values. Four subjects (E0026009, E0041004, E0041022 and E0083003) had elevated serum creatinine > 25% on 2 or more visits (detailed narratives below). Subject E0026009 was previously discussed under the musculoskeletal events. This subject had CK elevated >5 *x* ULN, however, the protein: creatinine ratio remained within normal limits during the double-blind phase. No measurements were taken during the open-label phase, so a pattern cannot be established for that phase. The GFR remained within normal limits, but declined from baseline.

Table 36: Number of subjects (%) with serum creatinine increased >25% above baseline during the double-blind and open-label phases

	Rosuvastatin				
	5 mg	**10 mg**	**20 mg**	**Total**	**Placebo**
12-week, double-blind phase[a]	**N=42**	**N=44**	**N=44**	**N=130**	**N=46**
>25% increase from baseline	1 (2.4)	0	2 (4.5)	3 (2.3)	0
>50% increase from baseline	0	0	0	0	0
40-week, open-label phase[a]				**N=173**	
>25% increase from baseline	NA	NA	NA	13 (7.5)	NA
>50% increase from baseline	NA	NA	NA	1 (0.6)[b]	NA

Adapted from applicant CSR D3561C00087 Table 38
[a] Baseline for both the double-blind period and the open-label period was the randomization visit (Week 0; Visit 3). Subjects E0041004 and E0041022 had elevations > 25% in both phases, and were counted twice.
[b] This subject was treated with 20 mg rosuvastatin during the open-label phase

Subject with serum creatinine elevated >50% above baseline:

Subject E0021012 (randomized to placebo) was an 11-year-old Caucasian male whose serum creatinine increased > 50% above baseline (0.50 to 0.80 mg/dL) at Week 44 of the open-label phase (titrated to 20 mg on Week 30). The serum creatinine returned to baseline by the next visit. All other labs, including protein: creatinine ratio, GFR, liver transaminases and CK were within normal limits. The subject experienced one AE during the trial: dental pain due to complications with orthodontics.

Subjects with serum creatinine elevated >25% from baseline, on 2 or more visits:

Subject E0041004 was a 14-year-old Caucasian male (randomized to 5 mg rosuvastatin) who was treated with cholestyramine prior to starting the trial. The subject's serum creatinine level increased >25% on 5 visits during the trial. This subject also had an increase in protein: creatinine ratio once during the double-blind phase. These labs were all normal at the end of the trial. All other labs, including BUN, liver transaminase and CK remained within normal limits**.** No action was taken and the subject completed the trial.

Table 37: Renal function labs for subject E0041004

	Dietary lead-in phase		**Double-blind phase**			**Open-label phase**							
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Treatment	**-**	**-**	**-**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	
Urine protein	trace	-	neg			trace						trace	
Serum creatinine (mg/dL)	0.69	-	0.63	0.69	0.80 [f]	0.63	0.63	0.80 [f]	0.80 [f]	0.80 [f]	0.80 [f]	0.69	0.5-1.0
Protein/ creatinine ratio	-	-	0.15			0.21	-	-	-	-	-	0.10	<0.20
GFR (ml/min/1.73m^2)	175	-	205	-	-	178	-	-	156	-	-	179	89-165

[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN
[f] >25% increase over baseline
neg Negative

<u>Reviewer comment</u>: In the absence of other explanatory factors, rosuvastatin may have played a role in the changes in the renal function. The relationship may have been clearer had more frequent protein: creatinine ratios and GFRs been measured to determine if there was a clearer pattern of renal function decline.

Subject E0041022 was a 14-year-old Caucasian male (randomized to 20 mg rosuvastatin) whose serum creatinine increased >25% during both phases of the trial (but remained within normal limits). During the double-blind phase, the serum creatinine increased by 34% above baseline, then decreased once the subject entered the open-label phase on 5 mg rosuvastatin. The serum creatinine again increased >25% above baseline after the subject had been up-titrated to 20 mg, but decreased by the end of the trial. All other labs, including BUN, liver transaminases and CK remained within normal limits. The only adverse event reported for this subject was influenza during the open-label phase, which was symptomatically treated with ibuprofen. No action was taken and the subject completed the trial. Table 38 summarizes the subject's renal function labs.

Table 38: Renal function labs for subject E0041022

	Dietary lead-in phase			Double-blind phase		Open-label phase							ULN
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Treatment				**20**	**20**	**20**	**5**	**5**	**10**	**10**	**20**	**20**	
CK	107		484[e]	124	98	151	67	104	89	91	98	67	187
Urine protein	trace	neg				neg						+1	
Serum creatinine	0.69		0.59	0.80[f]	0.80[f]	0.69	0.69	0.59	0.59	0.69	0.80[f]	0.69	0.5-1.0
Protein: creatinine ratio			0.10			0.15						0.09	<0.20
GFR (ml/min/1.73m^2)	162		190			164			193			166	89-165

[a] Baseline Start of double-blind phase (Visit 3, Week 0)
[b] >10 *x* ULN
[c] >3 *x* ULN
[d] >2 *x* ULN
[e] >1 *x* ULN
[f] >25% increase over baseline

Subject E0083003 was a 14-year-old Caucasian male (randomized to placebo) with a history of Attention Deficit Hyperactivity Disorder and allergic rhinitis, treated with methylphenidate HCl and other anti-allergy medications (see reviewer comment for other medications taken during the trial). This subject had a >25% increase from baseline in serum creatinine throughout the open-label phase of the trial, as well as ≥25% decrease in estimated GFR from baseline. The subject also had trace protein at baseline and Week 12; however, the protein: creatinine ratios were within normal limits. All other labs, including BUN, liver transaminases and CK remained within normal limits. No action was taken and the subject completed the trial.

Table 39: Renal function labs for subject E0083003

	Dietary lead-in phase			Double-blind phase		Open-label phase							ULN
Visit	**1**	**2**	**3** [a]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Week	**-6**	**-1**	**0**	**2**	**6**	**12**	**18**	**24**	**30**	**36**	**44**	**52**	
Treatment	**-**	**-**	**-**	**P**	**P**	**P**	**5**	**5**	**10**	**10**	**20**	**20**	
Urine protein	trace	neg	neg			trace						trace	
Serum creatinine	0.57		0.49	0.53	0.57	0.58	0.60	0.69[b]	0.63[b]	0.69[b]	0.71[b]	0.74[b]	0.5-1.0
Protein/ creatinine ratio			0.03			0.04						0.03	<0.20
GFR (ml/min/1.73m^2)	192		223			189			178			153	89-165

[a] Baseline, start of double-blind phase (Visit 3, Week 0), [b] >25% increase over baseline

Reviewer comment: The GFR was notably high at baseline. The subject took combinations of the following drugs intermittently throughout the open-label phase: bronquidiazina (immediate acting sulfonamide [insoluble sulfonamides can directly cause renal damage]), terbutaline, budesonide, methylphenidate HCL and ebastine (antihistamine). With the exception of bronquidiazina, the other drugs are not known affect renal function.

Mean serum creatinine values at baseline and at the end of the double-blind phase were comparable among the 4 treatment groups and the placebo group. There were negligible mean changes in serum creatinine from baseline to the end of the double-blind phases over time in all 4 treatment groups. Mean serum creatinine values at the beginning of the double-blind phase to the end of the open-label phase (the entire trial) were also comparable and the mean changes were negligible. The data are summarized in Table 40.

Table 40: Summary of the changes in serum creatinine (mg/dL) by dose from baseline to final visit week during the 12-week, double-blind and the 40-week, open-label phases

Serum Creatinine, mg/dL	**Rosuvastatin**				**Placebo**
	5 mg	**10 mg**	**20 mg**	**Total**	
12-week double-blind phase					
Baseline (Week 0)					
n	42	44	44	130	46
Mean (SD)	0.71 (0.15)	0.73 (0.12)	0.73 (0.14)	0.72 (0.13)	0.70 (0.11)
Median	0.70	0.70	0.70	0.70	0.70
Range	0.40-1.0	0.50-1.0	0.50-1.0	0.40-1.0	0.50-0.90
End of double-blind phase (Week 12)					
n	41	44	44	129	45
Mean (SD)	0.71 (0.13)	0.72 (0.12)	0.73 (0.14)	0.72 (0.13)	0.72 (0.12)
Median	0.70	0.70	0.70	0.70	0.70
Range	0.50-0.90	0.50-1.0	0.50-1.0	0.50-1.0	0.50-1.0
Change from baseline to final visit in double-blind phase					
n	41	44	44	129	45
Mean (SD)	0.0 (0.08)	0.0 (0.08)	0.0 (0.07)	0.0 (0.08)	0 (0.06)
Median	0.0	0.0	0.0	0.0	0.0
Range	-0.2-0.2	-0.2-0.2	-0.1-0.2	-0.2-0.2	-0.1-0.1
52 week total trial (N)	**NA**			**176**	**NA**
Baseline					
n				176	
Mean (SD)				0.71 (0.13)	
Median				0.70	
Range				0.40-1.1	
Change from baseline to final visit of the open-label phase					
n	NA			166	NA
Mean (SD)				0.0 (0.08)	
Median				0.0	

Serum Creatinine, mg/dL	Rosuvastatin				Placebo
	5 mg	10 mg	20 mg	Total	
Range				-0.2-0.2	

Adapted from applicant CSR D3561C00087 Table 37
SD Standard deviation

Urine protein: creatinine ratios
The cut-off point for the protein creatinine ratio was set at 0.2 mg/mg because a single-voided protein: creatinine ratio of ≥ 0.2 mg/mg is suggestive of proteinuria (Kupferman and Supavekin et al. 2003). There were 4 subjects with urine protein: creatinine ratios that increased to >0.2: 2 subjects on 5 mg rosuvastatin, 1 subject on 10 mg rosuvastatin and 1 subject on 20 mg rosuvastatin. Of the subjects with urine protein: creatinine ratios that shifted to >0.2, no serum creatinine values were outside of the normal range and there were no abnormal urinalysis findings (Table 41).

Subjects E0041001 and E0041006 had protein: creatinine ratios that remained elevated beyond the end of the open-label phase, and were monitored until it returned to the normal range. Subject E0041001 was discussed under musculoskeletal events. This subject had an increased CK (110 *x* ULN), in combination with increased protein: creatinine ratio and decreased GFR. Subject E0041006 is discussed below.

> Subject E0041006 was a 14-year-old Caucasian male (randomized to placebo) with an elevated urinary protein: creatinine ratio >0.2 on the last visit of the trial (Visit 12). The subject was followed for an additional 124 days until the protein: creatinine ratios were within normal limits. All other labs, including serum creatinine, creatinine clearance, liver transaminases and CK were within normal limits.

Table 41: Subjects with the urine protein: creatinine ratio increased from ≤0.2 mg/mg to >0.2mg/mg

Dose at onset	Patient number	Sex	Age (yrs)	Urine protein: creatinine ratio (mg/mg)			Serum creatinine (mg/dL)		
				Baseline[a]	Week 12	Week 52	Baseline[a]	Week 12	Week 52
Subjects with urine protein: creatinine ratio increased from ≤0.2 mg/mg at baseline to >0.2 mg/mg									
5 mg	E0041001	F	16	0.10	0.09	0.26[b]	0.80	0.70	0.90
5 mg	E0041004	M	14	0.15	0.21	0.1	0.59	0.70	0.70
10 mg	E0044004	M	15	0.11	0.22	0.09	0.70	0.59	0.80
20 mg	E0041006	M	12	0.11	0.11	0.22[b]	0.59	0.59	0.49

Adapted from applicant CSR D3561C00087 Table 41
[a] Measured at the randomization visit (Week 0; Visit 3).
[b] These 2 subjects were followed until resolution (Urine protein: creatinine ratio was <0.2). The post-week 52 value (Day 400) for subject E0041001 was <0.13; the post-52 week value for subject E0041006 (Day 404) was 0.09

GFR
No subject had ≥25% decrease in estimated GFR from baseline to the end of the randomized treatment period treatment period. Two subjects had ≥25% decrease in estimated GFR from baseline during the open-label period (E0041014 and E0083003). Neither of these 2 subjects had any renal adverse events. With the exception of trace protein in urinalysis at baseline and Week 12 for subject E0083003, all other labs were within normal limits.

Urinalysis Parameters
None of the subjects had proteinuria at the end of the double-blind period.

Subject E0061013, who was randomized to 20- mg, had dipstick positive protein 1+ at Visit 1 through Visit 12, and a baseline RBC 1+. The subject also had dipstick positive hematuria 2+ at the end of the open-label phase, an increase from negative at the beginning of the trial. The subject's BUN, creatinine, and protein: creatinine ratios were within normal limits at baseline and at the end of the trial. All other subjects were dipstick negative blood and protein at baseline and did not have a shift in urine dipstick of 2 grades, from 'negative' or 'trace' at baseline to ≥2+ or from 1+ at baseline to ≥3+.

Renal events (Pediatric Pharmacokinetic Study [4522IL/0086])

There were no renal AEs or clinically significant changes in renal laboratory values.

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concerns with rosuvastatin were discussed in the previous safety sections.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the double-blind phase, there was a similar distribution of AEs by organ system across the doses of rosuvastatin and placebo (Table 43). The most common treatment-emergent AEs, as categorized by system organ class (SOC), were infections and infestations, nervous system disorders, gastrointestinal disorders, and musculoskeletal and connective tissue disorders, with 26.2%, 18.5%, 10.0% and 9.2%, respectively, for rosuvastatin; and 37%, 21.7%, 8.7% and 6.5%, respectively, for placebo.

The most common AEs, by preferred term, for all rosuvastatin groups were headache (16.9%) and nasopharyngitis (13.1%). The most common AEs for the placebo group were headache (19.6%), nasopharyngitis (10.9%), and influenza (8.7%). They were generally similar in frequency and type across treatment groups. The majority of AEs were of mild or moderate intensity.

Table 42: Number (%) of subjects with investigator reported treatment-emergent adverse events during the randomized treatment phase by SOC and preferred term safety population

System organ class	Preferred term	Rosuvastatin Treatment group				Placebo
		5 mg	10 mg	20 mg	Total	
		42 (%)	44 (%)	44 (%)	130 (%)	46 (%)
Total		21 (50.0)	28 (63.6)	24 (54.5)	73 (56.2)	25 (54.3)
Infections and infestations	Total	8 (19.0)	12 (27.3)	14 (31.8)	34 (26.2)	17 (37.0)
	Nasopharyngitis	3 (7.1)	7 (15.9)	7 (15.9)	17 (13.1)	5 (10.9)
	Influenza	2 (4.8)	2 (4.5)	0 (0.0)	4 (3.1)	4 (8.7)
	Sinusitis	0 (0.0)	2 (4.5)	1 (2.3)	3 (2.3)	0 (0.0)
	Tonsillitis	0 (0.0)	0 (0.0)	3 (6.8)	3 (2.3)	1 (2.2)
	Gastroenteritis viral	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.5)	2 (4.3)
	Pharyngitis	1 (2.4)	0 (0.0)	1 (2.3)	2 (1.5)	1 (2.2)
	Respiratory tract infection	1 (2.4)	0 (0.0)	1 (2.3)	2 (1.5)	0 (0.0)
Nervous system disorders	Total	7 (16.7)	8 (18.2)	9 (20.5)	24 (18.5)	10 (21.7)
	Headache	6 (14.3)	7 (15.9)	9 (20.5)	22 (16.9)	9 (19.6)
	Dizziness	1 (2.4)	2 (4.5)	0 (0.0)	3 (2.3)	1 (2.2)
Gastrointestinal disorders	Total	5 (11.9)	3 (6.8)	5 (11.4)	13 (10.0)	4 (8.7)
	Nausea	2 (4.8)	0 (0.0)	2 (4.5)	4 (3.1)	2 (4.3)
	Abdominal pain	1 (2.4)	1 (2.3)	1 (2.3)	3 (2.3)	0 (0.0)
	Vomiting	1 (2.4)	1 (2.3)	1 (2.3)	3 (2.3)	1 (2.2)
	Abdominal pain upper	1 (2.4)	1 (2.3)	0 (0.0)	2 (1.5)	1 (2.2)
	Diarrhea	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	Total	3 (7.1)	5 (11.4)	4 (9.1)	12 (9.2)	3 (6.5)
	Myalgia	1 (2.4)	1 (2.3)	2 (4.5)	4 (3.1)	0 (0.0)
	Myopathy	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.5)	0 (0.0)
	Pain in extremity	0 (0.0)	2 (4.5)	0 (0.0)	2 (1.5)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	Total	3 (7.1)	3 (6.8)	2 (4.5)	8 (6.2)	2 (4.3)
	Pharyngolaryngeal pain	1 (2.4)	1 (2.3)	1 (2.3)	3 (2.3)	2 (4.3)
	Cough	1 (2.4)	0 (0.0)	1 (2.3)	2 (1.5)	0 (0.0)

System organ class	Preferred term	Rosuvastatin Treatment group 5 mg 42 (%)	10 mg 44 (%)	20 mg 44 (%)	Total 130 (%)	Placebo 46 (%)
	Epistaxis	1 (2.4)	1 (2.3)	0 (0.0)	2 (1.5)	0 (0.0)
General disorders and administration site conditions	Total	3 (7.1)	2 (4.5)	2 (4.5)	7 (5.4)	1 (2.2)
	Pyrexia	1 (2.4)	2 (4.5)	1 (2.3)	4 (3.1)	0 (0.0)
	Fatigue	1 (2.4)	1 (2.3)	1 (2.3)	3 (2.3)	0 (0.0)
Reproductive system and breast disorders	Total	1 (2.4)	3 (6.8)	0 (0.0)	4 (3.1)	0 (0.0)
	Dysmenorrhea	0 (0.0)	2 (4.5)	0 (0.0)	2 (1.5)	0 (0.0)
Skin and subcutaneous tissue disorders	Total	1 (2.4)	1 (2.3)	2 (4.5)	4 (3.1)	1 (2.2)
Injury, poisoning and procedural complications	Total	0 (0.0)	2 (4.5)	1 (2.3)	3 (2.3)	1 (2.2)
	Contusion	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.5)	0 (0.0)
Immune system disorders	Total	1 (2.4)	1 (2.3)	0 (0.0)	2 (1.5)	0 (0.0)
Investigations	Total	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.5)	1 (2.2)
Blood and lymphatic system disorders	Total	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Eye disorders	Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)

Adapted from applicant CSR D3561C00087 Tables 26 and 27
Events with an incidence of ≥1% for the total rosuvastatin group are included in this table
[a] Includes only AEs that started during the double-blind treatment period, or any AE that was ongoing from the dietary lead-in period and subsequently worsened during the double-blind period.
[b] Patients who had more than 1 adverse event assigned to the same MedDRA term were counted once for that term.
[c] An AE may be counted more than once if a patient had multiple occurrences of the event.
MedDRA Medical Dictionary for Regulatory Activities

During the open-label phase, the most common AEs by SOC were: infections and infestations (42.8%), nervous system disorders (20.8%), gastrointestinal disorders (20.2%) and, injury,

poisoning and procedural complications (13.9%) of the patients. The most common treatment-emergent AEs by preferred term were: nasopharyngitis (20.8%), headache (16.8%), influenza (8.1%), nausea (5.8%), and fatigue (5.2%). Most of the AEs were mild or moderate in intensity.

Table 43: Number (%) of patients with investigator-reported treatment-emergent adverse events during the open-label treatment phase by SOC and preferred term safety population (occurring in >1%)

System organ class	**Preferred term**	**Rosuvastatin**			
		5 mg	**10 mg**	**20 mg**	**Total**
		129 (%)	**123(%)**	**123(%)**	**173 (%)**
Total		53 (41.1)	59 (48.0)	82 (66.7)	130 (75.1)
Infections and infestations	Total	22 (17.1)	26 (21.1)	47 (38.2)	74 (42.8)
	Nasopharyngitis	11 (8.5)	10 (8.1)	23 (18.7)	36 (20.8)
	Influenza	2 (1.6)	3 (2.4)	9 (7.3)	14 (8.1)
	Gastroenteritis viral	0 (0.0)	2 (1.6)	5 (4.1)	7 (4.0)
	Gastroenteritis	2 (1.6)	2 (1.6)	1 (0.8)	5 (2.9)
	Upper respiratory tract infection	2 (1.6)	1 (0.8)	1 (0.8)	3 (1.7)
	Urinary tract infection	1 (0.8)	1 (0.8)	3 (2.4)	3 (1.7)
	Cystitis	1 (0.8)	1 (0.8)	2 (1.6)	2 (1.2)
	Respiratory tract infection	0 (0.0)	1 (0.8)	1 (0.8)	2 (1.2)
	Tonsillitis	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
Nervous system disorders	Total	10 (7.8)	13 (10.6)	20 (16.3)	36 (20.8)
	Headache	7 (5.4)	11 (8.9)	17 (13.8)	29 (16.8)
	Dizziness	4 (3.1)	0 (0.0)	0 (0.0)	4 (2.3)
Gastrointestinal disorders	Total	12 (9.3)	10 (8.1)	16 (13.0)	35 (20.2)
	Nausea	5 (3.9)	2 (1.6)	3 (2.4)	10 (5.8)
	Vomiting	1 (0.8)	3 (2.4)	4 (3.3)	8 (4.6)
	Abdominal pain, upper	2 (1.6)	1 (0.8)	4 (3.3)	7 (4.0)
	Abdominal pain	2 (1.6)	2 (1.6)	2 (1.6)	6 (3.5)
	Diarrhea	2 (1.6)	1 (0.8)	3 (2.4)	5 (2.9)
	Constipation	1 (0.8)	2 (1.6)	0 (0.0)	2 (1.2)
Injury, poisoning and procedural complications	Total	9 (7.0)	11 (8.9)	12 (9.8)	24 (13.9)
	Concussion	2 (1.6)	1 (0.8)	1 (0.8)	3 (1.7)

System organ class	Preferred term	Rosuvastatin 5 mg 129 (%)	Rosuvastatin 10 mg 123(%)	Rosuvastatin 20 mg 123(%)	Total 173 (%)
	Joint sprain	2 (1.6)	1 (0.8)	1 (0.8)	4 (2.3)
	Skin laceration	1 (0.8)	2 (1.6)	1 (0.8)	3 (1.7)
	Sports injury	1 (0.8)	2 (1.6)	1 (0.8)	3 (1.7)
	Clavicle fracture	1 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)
	Contusion	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
	Procedural pain	1 (0.8)	1 (0.8)	0 (0.0)	2 (1.2)
	Thermal burn	1 (0.8)	1 (0.8)	2 (1.6)	2 (1.2)
General disorders and administration site conditions	Total	3 (2.3)	7 (5.7)	8 (6.5)	15 (8.7)
	Fatigue	3 (2.3)	5 (4.1)	2 (1.6)	9 (5.2)
	Malaise	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
Musculoskeletal and connective tissue disorders	Total	5 (3.9)	6 (4.9)	8 (6.5)	15 (8.7)
	Myalgia	1 (0.8)	3 (2.4)	2 (1.6)	5 (2.9)
	Muscle spasms	2 (1.6)	1 (0.8)	0 (0.0)	3 (1.7)
	Back pain	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
Skin and subcutaneous tissue disorders	Total	4 (3.1)	3 (2.4)	9 (7.3)	14 (8.1)
	Eczema	1 (0.8)	1 (0.8)	4 (3.3)	5 (2.9)
	Acne	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
	Rash	2 (1.6)	1 (0.8)	0 (0.0)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	Total	2 (1.6)	0 (0.0)	9 (7.3)	11 (6.4)
	Cough	1 (0.8)	0 (0.0)	3 (2.4)	4 (2.3)
	Asthma	1 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)
Investigations	Total	4 (3.1)	1 (0.8)	4 (3.1)	9 (5.2)
	Blood CK increased	1 (0.8)	1 (0.8)	1 (0.8)	3 (1.7)
	Weight increase	1 (0.8)	0 (0.0)	2 (1.6)	3 (1.7)
Immune system disorders	Total	1 (0.8)	0 (0.0)	3 (2.4)	4 (2.3)
	Seasonal Allergy	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)

System organ class	Preferred term	Rosuvastatin 5 mg 129 (%)	Rosuvastatin 10 mg 123(%)	Rosuvastatin 20 mg 123(%)	Rosuvastatin Total 173 (%)
Reproductive system and breast disorders	Total	3 (2.3)	0 (0.0)	1 (0.8)	4 (2.3)
Eye disorders	Total	3 (2.3)	2 (1.6)	1 (0.8)	3 (1.7)
	Conjunctivitis	3 (2.3)	2 (1.6)	1 (0.8)	3 (1.7)
Ear and Labyrinth disorders		0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
	Total				
	Ear pain	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
Neoplasms benign, malignant and unspecified	Total	1 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)
Psychiatric disorders	Total	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
	Depression	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.2)
Renal and Urinary Disorders	Total	1 (0.8)	0 (0.0)	1 (0.8)	2 (1.2)

Adapted from applicant CSR D3561C00087 Tables 28 and 29
Events with an incidence of ≥1% for the total rosuvastatin group are included in this table. An AE may be counted more than once if a patient had multiple occurrences of the event.
[a] Includes only AEs that started during the double-blind treatment period, or any AE that was ongoing from the dietary lead-in period and subsequently worsened during the double-blind period.
[b] Patients who had more than 1 event within the same SOC were counted once for that SOC total. For that reason, separate AE totals may not sum to the SOC total.

Common adverse events (Pediatric Pharmacokinetic Study [4522IL/0086])
The most frequent AEs in at least 2 subjects were headache, abdominal pain, and nausea. No subject had the same adverse event more than once (Table 44).

Table 44: Number of subjects with adverse events by treatment group (safety population)

Body system/adverse events [a]	Rosuvastatin single dose 10 mg	40 mg	80 mg	Rosuvastatin multi-dose 80 mg
N	N=6	N=6	N=6	N=6
Any adverse event	2 (33)	3 (50)	1 (17)	2 (33)
Body as a whole				
Abdominal pain	0	2 (33)	0	1 (17)
Accidental injury	0	0	1 (17)	0

Body system/adverse events [a]	**Rosuvastatin single dose**			**Rosuvastatin multi-dose**
	10 mg	**40 mg**	**80 mg**	**80 mg**
N	**N=6**	**N=6**	**N=6**	**N=6**
Headache	1 (17)	2 (33)	0	1 (17)
Digestive system				
Gastroenteritis	1 (17)	0	0	0
Nausea	0	2 (33)	0	1 (17)
Vomiting	0	0	0	1 (17)
Metabolic and Nutritional disorder				
ALT increased	0	0	0	1 (17)
Nervous system				
Anxiety	0	1 (17)	0	0
Paresthesia	0	1 (17)	0	0

Adapted from applicant 4522IL/0086 CSR Table 16

[a] A subject may have had more than 1 adverse event. Subjects who had more than 1 adverse event assigned to the same COSTART term were counted once for that event. All events occurred 1 time in each subject.

7.4.2 Laboratory Findings

Hematology

During the double-blind and the open-label phases changes in mean values of the hematology parameters, with the exception of platelets, were small.

The mean changes in platelets from baseline to the end of the double-blind phase (Week 12) were –17.9 *x* 10^3/μL for rosuvastatin 5 mg, -24.9 *x* 10^3/μL for rosuvastatin 10 mg, –25.7 *x* 10^3/μL for rosuvastatin 20 mg, and -13.5 *x* 10^3/μL for placebo. The overall mean baseline platelet count was 275 *x* 10^3/μL. No subject developed a platelet count ≤50 × 10^3/μL and there were no associated bleeding events or platelet-related AEs in any of the treatment groups.

<u>Reviewer comment</u>: Reductions in mean platelet counts have been observed in other trials with rosuvastatin. This information is not included in the current rosuvastatin label.

Overall, there appeared to be no difference across the treatment groups for subjects that were outside the reference ranges for hematology parameters. Subject E0021004 had a reported AE of 'RBC count decreased' on Day 1 of double-blind phase, which subsequently normalized.

Subjects with abnormal hematologic labs:

> Subject E0044005 was a 15-year-old Caucasian female (randomized to 20 mg rosuvastatin), who had a platelet count ≤100 *x* 10^3/μL at baseline. The subject's

subsequent platelet counts rebounded to of 224 *x* 10^3/μL and 255 *x* 10^3/μL at Weeks 12 and 52, respectively. The subject's also had a pruritic rash.

Subject E0061022 was a 16-year-old female (randomized to 10 mg rosuvastatin) with a history of allergic wheezing treated with cortisone, received ferrous sulfate for low serum ferritin during the open-label phase (rosuvastatin 5 mg). Otherwise, there were no other hematology abnormalities reported.

7.4.3 Vital Signs

Blood Pressure

In general, a few subjects had isolated elevations in systolic blood pressure (BP) above the 90th percentile, which normalized on subsequent visits. One subject (E0021008) had elevated systolic blood pressure > 95th percentile on 3 visits while on 20 mg rosuvastatin during the open-label phase. Another subject who had been randomized to placebo had blood pressure values that started to increase from the beginning of the trial to the end. Seven (3.9%) subjects had systolic BPs mostly elevated above the 90th percentile for age from pre-randomization to the end of the trial. Of these 7 subjects, 1 subject was randomized to placebo, and then up-titrated from 5 mg to 20 mg during the open-label phase; 3 subjects were randomized to 5 mg, 2 of which were up-titrated from 5 mg to 20 mg rosuvastatin during the open-label phase, and the third was up-titrated from 5 mg to 10 mg rosuvastatin; 2 subjects were randomized to 10 mg rosuvastatin, 1 of which was up-titrated form 5 mg to 10 mg and the other up-titrated form 10 mg to 20 mg during the open-label phase; and one subject was randomized to 20 mg rosuvastatin and remained on that does for the rest of the trial.

Reviewer comment: The systolic BPs for those 7 subjects were elevated at baseline prior to rosuvastatin exposure. Some of these subjects had heath conditions requiring sub-chronic and chronic therapy with medications that may contribute to the systolic BP elevations (e.g., albuterol, cetirizine and ibuprofen). There were other subjects treated with these drugs that had normal blood pressures throughout the trial.

The changes in vital signs were relatively small during the double-blind phase. On average, the mean change in systolic and diastolic BP from the start of the randomized phase of the trial (Week 0) to the end of the trial (Week 52, end of the double-blind phase), were 0.9 mmHg and -1.1 mmHg respectively. The absolute and mean change in systolic BP and diastolic BP are summarized in (Table 45).

Table 45: Summary of systolic and diastolic BP, by dose and changes in systolic and diastolic blood pressure from study entry (Visit 3, Week 0) to the end of the double-blind phase

Blood Pressure (mmHg)	Systolic Blood Pressure Rosuvastatin				Placebo	Diastolic Blood Pressure Rosuvastatin				Placebo
	5 mg	10 mg	20 mg	Total		5 mg	10 mg	20 mg	Total	
12-week double-blind phase										
Baseline (Week 0)										
n	42	44	45	131	46	42	44	45	131	46
Mean (SD)	110.2 (10.1)	109.4 (8.6)	111.2 (11.1)	110.3 (10.0)	108.2 (10.6)	65.2 (7.0)	65.7 (6.3)	65.9 (6.8)	65.6 (**)	64.7 (8.5)
Median	110.0	110.0	113.0	111.0	109.5	64.5	65.5	65.0	65.0	63.0
Range	90.0-131.0	90.0-125.0	80.0-136.0	80-136.0	90.0-130.0	48.0-82.0	53.0-81.0	51.0-83.0	48.0-83.0	48.0-96.0
z-score range	-2.4, 1.2	-1.9, 1.8	-2.5, 2.3	-2.5, 2.3	-2.0, 2.0	-1.7, 1.6	-1.3, 1.4	-1.3, 1.4	-1.7, 1.6	-1.3, 2.6
Change from baseline to end of double-blind phase										
n	42	44	43	131	46	42	44	43	129	45
Mean (SD)	2.0 (9.7)	0.9 (10.9)	-0.2 (9.4)	0.9 (10.0)	1.8 (10.1)	0.0 (8.8)	-1.8 (9.5)	-1.5 (6.4)	-1.1 (8.3)	-0.5 (9.1)
Median	3.0	2.0	-1.0	1.0	2.0	0.5	-1.0	-1.0	-1.0	0.0
Range	-32.0, 32.0	-20, 20.0	-20.0, 27.0	-32.0, 31.0	-26.0, 18.0	-33.0, 15.0	-23.0, 25.0	-12.0, 14.0	-33.0, 25.0	-41.0, 18.0
z-score range	-3.1, 2.9	-1.9, 1.9	-1.9, 2.4	-3.1, 2.9	-2.5, 1.7	-2.9, 1.3	-2.0, 2.1	-1.1, 1.2	-2.9, 2.1	-3.6, 1.6

Adapted from applicant CSR D3561C00087 Table 43
[a] Baseline Start of double-blind phase (Visit 3, Week 0)

7.4.4 Electrocardiograms (ECGs)

There were no electrocardiogram data submitted with this sNDA.

7.4.5 Special Safety Studies

There were no special safety studies submitted with this sNDA.

7.4.6 Immunogenicity

There was no rationale for immunogenicity studies so no immunogenicity data were collected for this sNDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

During the double-blind phase there did not appear to be a dose dependency for the most common adverse events. The numbers of subjects experiencing common AEs were almost equally distributed across the rosuvastatin treatment groups and the placebo group. When analyzed by the system organ class, there is an increase in the occurrence of musculoskeletal and connective tissue disorders with increasing rosuvastatin dose. In particular the combined frequency for myalgia and myopathy by dose was 1 (2.4%), 2 (4.5%) and 3 (6.8%) with 5 mg, 10 mg and 20 mg rosuvastatin, respectively. There were no reports for these two AEs in the placebo group (Table 23).

During the open-label phase, there appeared to be a dose dependency for the occurrences of common AEs increased across the rosuvastatin treatment groups. When analyzed by the system organ class (and preferred terms ≥3%), there appeared to be an increase in the occurrence of infections and infestations, nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions, skin and subcutaneous tissue disorders, and musculoskeletal and connective tissue disorders with increasing rosuvastatin dose.

7.5.2 Time Dependency for Adverse Events

Fifty-six percent of the subjects experienced an AE in the double-blind phase. The AEs in subjects randomized to 5 mg occurred on average 47 days after randomization, subjects randomized to 10 mg, 45 days, the subjects randomized to 20 mg, 40 days, and those randomized to placebo, 31 days.

Seventy-six percent of 130 subjects experienced an AE in the open-label phase. The AEs in the open-label phase occurred on average 152 days after randomization.

7.5.3 Drug-Demographic Interactions

AEs were examined in the subgroup populations, sex (male, female), age (10-13, 14-17 years old), and race (Caucasian, non-Caucasian). There were no differences in the distribution of AEs by sex or age groups. There was insufficient information to determine if there were differences by race, as the non-Caucasian sample size was very small.

7.5.4 Drug-Disease Interactions

All subjects in this trial had HeFH, and the number of subjects with co-morbidities in addition to HeFH was very small. There were no observed drug-disease interactions.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

There were no human carcinogenicity data submitted with this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies during the trial.

7.6.3 Pediatrics and Effect on Growth

Overall, there was no notable impact of treatment on growth from the beginning of the randomized phase (Week 0) to Week 52 as assessed by height, weight, or body mass index (BMI) based on mean values or on z-scores. Table 46 summarizes the changes in height, weight and BMI over the course of the trial.

Table 46: Change in weight and BMI from study entry (Week -6) to final study visit (Week 52) for all patients (Rosuvastatin 5 mg, 10 mg, or 20 mg during double-blind or open-label periods, or placebo during double-blind period) (N=176)

Study entry (Week -6)	**Height**	**Weight**	**BMI**
N	176	176	176
Mean (SD), cm	164.7 (10.4)	58.6 (13.1)	21.5 (3.8)
Median, cm	165.0	57.0	20.8
Range, cm	140.0 to 193.0	32.0 to 94.0	14.7 to 34.5
Mean (SD), z-score[a]	0.31 (1.00)	0.44 (0.97)	0.30 (1.01)
Median, z-score	0.30	0.41	0.34
Range, z-score	-2.04 to 2.80	-3.03 to 2.45	-3.91 to 2.34
Change from study entry to final visit (Week 52)			
N	164	164	164
Mean (SD), cm	3.2 (3.4)	4.7 (4.6)	0.9 (1.4)
Median, cm	2.00	4.0	0.8
Range, cm	-2.0 to 12.0	-9.0 to 17.0	-3.0 to 4.5
Mean (SD), z-score[a]	-0.02 (0.28)	0.03 (0.30)	0.03 (0.37)
Median, z-score	-0.04	0.05	0.04
Range, z-score	-0.99 to 0.96	-0.89 to 0.78	-1.14 to 1.42

Adapted from applicant CSR D3561C00087 Table 45

[a] Z-score represents normalized data relative to the mean for children of the same age and sex according to National Health and Nutrition Examination Survey (NHANES) growth data. A z-score for weight of zero is equivalent to the mean weight for age and sex. A z-score for weight of -1 indicates weight is 1 SD below the mean for age and sex; a z-score of +1 indicates weight is 1 SD above the mean.

SD Standard deviation.

Reviewer comment: **There were 6 subjects at 5 sites with heights that decreased between 1 and 2 cm from baseline to the end of the trial. This is likely due to measurement error.**

The peak height velocity for girls is 9 cm per year, which occurs early in puberty. The peak height velocity for boys is 10.3 cm per year, and that occurs later in puberty (Adelman and Johnson 2002). In this trial, girls experienced an average 0.9 cm growth over the year-long trial, and boys experienced 5.0 cm growth. The mean ages of randomized males and females were 13.9 and 14.8 years, respectively. The girls were likely to be further along in puberty, which may explain the smaller height gain over the year trial, and the males were likely on average just entering puberty, so their height gain over the year may be less that expected.

The majority of the subjects remained in their Tanner stages for the duration of the trial, as assessed by the change from the beginning of the double-blind phase (Week 0) in the percentages of subjects at each Tanner stage.

Table 47: N (%) change in Tanner stage from study entry (Week -6) to final study visit (Week 52)

Tanner stage at study entry[a] **(Week -6)**	**Tanner stage at final visit (Week 52)**					**Total**
	II	**III**	**IV**	**V**	**NR**	
II	9 (100.0)	15 (65.2)	3 (5.9)	0	3 (21.4)	30 (17.0)
III	0	8 (34.8)	17 (33.3)	3 (3.8)	3 (21.4)	31 (17.6)
IV	0	0	31 (60.8)	34 (43.0)	5 (35.7)	70 (39.8)
V	0	0	0	42 (53.2)	3 (21.4)	45 (25.6)
Total	9 (100.0)	23 (100.0)	51 (100.0)	79 (100.0)	14 (100.0)	176 (100.0)

Adapted from applicant CSR D3561C00087 Table 46
[a] Measured at the enrollment visit (Visit 1; Week -6)
NR Not recorded.

Reviewer comment: **On average, an individual spends 3 to 4 years in puberty, with the duration in each stage ranging from 12-15 months (Lee and Houk 2007). The trial lasted 12 months and most of the subjects remained in their baseline Tanner stage.**

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdose, drug abuse potential, withdrawal or rebound data submitted with this sNDA.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarketing Experience

AEs reports in children and adolescents with potential rosuvastatin exposure were retrieved from the AstraZeneca safety surveillance database (SAPPHIRE). These reports included AEs from rosuvastatin exposures due to off label use, accidental exposures, in-utero and other exposures (Table 48).

Known safety issues with the statins in general and rosuvastatin in particular have been discussed in detail in other sections.

Table 48: AEs in children and adolescents with potential post-marketing exposure to rosuvastatin

SAPPHIRE Case ID	Sex/Age (yrs)	Adverse event MedDRA preferred term	Rosuvastatin Dose	Comment	SAE	Outcome
2003UW04668	F/0.5	Drug exposure via breast milk, erythema, swelling face, edema peripheral	10 mg		No	Unk
2004UW00813	M/17	Myalgia	Unk	CK normal	No	Not recovered
2004UW09934	M/4	Wrong drug administered	10 mg		No	Unk
2004UW16365	M/ Neonate	Jaundice neonatal	10 mg	Mother treated with 10 mg CRESTOR while pregnant		Unk
2004UW23673	F/4	Medication error	20 mg		No	NR
2005SE00086	M/15	Angina pectoris	40 mg		Hosp	Recovered
2005UW09986	M/3	Accidental drug intake by child	10 mg		No	NR
2005UW12576	F/3	Accidental drug intake by child	20 mg		No	NR
2005UW12872	F/2	Accidental drug intake by child	10 mg		No	NR
2005UW08543	M/Child	Medication error	5 mg	22.7 lb child swallowed 5 mg tab	No	NR
2006CG00462	M/3	Accidental drug intake by child	10 mg		No	Recovered
2006UW00017	M/3	Accidental exposure	10 mg		No	NR
2006UW03659	M/Child	Speech disorder	5 mg and 10 mg	5 mg and 10 mg transplacental and transmammary	Hosp No	Unk

SAPPHIRE Case ID	Sex/Age (yrs)	Adverse event MedDRA preferred term	Rosuvastatin Dose	Comment	SAE	Outcome
2006UW13247	Unk/ Child	Accidental drug intake by child	Unk		No	NR
2007AC01993	M/13	Pyrexia, myalgia, headache	10 mg		No	Recovering
2007UW14838	M/1	Accidental exposure	Unk		No	NR
2007UW24832	M/2	Accidental drug intake by child	Unk		No	NR
2007UW28996	Unk/ Child	Medication error	10 mg		No	NR
2008AP03827	Unk/1	Medication error	2.5 mg	Japan	No	NR
2008AP05174	Unk/1	Medication error	Unk		No	NR
2008GB00026	M/3	Medication error	20 mg		No	Unk
2008GB00641	M/3	Accidental exposure	10 mg		No	Recovered
2008SE01079	M/2	Accidental drug intake by child	10 mg		No	Recovered
2008UW02784	M/ Neonate	Multiple congenital anomalies	10 mg	transplacental	Fatal	Died
2008UW15219	Unk/ Child	Muscle injury	Unk		No	Unk
2008UW16361	M/5	Accidental drug intake by child	10 mg		No	Unk
2008UW17452	M/13	Burning sensation (calves & forearms)	5 mg		No	Not recovered

M male; F female; NR not recorded; Unk Unknown, MedDRA Medical Dictionary for Regulatory Activities

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling discussions are ongoing.

9.3 Advisory Committee Meeting

There were no significant safety issues identified with rosuvastatin in this population compared to other statins marketed for this population to justify convening an Advisory Committee meeting.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-17	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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