



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-366 Application Supplement Number 17
(GlobalSubmit Sequence Number 12)

Drug Name: Crestor (rosuvastatin calcium)

Indication(s): Treatment of hyperlipidemia

Applicant: AstraZeneca Pharmaceuticals LP

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The applicant has presented the results of a single trial (named PLUTO) in pediatric patients aged 10 to 17 years to demonstrate the safety and efficacy of rosuvastatin in the treatment of heterozygous familial hypercholesterolemia. Patients randomized to placebo, rosuvastatin 5 mg, 10 mg or 20 mg were followed for 12 weeks and then entered a 40 week open label phase where all patients were treated with rosuvastatin and titrated to a goal of less than 100 mg/dL.

A total of 176 patients were randomized and treated with 93% of these patients completing the open label phase. Statistically significant lowering of LDL, total cholesterol (TC), non-HDL and ApoB were seen for each dose of rosuvastatin compared to placebo. The percent change in LDL ranged from -38% to -50%. About 41% of patients on doses of 10 mg and 20 mg were able to achieve an LDL level less than 110 mg/dL after 12 weeks of therapy; this response 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 below 110 mg/dL; however, the percentage of responders remained at about 40% suggesting that the maximum dose of 20 mg may not be necessary for obtaining the maximum effect for any given patient.

Subgroup analyses by this reviewer revealed no significant differential treatment effects among subgroups defined by age, sex, baseline LDL and Tanner stage. The applicant performed additional subgroup analyses none of which yielded significant subgroup by treatment interactions.

The statistical evidence provided by the study PLUTO sufficiently establishes the effectiveness of rosuvastatin to treat pediatric patients with heterozygous familial hypercholesterolemia.

2. Introduction

2.1 Overview

A final written request was issued from FDA to the applicant on March 7, 2006 describing a trial in pediatric patients (ages 10-17) treated with rosuvastatin (Crestor), a lipid lowering drug product. The target population was children with heterozygous familial hypercholesterolemia. Rosuvastatin, a HMG-CoA reductase inhibitor, was approved for adults in August, 2003.

The applicant conducted a 12-week double blind trial with 4 treatment arms; placebo, rosuvastatin 5 mg, 10 mg and 20 mg to assess safety and efficacy. After completing 12 weeks on study, all patients were treated with rosuvastatin and titrated to the maximum dose required to lower LDL below 110 mg for an additional 40 weeks.

2.2 Data Sources

This reviewer requested the lab data submitted for efficacy in the original submission, that contained over 400 variables, be modified to include only primary and secondary efficacy variables in addition to the demographic variables; this dataset (FDA1LABS) was submitted June 16, 2009. The medical reviewer requested a revised safety dataset which was submitted June 24, 2009 and named FDA1ADV.

The data may be accessed at <\\CDSESUB1\EVSPROD\NDA021366\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\request-for-pediatric-exclusivity\5351-stud-rep-contr\d3561c00087\crt\datasets\>.

3. Statistical Evaluation

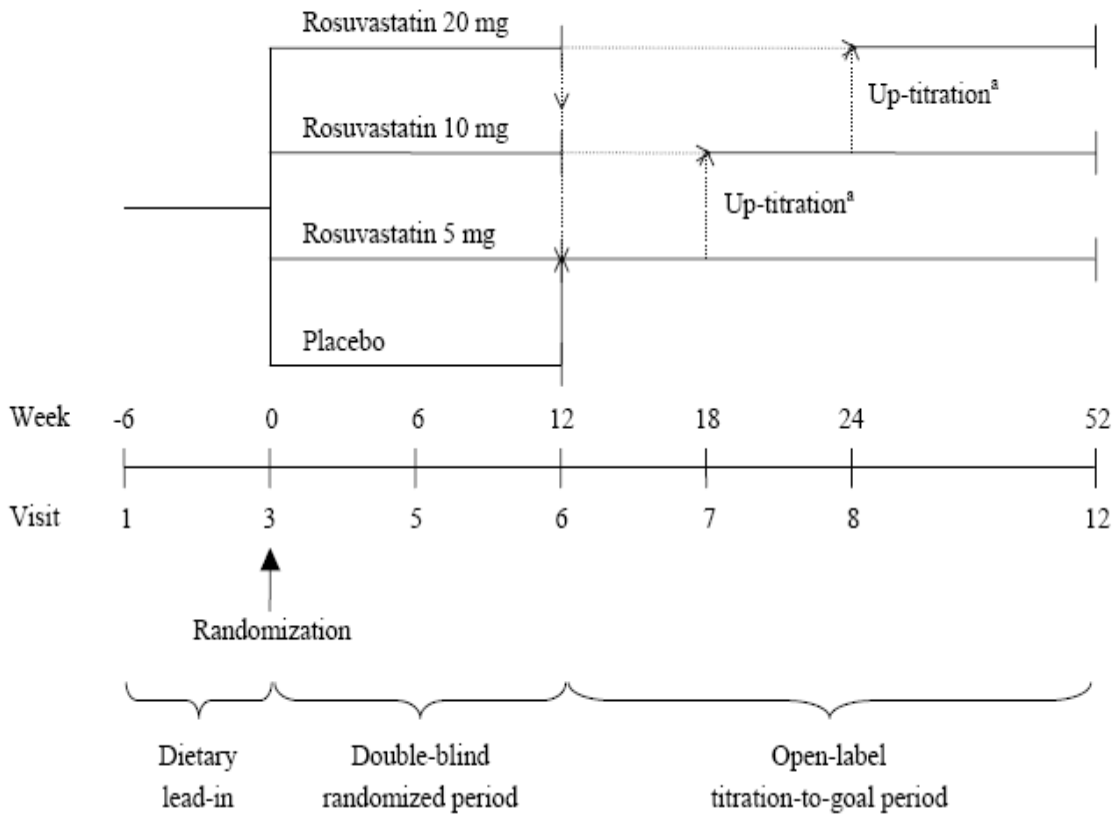
3.1 Evaluation of Efficacy Study PLUTO (conducted 7/06 to 6/08)

Design

PLUTO is a randomized, double-blind, placebo-controlled, parallel group, 12-week study in adolescents with heterozygous familial hypercholesterolemia (HeFH). After screening, patients were asked to follow a low cholesterol diet and to stop all lipid lowering medications during a 6-week lead-in (Figure 3.1.1). Based on meeting LDL criteria at Week -1, patients were randomized, blocking on center, to one of four treatment arms; placebo, rosuvastatin 5 mg, 10 mg or 20 mg. At the end of the 12-week double-blind treatment period, patients remaining on study were switched to 5 mg of rosuvastatin and titrated to LDL-C goal of <110mg/dL over a 40-week open-label extension.

Figure 3.1.1. Schematic of PLUTO study design extracted from the applicant’s study report

Figure 1 Study flow chart



The primary objective of Pluto was to assess the treatment effect measured as the percent change in LDL at Week 12 for each dose of Crestor compared to placebo. Secondary objectives included assessing treatment effects at Week 6 and Week 12 for the following lipid parameters: HDL-C, TC, TG, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-1, ApoB/ApoA-1 and hsCRP. Lipid profiles were obtained at Weeks -6, -1, 0, 2, 6, 12, 18, 24, 30, 36, 44, and 52.

Inclusion criteria included the following (see pages 27-28 of the study report for a complete listing):

- Tanner Stages II to V (females at least one year post-menarche)
- Aged 10 to 17
- HeFH defined as follows
 - Genetic defect in LDL receptor or ApoB by DNA analysis OR
 - FH in a first-degree relative
- LDL>160 at Week -1 and
 - Family history of premature CVD OR
 - 2 or more CVD risk factors (HDL<35, hypertension, smoking, severe obesity, diabetes, inactive)
- No history of statin-induced myopathy
- TG<250

Patient Disposition

According to the protocol, a total sample size of 148 patients (37 per group) was planned to detect a treatment difference of 12% with 90% power. A total of 222 patients were screened and 177 were randomized as shown in Table 3.1.1 below. Eighteen centers in 5 countries recruited patients with the most patients (72%) randomized in centers in the Netherlands (72 with 35 in one center) and Canada (55); only 14 patients (8%) were randomized in the US at 2 centers.

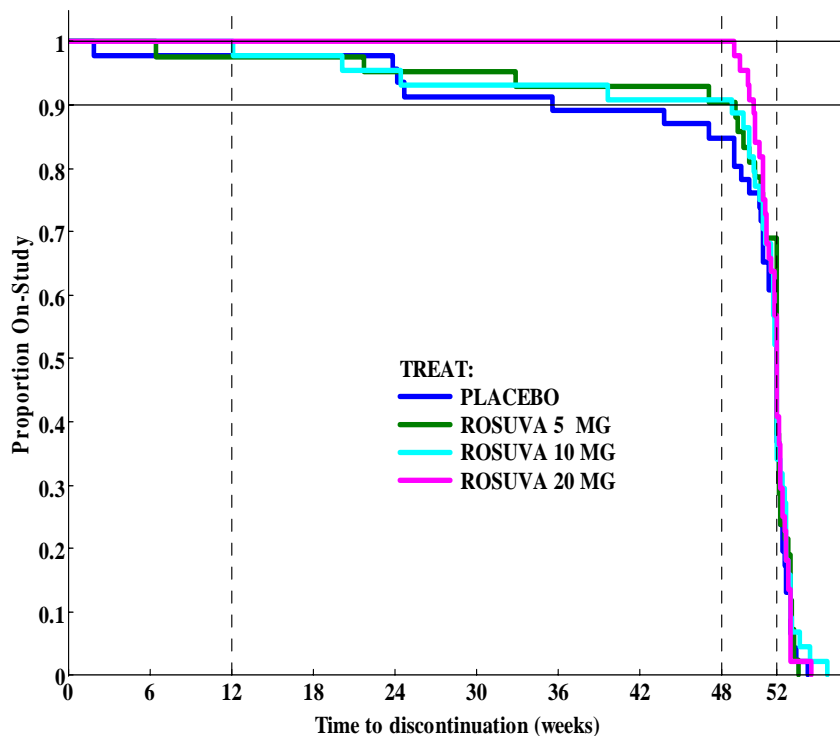
One patient randomized to rosuvastatin 20 mg was not treated and is not included in the intent-to-treat (ITT) population. Two patients discontinued during the 12-week initial treatment period due to an adverse event (1 placebo due to blurred vision and 1 rosuvastatin 5 mg due to menorrhagia).

Table 3.1.1. Patient Disposition

	Placebo	ROSU 5	ROSU 10	ROSU 20
Randomized	46	42	44	45
Not treated	0	0	0	1
Completed Wk 12	45 (98%)	41 (98%)	44 (100%)	44 (98%)
Week 12 ITT	46 (100%)	42 (100%)	44 (100%)	44 (98%)
Completed OLE	41 (89%)	39 (93%)	40 (91%)	44 (98%)

A total of 173 of the 174 patients completing Week 12 entered the open-label period; a patient on rosuvastatin 10 mg decided not to continue. About 93% of the patients completed the open-label extension; all patients randomized and treated with rosuvastatin 20 mg remained on study for the full study duration (Figure 3.1.2 on the following page). Nine patients did not complete the open label period; 4 due to an adverse event (2 due to nausea (ROSU 5 mg OL), 1 due to fatigue (ROSU 10 OL) and 1 due to a severe vesicular skin eruption (ROSU 20 OL)).

Figure 3.1.2 Proportion of patients on study by randomized treatment



Baseline Demographics

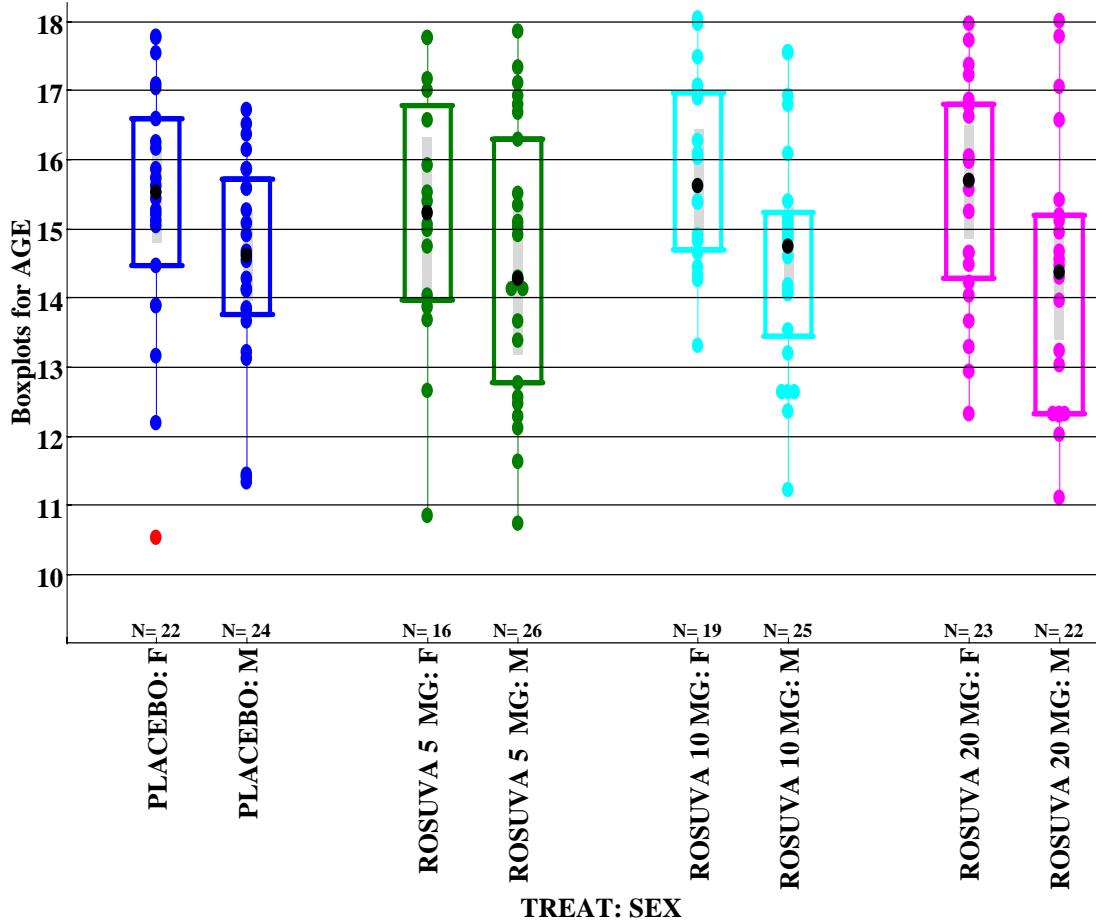
There were no notable treatment group differences regarding baseline demographics (Table 3.1.2). The mean age was about 15 years with a range of 10.5 to 18 at time of randomization; only 3 patients were the youngest allowed age of 10. The majority of patients were Caucasian.

Table 3.1.2 Patient Demographics for All Randomized Treated Patients

	Placebo (n=46)	ROSU 5 (n=42)	ROSU 10 (n=44)	ROSU 20 (n=44)
Age				
Mean (SD)	14.9 (1.7)	14.8 (1.9)	15.1 (1.6)	14.9 (1.9)
Range	10.5 – 17.8	10.7-17.9	11.2 – 18.1	11.1-18.0
Gender				
% female	48%	38%	43%	50%
Race				
% Caucasian	89%	95%	95%	93%
Tanner Stage				
I	17%	14%	16%	20%
II	17%	33%	9%	11%
III	43%	26%	45%	43%
IV	22%	26%	30%	25%

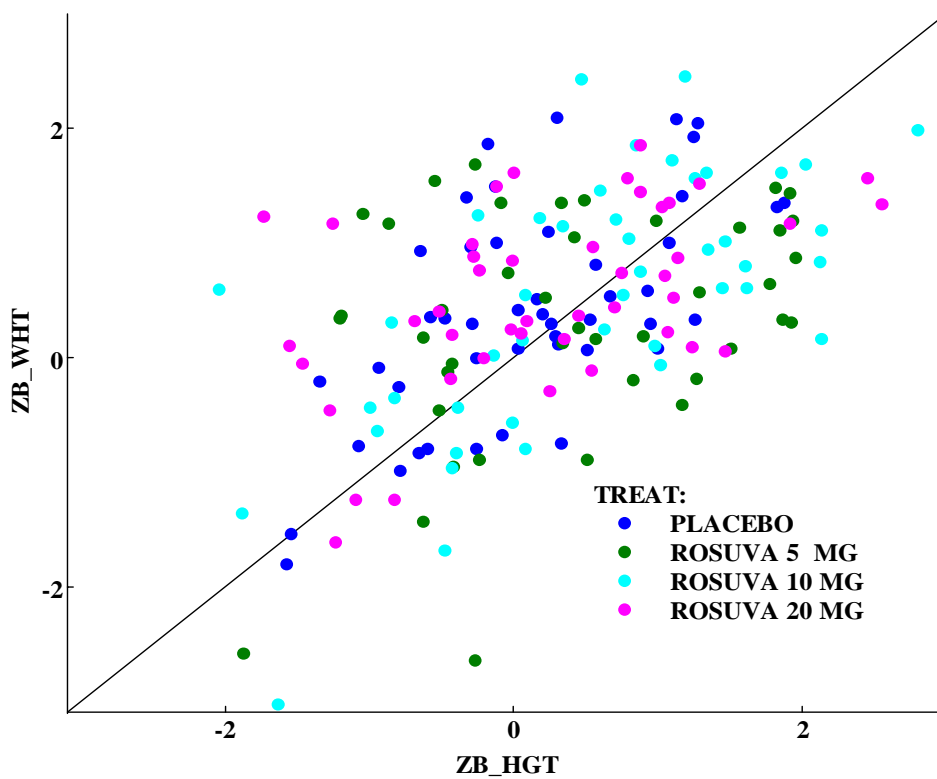
Females were slightly older (~1 year) than males as illustrated in the graph below; this was true across all the treatment groups.

Figure 3.1.3 Boxplots of age by gender and treatment group



The final written request for PLUTO (3/7/06) stated that boys and girls with height < 3rd percentile OR height-weight ratio > 97th percentile for age and sex should be excluded. After discussions between the applicant and DMEP, the exclusion for height-weight ratio > 97th percentile was not actually applied, however, the protocol was not modified. It seems reasonable to estimate how many patients would have been excluded due to height-weight ratio > 97th percentile. In a communication with DMEP, the applicant stated that they were not able to calculate the z-score for the height-weight ratio but estimated that about 5 patients may have had a large height-weight ratio. This reviewer has graphed the z-scores (Figure 3.1.4) to illustrate the relationship between the measures of height and weight. It is clear that very few patients are likely to fall into the 97th percentile for the ratio and so the exclusion of these patients is unlikely to impact the study results. This reviewer does not think that any adjustments need to be made to the analyses for the inclusion of a few patients that may have met this originally proposed exclusion criterion.

Figure 3.1.4 Z-score for weight at baseline versus Z-score for height at baseline



Efficacy Results

The primary analysis population is the set of randomized subjects with a baseline LDL-C and at least one post-baseline LDL-C. With the exception of one patient who was not treated, all patients were included in the primary analysis population.

LDL was computed using the Friedewald equation using mg/dL as follows:

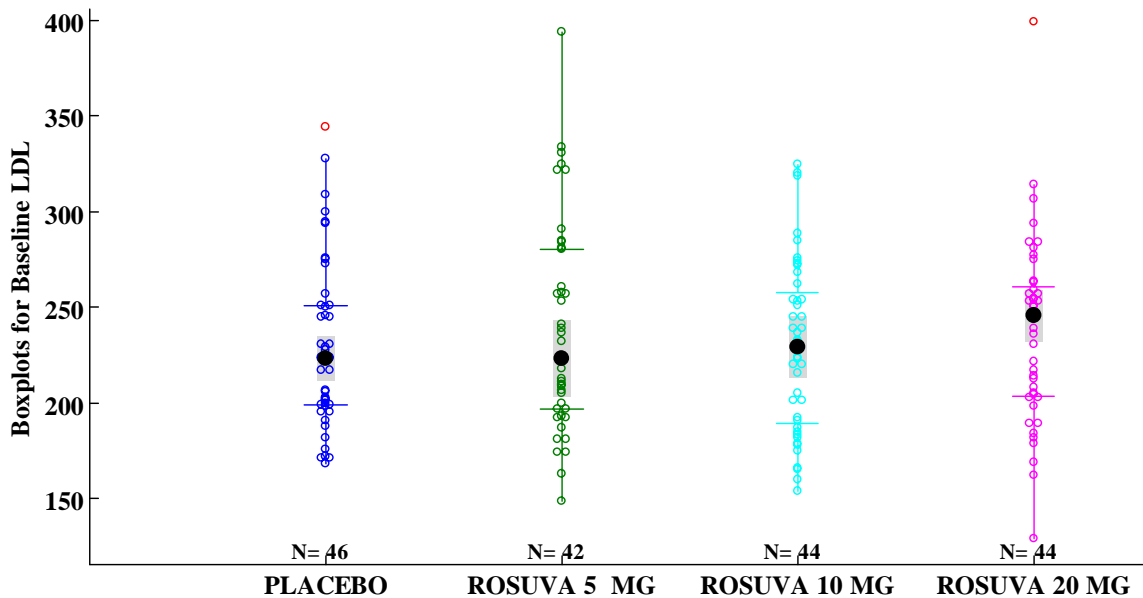
$$\text{LDL-C} = \text{Total cholesterol} - \{\text{HDL-C} + \text{TG}/5\}$$

If TG was greater than 400 mg/dL, LDL was measured by β -quantification.

The lipid endpoints were analyzed using an analysis of covariance model including treatment as a fixed effect and baseline as a covariate. Other models including other covariates and center were also performed by the applicant and yielded consistent results. Missing values were imputed using the last valid observation (LOCF). The primary endpoint then was the last value on study for all patients. Only 3 randomized patients did not complete the 12-week efficacy period; one of the three was not treated and had no post-baseline data. With only 2 patients having imputed data at Week 12, missing data does not play a role in interpretation of the efficacy results.

Baseline LDL was measured at Week 0, the randomization visit. Note that the criterion for randomization was based on LDL > 160 at Week -1; there were four patients at Week 0 with values below or at 160 due to fluctuation in LDL levels. The distribution of baseline LDL was comparable across the randomized treatment groups and is illustrated in the boxplots below.

Figure 3.1.5 Baseline LDL by treatment; black symbol represents the median



This reviewer ran an analysis of covariance model with baseline as a covariate. The results of these analyses for the primary endpoint matched the results presented by the applicant in the study report.

The results for the primary endpoint of LDL percent change from baseline during the double-blind period showed statistically significant differences from placebo ($p < 0.001$) for all doses with decreases in ranging from 38% to 50% (Table 3.1.3); for most patients the maximum response is reached by Week 6 with the bulk of the response achieved by Week 2.

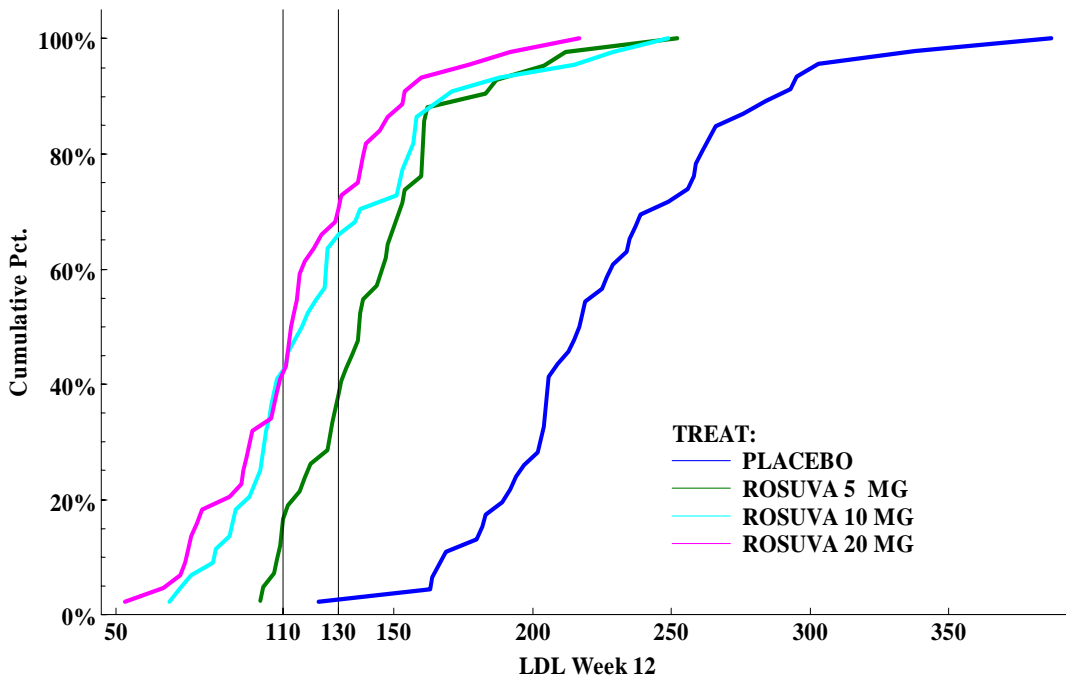
Table 3.1.3 LDL at baseline and percent change from baseline at Week 6 and 12

	Placebo (n=46)	ROSU 5 (n=42)	ROSU 10 (n=44)	ROSU 20 (n=44)
LDL baseline Mean (SD)	229 (43)	238 (55)	229 (45)	237 (48)
LDL % change Mean (SD)				
Week 6	-0.6% (14)	-40% (12)	-45% (11)	-50% (12)
Week 12	-0.5% (13)	-38% (11)	-44% (12)	-50% (13)
LSM Difference from Placebo (95% CI)				
Week 6		-39% (-44%, -34%)	-45% (-49%, -42%)	-50% (-54%, -46%)
Week 12	NA	-38% (-42%, -32%)	-44% (-62%, -1%)	-50% (-54%, -44%)
Week 12 LDL				
%<130 mg/dL	2%	33%	64%	68%
%<110 mg/dL	0%	12%	41%	41%

LSM= Least Square Mean from ANCOVA model with baseline as covariate

The difference between doses 10 mg and 20 mg would not be considered statistically significant with an observed p-value of 0.05 (p=0.08 at Week 6) and probably not clinically significant with a LSM difference of 5.3%. Also it should be noted that the achievement of LDL levels of 110 mg and 130 mg are similar for the two top doses (Figure 3.1.6). This data does not suggest a significant benefit to doubling the dose from 10 mg to 20 mg, particularly if there are any safety concerns in children with the highest dose of 20 mg.

Figure 3.1.6 Cumulative distribution plots of final LDL at Week 12



The secondary variables summarized in Table 3.14 below show a dose response for total cholesterol (TC), non-HDL and ApoB with statistically significant differences for each dose compared to placebo (p<0.001); no significant dose response (this reviewer confirmed this finding with a non-parametric analysis) is seen

for triglycerides (TG), HDL nor ApoA-1 as would be expected for these endpoints with use of a statin drug.

Table 3.1.4 Mean (SD) for baseline and percent change from baseline at Week 12 for secondary lipid parameters

	Placebo (n=46)	ROSU 5 (n=42)	ROSU 10 (n=44)	ROSU 20 (n=44)
Baseline				
TC mg/dL	293 (50)	300 (60)	297 (49)	302 (50)
non-HDL mg/dL	248 (47)	254 (59)	247 (46)	255 (51)
Apo B g/L	1.4 (0.3)	1.5 (0.4)	1.4 (0.2)	1.4 (0.3)
TG mg/dL Mean	95 (54)	82 (38)	92 (56)	89 (42)
Median	82	80	81	81
HDL mg/dL	45 (11)	46 (12)	54 (11)	47 (13)
Apo-A 1 g/L	1.4 (0.3)	1.3 (0.2)	1.4 (0.2)	1.4 (0.3)
% change				
TC	+0.2% (11)	-30% (10)	-34% (10)	-39% (12)
non-HDL	-0.8% (12)	-36% (10)	-43% (12)	-48% (14)
Apo B	-1.5% (15)	-32% (9)	-38% (12)	-41% (14)
TG Mean	+3% (48)	+3% (49)	-14% (30)	-8% (56)
Median	-7%	-13%	-15%	-16%
HDL	+8% (18)	+5% (16)	+10% (14)	+9% (14)
Apo-A 1	+4% (16)	+2% (10)	+4% (10)	+4% (11)

LSM= Least Square Mean from ANCOVA model with baseline as covariate

The applicant measured CRP on a total of 106 randomized patients and found levels of CRP at baseline of ~0.2 mg/L and small changes in CRP at any dose (changes less than 0.1 mg/L).

Following the 12-week double-blind period, all patients who had completed the double-blind period were eligible to be treated in an open-label period of 40 weeks. The starting dose during the OL period is shown in the table below:

Table 3.1.5 Initial dosing plan for the OL period

Randomized Dose in DB	LDL<110 at Visit 6?	Starting Dose in OL
Placebo 5 mg	all patients regardless of LDL level	5 mg 5 mg
10 mg 10 mg	Y N	5 mg 10 mg
20 mg 20 mg	Y N	5 mg 20 mg

Doses were titrated to a maximum level of 20 mg to achieve a lowering of LDL to below 110 mg/dL.

This reviewer created the table below to look at the pattern of dosing in the OLE and notes the following:

- Majority of patients (122; 71% of patients) were titrated to the highest dose in an attempt to lower LDL below 110 mg/dL
- Only about 1/3 of patients titrated to the highest dose of 20 mg achieved LDLs lower than 110 mg/dL at the end of the trial

Table 3.1.6 Number of responders by randomized dose and final dose

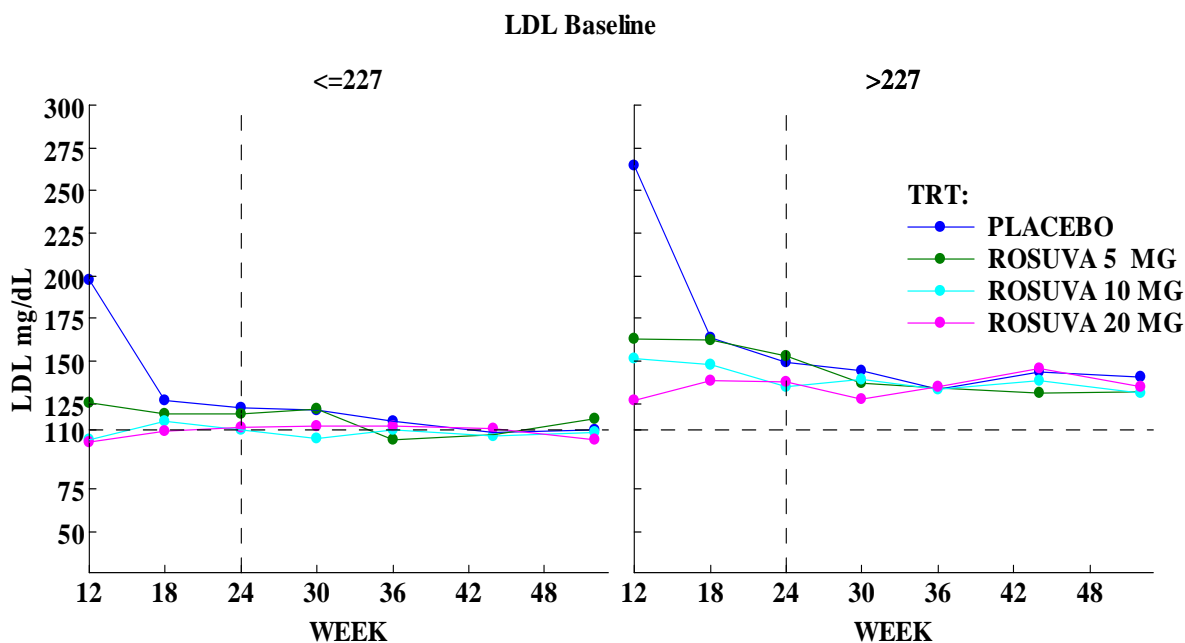
Final Dose → Randomized group	5	10	20	TOTAL
Placebo	5/7	1/5	12/33	18/45
5	3/6	4/9	9/26	16/41
10	7/11	3/5	9/27	19/43
20	2/2	6/6	9/36	17/44

Of the 173 patients that entered the OL period, 70 (40%) had LDL lower than 110 mg/dL at the end of the 52-week study. This response was dependent on the baseline LDL as can be seen below;

Baseline LDL <204 37/57 66% responders
 Baseline LDL 204 to 251 22/60 37% responders
 Baseline LDL >251 11/57 19% responders

These findings illustrate that even with titration to the highest dose, patients generally are not able to lower LDL below the target 110 mg/dL, particularly if their baseline LDL is high (Figure 3.1.7).

Figure 3.1.7 Mean LDL during the open-label period by randomized group and by median baseline LDL (227 mg/dL). After titration up to Week 24, the final dose during the OLE for each randomized group is shown in Table 3.1.6 for each randomized group.



3.2 Evaluation of Safety

There are no comparative data during the 40-week extension so no statistical analyses of long-term effects on safety outcomes can be performed. Standardized scores could be analyzed to determine whether patients on rosuvastatin maintain normal values compared to a standard population; this reviewer looked at height z-scores over the 52 week period and saw no suggestion that rosuvastatin was having an impact on normal growth. Safety results reported by the applicant for the 12-week double blind period do not suggest any significant imbalance among treatment groups or any evidence of dose-related changes on safety outcomes.

For further details regarding safety, please refer to the medical officer's review.

4. Findings in Special/Subgroup Populations

4.1 Gender and Age

Analyses of the primary endpoint by gender and age showed no subgroup differences in treatment effects (Table 4.1.1) with all interactions not significant ($p > 0.5$). More than 90% of the patients were Caucasian so this reviewer did not perform any analyses by race.

Table 4.1.1 LSM difference (95% CI) compared to placebo by subgroup for LDL percent change from baseline at Week 12

	ROSU 5	ROSU 10	ROSU 20
Sex			
Male (n=97)	-36% (-41%, -32%)	-45% (-49%, -40%)	-50% (-55%, -45%)
Female (n=79)	-41% (-47%, -35%)	-45% (-50%, -39%)	-50% (-55%, -45%)
Age			
10-13 (n=52)	-43% (-49%, -37%)	-50% (-59%, -42%)	-50% (-56%, -44%)
14+ (n=124)	-36% (-40%, -31%)	-43% (-47%, -39%)	-50% (-54%, -45%)

LSM= Least Square Mean from ANCOVA model with baseline as covariate

4.2 Other Special/Subgroup Populations

Analyses by tanner stage showed no important differences with interaction of $p = 0.5$. Analyses of subgroups defined by the median baseline LDL of 227 yielded an interaction p-value of 0.15; changes in LDL are related to baseline with larger changes seen with larger baseline values (Table 4.2.1) although the differences seen among the subgroups as defined by the median are likely of only marginal clinical significance.

There were only 14 patients followed in US sites so an analysis of US sites and non-USA sites was not warranted.

Table 4.2.1 LSM difference (95% CI) compared to placebo by subgroup for LDL percent change from baseline at Week 12

	ROSU 5	ROSU 10	ROSU 20
Tanner Stage			
II/III (n=61)	-40% (-48%, -32%)	-47% (-57%, -38%)	-52% (-61%, -43%)
IV (n=70)	-38% (-47%, -29%)	-44% (-51%, -36%)	-52% (-60%, -41%)
V (n=45)	-31% (-41%, -20%)	-40% (-50%, -30%)	-39% (-50%, -29%)
Baseline LDL (median)			
<227 mg/dL (n=87)	-35% (-42%, -28%)	-47% (-54%, -40%)	-47% (-54%, -40%)
≥227 mg/dL (n=89)	-40% (-48%, -33%)	-53% (-62%, -43%)	-52% (-62%, -43%)

LSM= Least Square Mean from ANCOVA model with baseline as covariate.

5. Summary and Conclusions

The applicant has presented the results of a single trial (named PLUTO) in pediatric patients aged 10 to 17 years to demonstrate the safety and efficacy of rosuvastatin in the treatment of heterozygous familial hypercholesterolemia. Patients randomized to placebo, rosuvastatin 5 mg, 10 mg or 20 mg were followed for 12 weeks and then entered a 40 week open label phase where all patients were treated with rosuvastatin and titrated to a goal of less than 100 mg/dL.

A total of 176 patients were randomized and treated with 93% of these patients completing the open label phase. Statistically significant lowering of LDL, total cholesterol (TC), non-HDL and ApoB were seen for each dose of rosuvastatin compared to placebo. The percent change in LDL ranged from -38% to -50%. About 41% of patients on doses of 10 mg and 20 mg were able to achieve an LDL level less than 110 mg/dL after 12 weeks of therapy; this response 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 below 110 mg/dL; however, the percentage of responders remained at about 40% suggesting that the maximum dose of 20 mg may not be necessary for obtaining the maximum effect for any given patient.

Subgroup analyses by this reviewer revealed no significant differential treatment effects among subgroups defined by age, sex, baseline LDL and Tanner stage. The applicant performed additional subgroup analyses none of which yielded significant subgroup by treatment interactions.

The statistical evidence provided by the study PLUTO sufficiently establishes the effectiveness of rosuvastatin to treat pediatric patients with heterozygous familial hypercholesterolemia.

6. Labeling

The applicant has proposed the following in the clinical trials section of the product labeling to describe the study reviewed here.

(b) (4)



(b) (4)



Comments regarding the clinical trials section:

- The heading should include “heterozygous familial.”

(b) (4)



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21366	SUPPL 17	IPR PHARMACEUTICA LS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80
NDA 21366	SUPPL 17	IPR PHARMACEUTICA LS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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JOY D MELE
08/28/2009

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