Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Lovastatin

Mevacor, Altocor, Altoprev

UK/W/031/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	15 August 2012
Date of finalisation of PAR	8 March 2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Mevacor, Altocor, Altoprev
INN (or common name) of the active substance(s):	Lovastatin
MAH (s):	Merck Sharp & Dohme
Pharmaco-therapeutic group (ATC Code):	C10AA02
Pharmaceutical form(s) and strength(s):	10, 20 & 40 mg tablets

I. EXECUTIVE SUMMARY

This is an assessment of data for lovastatin, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 Jan 2007. The UK is Rapporteur for this procedure.

Lovastatin was the first 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor introduced into therapeutic use. Lovastatin was first approved in Austria in 1987 and is currently registered and approved in 33 countries.

The current submission includes three clinical studies of lovastatin in children with familial hypercholesterolemia: an efficacy and safety 1-year base study in Adolescent Males 10-17 years old, followed by a 2-year open-label extension study; an efficacy and safety in Adolescent Girls one year post menarche, a brief clinical overview, and a brief summary of the literature (1990-present) and a 3 year PSUR covering the period of (September 2000 –July 2010).

No PK study was carried out. The total number of paediatric patients exposed to lovastatin in the three clinical studies is approximately 100. These studies have been conducted in response to a written request for paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity list.

The applicant states that: Taking into account the extensive experience of lovastatin in adult patients with hypercholesterolemia, these data are considered sufficient to support a proposed indication for the treatment of heterozygous FH in children 10- 17 years of age. The applicant has proposed SmPC changes in sections 4.1, 4.2, 4.4, 4.8, 5.1 and PIL sections 3 and 4.

The risk benefit evaluation carried out in this assessment, is negative. The study and the response document do not support a paediatric indication, however a summary of the studies should be captured in section 5.1 of the SmPC. In the adolescent girls the LH levels in the lovastatin group were significantly reduced, it should be captured in section 4.8. No alteration to PIL is required.

Summary of outcome

☒ New study data: sections 4.8, 5.1 and cross referenced 4.2

II. RECOMMENDATION

Based on the review of the presented paediatric data on safety and efficacy; and the assessment of responses to the list of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies do not support a paediatric posology. However, the incorporation of summaries of efficacy study in section 5.1, and a cross reference in section 4.2 of the SmPC will be helpful to the prescriber.

The safety profile of lovastatin generally resembles that of adults and no new adverse events in children have emerged as a result of the submitted data. In the adolescent girls the LH levels in the lovastatin group was significantly reduced ($p<0.04$). This should be captured in section 4.8.

The following changes to the SmPC were proposed by the applicant. The assessor's amendments and recommendations on the text are in italics and strike through:

Summary of Product Characteristics

4.2 Posology and method of administration

The safety and efficacy of MEVACOR in children has not yet been established. Currently available data are described in section 4.8, 5.1 but no recommendation on a posology can be made.

4.4 Special warnings and precautions for use

Paediatric Population

In limited controlled studies (See sections 4.8, and 5.1), there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. Adolescent females should be counselled on appropriate contraceptive methods while on lovastatin therapy (see sections 4.3 and 4.6). MEVACOR has not been adequately studied in pre-pubertal children or pre-menarchal girls, nor in patients younger than 10 years of age.

4.8 Undesirable effects

Paediatric population

Safety and effectiveness of lovastatin (10, 20 & 40 mg daily) in 100 children 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and 24 weeks duration in girls who were at least one year post-menarche. Doses greater than 40 mg have not been studied in this population.

The safety profile of MEVACOR obtained from these limited controlled studies was generally similar to adults; with the exception of a statistically significant reduction in LH levels in the adolescent girls treated with lovastatin.
There was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls (See sections 4.4 and 5.1).

5.1 Pharmacodynamic properties

Paediatric population

In a randomized, double-blind, placebo-controlled study, 132 boys, 10-17 years of age with heterozygous familial hypercholesterolemia (baseline LDL-C 189-500 mg/dL) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. The dosage of lovastatin once daily in the evening was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 19.3%, mean LDL-C by 24.2% and mean apolipoprotein B levels by 21%.

Similarly in another randomized, double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least one year post-menarche with heterozygous familial

hypercholesterolemia (baseline LDL-C 160-400 mg/dL) were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. The dosage of lovastatin once daily in the evening was 20 mg for the first 4 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 22.4%, mean LDL-C by 29.2%, mean apolipoprotein B levels by 24.4% and median triglycerides levels by 22.7%.

The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Package Leaflet:

Children

Lovastatin is not recommended for use in children and adolescents below 18 years of age because safety and efficacy of lovastatin in children has not been established.

III. INTRODUCTION

The MAH has submitted 3 completed paediatric studies for lovastatin, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do influence the benefit risk for lovastatin and that there should be consequential regulatory action, as follows:.

These data are considered sufficient to support a proposed indication for the treatment of heterozygous FH in children 10- 17 years of age.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, and related PL wording

IV. SCIENTIFIC DISCUSSION

Product characteristics

Lovastatin, has been available for the treatment of hypercholesterolemia since 1987as the first drug of it class.

Lovastatin is an inhibitor of 3-hydroxy-3methylglutaryl-coenzyme A reductase (HMG-CoA reductase), an enzyme that catalyzes the conversion of HMG-CoA to mevalonate. Mevalonate is a required building block for cholesterol biosynthesis and lovastatin interferes with its production by acting as a reversible competitive inhibitor for HMG-CoA, which binds to the HMG-CoA reductase. Lovastatin is hydrolysed to its active form β-hydroxy acid in the body.

Paediatric Hypercholesterolemia

Evidence accumulated over the past 40 years indicates that the atherosclerotic disease process begins early in childhood and that the rate of progression is greatly increased by lipid abnormalities and their severity. Autopsy studies, such as the pathobiological determinants of atherosclerosis in youth (PDAY, 2006) study and the Bogalusa Heart Study (2002), have demonstrated that the atherosclerotic process begins in childhood and is progressive throughout the life span. Furthermore impaired endothelium-dependent dilation is present in children with familial hypercholesterolemia as young as 7 years of age and the degree of impairment is related to the lipoprotein(a) (Sorensen *et al.,* 1994).

Hypercholesterolemia develops as a consequence of abnormal lipoprotein metabolism, mainly reduction of LDL receptor expression or activity, and consequently diminishing hepatic LDL clearance from the plasma. This could be due to a single or multiple gene mutations that vary in location of genetic defect, inheritance pattern, prevalence and clinical features. At least 18 separate entities have been described.

Cholesterol concentrations change with age and are particularly variable during puberty. By approximately 2 years of age, these concentrations reach levels similar to those seen in young adults. At 14-16 years of age, cholesterol values are generally lower, whereas the highest cholesterol values are seen at 9-11 and 17-19 years of age. There are also differences in cholesterol concentrations related to gender. Lipid and lipoprotein concentrations are higher in women and changed in different ways for males and females during development. There are also differences in cholesterol and triglyceride concentrations according to ethnic group, with black children having higher HDL and lower triglyceride concentrations than children of white and Hispanic descent.

The American Academy of Paediatrics (AAP) 2008 guidelines recommend that in: patients 8 years and older with an LDL concentration of ≥190 mg/dL (or ≥160 mg/dL with a family history of early heart disease or ≥2 additional risk factors present or ≥130 mg/dL if diabetes mellitus is present), pharmacologic intervention should be considered. The initial goal is to lower LDL concentration to <160 mg/dL. However, targets as low as 130 mg/dL or even 110 mg/dL may be warranted when there is a strong family history of CVD, especially with other risk factors including obesity, diabetes mellitus and the metabolic syndrome.

Lipid-lowering drug therapy is recommended for children 10 years and older whose LDL-C levels remain extremely elevated after six months to one year of dietary modification. Statins are the first-line treatment in children. Currently, atorvastatin, pravastatin, and rosuvastatin have paediatric indications in the UK for children aged 10-17 years of age with heterozygous familial

hypercholesterolaemia. Lovastatin has paediatric indication for use in children with familial hypercholesterolemia in the US.

Overview of Clinical Literature

A formal review of the literature was conducted focusing on clinical trials with lovastatin in paediatric patients with Primary Hypercholesterolemia and other diseases.

Sources included the following databases:

- MEDLINE 1990-2011
- Biosis Previews 1993-2011
- EMBASE 1993-2011
- SciSearch 1990-2011
- ToxFile 1965-2010
- Derwent Drug File 1983-2011

Terms included in the search included:

- lovastatin or mevacor or MK-0803
- human (paediatric or child or teen or adolescent or infant or neonatal or newborn)

Review of the current literature, other than the publications of three MAH-sponsored studies (P040, P040X and P083), and Lambert et al 1996, revealed there is little new published information with lovastatin monotherapy in paediatric patients. However, literature continues to support that lipid management starts with stratification of risk, followed by dietary modification, and in high-risk cases, pharmacologic treatment initiated (Tonstad & Thompson 2004). Results of clinical trials with statins continues to support the notion that statin treatment is efficacious in paediatric patients with heterozygous familial hypercholesterolemia and the safety profile is consistent with previously reported studies with statins (Clauss et al., 2005, Avis et al., 2010, Van Der Graaf et al., 2006)

Assessor's comments: the applicant has provided a list of 21 references, most of which are reviews and general articles on the use of statins in paediatric patients. The assessor's own literature search produced similar results to the applicant's. The applicant's position that "there is little new published information with lovastatin monotherapy in paediatric patients", is acceptable.

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Conventional lovastatin (10, 20, or 40 mg) or matching placebo tablets, were used in all 3 clinical studies.

IV.2 Non-clinical aspects

No non clinical studies were submitted.

IV.3 Clinical aspects

1. Introduction

The MAH submitted 3 reports for:

- P040 A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Lovastatin as an Adjunct to Diet in the Treatment of Adolescent Males with Hypercholesterolemia of Familial Basis

- P040X An Open, Multicenter, Extension Study of Lovastatin as an Adjunct to Diet in the Treatment of Adolescent Males with Hypercholesterolemia of Familial Basis

- P083 A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lovastatin in Adolescent Girls

In addition the MAH has submitted

- Summary of MAH's postmarketing experience with lovastatin (September 2000 –July 2010)

- Brief summary of the literature (1990-present) on the use of lovastatin in paediatric patients have also been provided.

2. Clinical studies

2.1. Study P040: Multicenter Study: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Lovastatin as an Adjunct to Diet in the Treatment of Adolescent Males With Hypercholesterolemia of Familial Basis.

- **Description**

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Lovastatin as an Adjunct to Diet in the Treatment of Adolescent Males With Hypercholesterolemia of Familial Basis

- **Methods**

- Objective(s)

To compare the safety and efficacy of lovastatin plus a lipid-lowering diet to diet alone in the treatment of adolescent 10-17 years old male, with heterozygous familial hypercholesterolemia.

- Study design

This was a 1-year, randomized, double-blind, balanced, placebo-controlled study in male patients between 10 and 17 years of age with familial hypercholesterolemia with a 4-week diet/placebo run-in period. The active-treatment phase of this study consisted of 2 periods, each 24 weeks in length. During the first 24-week period, patients randomized to lovastatin received 10 mg once daily for 8 weeks, followed by 20 mg once daily for 8 weeks, and then 40 mg once daily for 8 weeks. During the second treatment period, patients in the lovastatin group continued to receive 40 mg once daily for an additional 24 weeks. There was no washout period between

the treatment periods. If an increase in dose could not be tolerated, the highest tolerated dose was continued for the remainder of the study. Table 1 summarizes the Schedule of Clinical Observations and Laboratory Measurements.

Table 1- Schedule of Clinical Observations and Laboratory Measurements

		Diet Run-In		Placebo Run-In		Period I Step 1		Period I Step 2		Period I Step 3		Period II			
Visit Number:	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week:	†	-8	-4	-2	0	4	8	12	16	20	24	30	36	42	48
Clinic visit‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X				X			X			X		X		X
Red blood cell indices					X						X				X
Coagulation					X						X				X
Urinalysis					X						X				X
Serum chemistry-1	X				X	X	X	X	X	X	X	X	X	X	X
Serum chemistry-2	X				X		X		X		X		X		X
Serum chemistry-3					X						X				X
Thyroid function tests	X				X						X				X
Lipid Profile: Partial	X	X	X			X	X	X	X	X		X	X	X	
Lipid Profile: Complete				X§	X						X				X§
Physical examination (including growth development)‖	X				X						X				X
Height measurement	X				X			X			X		X		X
Plot height and weight on growth curve					X						X				X
ECG	----------X----------														X
Reserve blood					X		X		X		X		X		X
Ophthalmology	----------X----------														X
Diet Review: Qualitative	X	X					X		X			X	X	X	
Diet Review: Quantitative			X		X						X				X

† Performed within one month of diet run-in period (Week -8).
‡ With routine physical examination including height, weight, and vital signs.
§ Included apolipoprotein B concentrations in the LDL-C fraction.
‖ Included weight and assessment of pubertal development (Tanner staging) and testicular volume.

There were a total of 41 specimens per patient for the entire study. A dietician reviewed the diet with each patient at Weeks -8, -4, 0, 8, 16, 24, 30, 36, 42, and 48 to reinforce dietary advice and compliance.

Efficacy measurements:

Blood was drawn at the screening visit and at Weeks -8, -4, -2, 0, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48 for the analysis of lipids and lipoproteins. The lipid parameters LDL-C, total-C, high-density lipoprotein cholesterol (HDL-C), and TG were measured at each visit. The lipid parameters apolipoprotein B (apo B), apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), and lipoprotein (a) (Lp a) were measured at Weeks -2, 0, 24, and 48.

Safety Measurements:

Adverse experiences, ALT, AST, CK , Endocrine function, Testicular volume, Tanner stage, Vital signs Ophthalmologic and Serum nutritional parameters were measured as detailed below and in table 1.

Liver function tests (ALT and AST) and CK were measured at the screening visit and at Weeks 0, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48.

Thyroid function tests (thyroid stimulating hormone [TSH], thyroxine, and T_3 resin uptake) were performed at the screening visit and at Weeks 0, 24, and 48. Measurements of other endocrine parameters including testosterone, cortisol, dehydroepiandrosterone sulfate (DHEA-SO_4), luteinizing hormone (LH), and follicle stimulating hormone (FSH), were carried out at Weeks -2, 0, 24, and 48.

Measurement of nutritional parameters including 25-hydroxyvitamin D, albumin, alpha-carotene, alpha-tocopherol, beta-carotene, ferritin, gamma-tocopherol, glucose, lycopene, retinol, and total protein were carried out at Weeks -2, 0, and 48. Measurement of other serum chemistry parameters, were carried out at the screening visit and at Weeks 0, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48. Additional samples for routine hematology tests, and routine urinalyses, including measurements of bilirubin, blood, glucose, ketone, nitrates, pH, and protein, were performed at Weeks 0, 24, and 48.

- Study population /Sample size

Patients were eligible for enrolment in the study if they met all of the following criteria:

- Adolescent males between 10 and 17 years of age.
- Adolescent males whose height and weight were between the 5th and 95th percentiles for age and who weighed at least 32 kg.
- LDL-C measurements ≥190 mg/dL but <500 mg/dL at Week -4 and Week -2.

Of the 132 patients entered, 109 (82.6%) completed the study including 60 patients in the lovastatin group and 49 patients in the placebo group (Table 2).

Table 2- Patient Accounting

	Lovastatin	Placebo	Total
ENTERED: (age range)[†]	67 (9 to 17)	65 (10 to 17)	132 (9 to 17)
COMPLETED:	60	49	109
DISCONTINUED:			
Clinical adverse experience	1	2	3
Laboratory adverse experience	0	0	0
Deviation from protocol	0	1	1
Lost to follow-up	1	3	4
Other	5	10	15
FDA request	2	4	6
Miscellaneous	3	6	9

During the study if the LDL-C level was confirmed to be below 70 mg/dL, either the dose of lovastatin was reduced to the next lower dose or the patient was discontinued from the study if already on the lowest dose. Similarly if a patient's LDL-C level was confirmed to be higher than 500 mg/dL, he was excluded from the study.

Assessor's comment: in the title and proposed posology section 4.2 of the SmPC the age group is 10-17, whilst in this table there seem to be some 9 year old children included. The applicant needs to clarify this point.

- Treatments

One lovastatin (10, 20, or 40 mg) or matching placebo tablet was taken once daily immediately before the evening meal. Table 3 shows treatment schedule for Period I, in period II all patients received the 40 mg tablets or the matching placebo.

Table 3- Drug Treatment Schedule for Period I

Step	Duration (Weeks)	Treatment Group	Lovastatin Dosage
1	8	Lovastatin	10 mg once daily
2	8	Lovastatin	20 mg once daily
3	8	Lovastatin	40 mg once daily
1	8	Placebo	--
2	8	Placebo	--
3	8	Placebo	--

A missed dose was allowed to be taken up to 6 hours later than the scheduled time.

- Outcomes/endpoints

- <u>The primary efficacy endpoint</u> was the percent change in LDL-C from baseline (mean of Week -2 and Week 0) at Week 48. In addition, percent change in LDL-C from baseline at Week 48 was evaluated by baseline Tanner stage.

- **<u>The Secondary efficacy endpoints</u>** were percent changes in total-C, HDL-C, TG, apo B, apo A-I, apo A-II, and Lp (a) from baseline at Week 48.

<u>The primary safety measures</u> were the effect of lovastatin compared with placebo on growth and sexual development, biochemical and nutritional safety parameters, adverse experience rates and vital signs.

- Statistical Methods

EFFICACY: The percent change from baseline at Weeks 8, 16, 24, and 48 was analyzed for each lipid parameter. A t-test was used to compare mean percent change equal to 0 within a treatment group. The differences in percent change between groups were analyzed using an analysis of variance (ANOVA) model with factors for treatment and center. Between-group tests were limited to Week 48 as the primary endpoint; other analyses were supportive.

Since both the t-test and the ANOVA were based on the normal distribution assumption, each lipid parameter was tested for normality using the Shapiro-Wilk test. In cases where the normal distribution assumption was not satisfied for at least 1 treatment group for a parameter, nonparametric test results were presented. A Wilcoxon Signed Rank test was used instead of a t-test, and a General Linear Model SAS Procedure (PROC GLM) based upon the normalized ranks of the raw data was used instead of the parametric ANOVA.

All tests for main effects were two-sided and conducted at the $\alpha=0.05$ level of significance, while tests for interaction effects were conducted at the $\alpha=0.10$ level of significance.
This study called for 100 patients to be recruited. Assuming that 82 (41 per treatment group) of the 100 screened patients would have evaluable data and a population standard deviation (SD) of 15 percentage points, a difference of 12 percentage points in mean LDL-C changes from baseline to end of Period II could be detected with 95% power ($\alpha=0.05$, two-tailed).

SAFETY: The effect of lovastatin on growth factors, endocrine function, and nutritional parameters was assessed by comparing the changes or percent changes from baseline of the lovastatin and placebo-treated groups using an ANOVA model with factors for treatment and centre.

➢ Results

- Recruitment/ Number analysed

Of the 132 patients entered, 109 (82.6%) completed the study including 60 patients in the lovastatin group and 49 patients in the placebo group. The reasons for discontinuation are captured in table 4 below:

Table 4- Patient Accounting

	Lovastatin	Placebo	Total
ENTERED: (age range)†	67 (9 to 17)	65 (10 to 17)	132 (9 to 17)
COMPLETED:	60	49	109
DISCONTINUED:			
Clinical adverse experience	1	2	3
Laboratory adverse experience	0	0	0
Deviation from protocol	0	1	1
Lost to follow-up	1	3	4
Other	5	10	15
FDA request	2	4	6
Miscellaneous	3	6	9

Deviations from Planned Analysis
Source documents for the study were found to be missing for 17 patients at 4 investigator sites. Thus, an additional analysis was performed to exclude these 17 patients for the key efficacy endpoint, LDL-C, and the secondary endpoints total-C, HDL-C, and TG.

Assessor's comment: the applicant must provide the reason for FDA request to withdraw 6 children from the study.

Regarding the missing 17 source documents, the applicant needs to clarify the following:
- Was there a complete loss of all records on these 17 patients?
- Have they been included in baseline or any other stages of the study analysis?
- What additional analysis was performed to exclude these 17 patients for the key efficacy endpoint?
- Dose this mean the final number of patients that completed the study and were analyzed is actually 92?
- Of this 17 patients how many were in lovastatin and how many in placebo group?

- Baseline data

A summary of baseline data by treatment group for age, race, height, weight, BMI, and smoking status is in Table 5 below. There were no clinically meaningful differences between treatment groups for these characteristics.

Table 5- Baseline Patient Characteristics by Treatment Group

	Lovastatin (N=67)		Placebo (N=65)		Total (N=132)	
	n	(%)	n	(%)	n	(%)
Race						
Caucasian	62	(92.5)	61	(93.8)	123	(93.2)
Black	2	(3.0)	2	(3.1)	4	(3.0)
Other	3	(4.5)	2	(3.1)	5	(3.8)
Age (Years)						
N	67		65		132	
Mean	12.8		12.6		12.7	
SD	2.2		2.1		2.2	
Median	12.0		12.0		12.0	
Range	9.0 to 17.0		10.0 to 17.0		9.0 to 17.0	
Height (cm)						
N	67		65		132	
Mean	157.8		156.7		157.3	
SD	13.7		13.0		13.3	
Median	158.4		153.0		157.0	
Range	130.7 to 182.6		129.5 to 184.0		129.5 to 184.0	
Weight (kg)						
N	67		65		132	
Mean	51.7		51.3		51.5	
SD	16.1		14.6		15.3	
Median	51.8		52.3		52.2	
Range	25.7 to 103.4		28.9 to 88.2		25.7 to 103.4	
Body Mass Index (kg/m^2)						
N	67		65		132	
Mean	20.3		20.5		20.4	
SD	3.9		3.4		3.7	
Median	19.6		20.3		19.7	
Range	14.6 to 33.9		15.4 to 29.3		14.6 to 33.9	
Smoking Status						
No	65	(97.0)	63	(96.9)	128	(97.0)
Yes	2	(3.0)	2	(3.1)	4	(3.0)

Risk factors for CHD listed by treatment group are in Table 6 below. Compared with the lovastatin group, the placebo group had a higher percentage of patients with xanthomas (7.5% lovastatin, 15.4% placebo).

Table 6- Risk Factors for Cardiovascular Heart Disease by Treatment Group

	Lovastatin (N=67)		Placebo (N=65)		Total (N=132)	
	n	(%)	n	(%)	n	(%)
Xanthomas						
Yes	5	(7.5)	10	(15.4)	15	(11.4)
No	61	(91.0)	55	(84.6)	116	(87.9)
Mother With LDL-Cholesterol ≥190 mg/dL						
Yes	30	(44.8)	33	(50.8)	63	(47.7)
No	33	(49.3)	29	(44.6)	62	(47.0)
Mother With Xanthomas						
Yes	10	(14.9)	17	(26.2)	27	(20.5)
No	49	(73.1)	44	(67.7)	93	(70.5)

Mother With Corneal Arcus						
Yes	6	(9.0)	5	(7.7)	11	(8.3)
No	50	(74.6)	54	(83.1)	104	(78.8)
Father With LDL-Cholesterol ≥190 mg/dL						
Yes	33	(49.3)	30	(46.2)	63	(47.7)
No	28	(41.8)	29	(44.6)	57	(43.2)
Father With Xanthomas						
Yes	15	(22.4)	11	(16.9)	26	(19.7)
No	34	(50.7)	33	(50.8)	67	(50.8)
Father With Corneal Arcus						
Yes	9	(13.4)	3	(4.6)	12	(9.1)
No	36	(53.7)	39	(60.0)	75	(56.8)
Heterozygous Familial Hypercholesterolemia						
Yes	56	(83.6)	52	(80.0)	108	(81.8)
No	11	(16.4)	13	(20.0)	24	(18.2)
Familial Combined Hyperlipidemia						
Yes	1	(1.5)	2	(3.1)	3	(2.3)
No	66	(98.5)	63	(96.9)	129	(97.7)
Other						
Yes	9	(13.4)	11	(16.9)	20	(15.2)
No	58	(86.6)	54	(83.1)	112	(84.8)

- **Efficacy results**

Primary end point

The primary analysis of the study was the percent change from baseline in LDL-C at Week 48 (40 mg/day lovastatin). Additional analyses included the percent change from baseline in LDL-C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day). The results of these parametric analyses are in Table 7 below.

Table 7- Analysis of Percent Change From Baseline in LDL Cholesterol at Weeks 8, 16, 24 & 48

	Week 8 (10 mg/day)		Week 16 (20 mg/day)		Week 24 (40 mg/day)		Week 48 (40 mg/day)	
LDL Cholesterol (mg/dL)	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
N	64	61	64	61	64	61	64	61
Baseline								
Mean	252.6	248.7	252.6	248.7	252.6	248.7	252.6	248.7
SD†	43.7	47.3	43.7	47.3	43.7	47.3	43.7	47.3
Endpoint								
Mean	208.1	255.6	191.5	256.2	183.8	247.1	190.9	244.8
SD	46.0	52.8	37.8	53.0	41.4	49.8	47.3	51.9
Percent Change								
Mean	-17.6	3.0	-23.9	3.3	-27.0	-0.4	-24.2	-1.4
SD†	11.4	10.8	10.3	10.7	12.1	10.7	14.5	10.8
95% CI‡	(-20.5, -14.7)	(0.2, 5.7)	(-26.4, -21.3)	(0.5, 6.0)	(-30.0, -24.0)	(-3.1, 2.4)	(-27.9, -20.6)	(-4.2, 1.3)
p-Value	<0.001	0.034	<0.001	0.020	<0.001	0.788	<0.001	0.302
Between-treatment p-value	<0.001		<0.001		<0.001		<0.001	

† SD=Standard deviation.
‡ CI=Confidence interval.

At Week 48, mean LDL-C was reduced by 24.2% (p<0.001) in the lovastatin group and by 1.4% (p=0.302) in the placebo group. The between-group difference was significant (p<0.001). This analysis of percent reduction in LDL-C at Week 48, excluding the 17 patients with missing source documents, yielded similar results. The results of this analysis are in [4.1.6].

Assessor's comment: the LDL concentration was reduced by approximately 60 mg/dl after 48 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant

and clinically meaningful compared with the placebo group. The primary objective is reached.

The additional analysis of LDL-C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day), shows that the reduction in LDL concentration reached a plateau at around 20 mg on16 weeks. In the absence of a PK study, the applicant must clarify the dose selection and the reasoning behind the 40 mg dose.

It is unclear whether the applicant was attempting to establish dose/response relationship or not. If so, the applicant must provide the linear regression analysis of dose versus change from baseline levels of LDL.

A number of subgroup analyses were performed to determine whether various subgroups were influential to LDL-C response. An ANCOVA model was tested for percent change from baseline in LDL-C at Week 48 with treatment, race (categorized as either Caucasian or Noncaucasian), and centre as main factors and age as covariate. This inferential analysis indicated that race (p=0.737), centre (p=0.182), and age (p=0.986) were not significant factors that influenced LDL-C reduction.

In addition, analysis of covariance indicated that baseline testicular volume and baseline Tanner stage were not a significant factor that influenced LDL-C reduction at Week 48 with (p=0.093) (p=0.537) respectively.

Assessor's comment: the sub group analysis of centre, baseline testicular volume and baseline Tanner stage, showed no significant influence on LDL-C reduction. The analysis of race is rather pointless as 92.2% of children recruited were Caucasian and only 6.8% black or other.

In the general population the age-specific values for mean total cholesterol concentration actually peak at 171 mg/dL at 9 to 11 years of age (Hickman et al., 1998). The values subsequently decrease during pubertal development and then increase thereafter. It is commonly accepted that lipid concentrations are age and maturation dependent (Friedman et al., 2006).

Secondary endpoints

Total Cholesterol

Secondary Efficacy analysis included the percent change from baseline in total-C at Week 48 (40 mg/day lovastatin). Additional analyses included the percent change from baseline in total-C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day). The results of these parametric analyses are in Table 8 below.

Table 8- Analysis of Percent Change From Baseline in Total Cholesterol at Weeks 8, 16, 24, and 48

LDL Cholesterol (mg/dL)	Week 8 (10 mg/day)		Week 16 (20 mg/day)		Week 24 (40 mg/day)		Week 48 (40 mg/day)	
	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
N	64	61	64	61	64	61	64	61
Baseline								
Mean	319.8	314.4	319.8	314.4	319.8	314.4	319.8	314.4
SD†	47.0	48.4	47.0	48.4	47.0	48.4	47.0	48.4
Endpoint								
Mean	275.7	319.7	258.3	321.4	251.7	314.2	257.3	310.6
SD	48.1	55.5	39.6	54.7	44.2	51.3	50.8	52.9
Percent Change								
Mean	-13.7	1.7	-18.8	2.4	-21.1	0.1	-19.3	-1.1
SD†	9.1	9.2	8.9	9.4	10.1	9.0	11.9	8.9
95% CI‡	(-16.0, -11.4)	(-0.6, 4.1)	(-21.1, -16.6)	(0.0, 4.8)	(-23.6, -18.5)	(-2.2, 2.4)	(-22.3, -16.4)	(-3.3, 1.2)
p-Value	<0.001	0.148	<0.001	0.047	<0.001	0.923	<0.001	0.350
Between-treatment p-value	<0.001		<0.001		<0.001		<0.001	

At Week 48, mean total-C was reduced by 19.3% (p<0.001) in the lovastatin group and by 1.1% (p=0.350) in the placebo group. The between-group difference was significant (p<0.001). This analysis of percent reduction in total-C at Week 48, excluding the 17 patients with missing source documents, yielded similar results.

Assessor's comment: the total cholesterol concentration was reduced by approximately 63 mg/dl after 48 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant and clinically meaningful compared with the placebo group.

The additional analysis of total -C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day), shows that the reduction in total cholesterol concentration reached a plateau at around 20 mg on16 weeks. In the absence of a PK study, the applicant must clarify the dose selection and the reasoning behind the 40 mg dose.

Similar to the primary objective of reduction in LDL concentration, it is unclear whether the applicant was trying to establish dose/response relationship or not. If so, the applicant must provide the linear regression analysis of dose versus change from baseline in total cholesterol concentration.

HDL Cholesterol

Efficacy analysis included the percent change from baseline in HDL-C at Week 48 (40 mg/day lovastatin). Additional analyses included the percent change from baseline in HDL-C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day). At Week 48, mean HDL-C was increased by 1.1% (p=0.451) in the lovastatin group and reduced by 2.2% (p=0.145) in the placebo group. The between-group difference was not significant (p=0.121).

Triglycerides

Efficacy analysis included the percent change from baseline in Triglycerides **(**TG) at Week 48 (40 mg/day lovastatin). Additional analyses included the percent change from baseline in TG at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day). At Week 48, median TG were reduced by 1.9% (p=0.845) in the lovastatin group and by 1.4% (p=0.428) in the placebo group. The between-group difference was not significant (p=0.216).

Apolipoprotein B

Efficacy analysis included the percent change from baseline in apo B at Week 48 (40 mg/day lovastatin). Additional analyses included the percent change from baseline in apo B at Week 24 (40 mg/day lovastatin). The results of these parametric analyses are in Table 9 below.

At Week 48, mean apo B was reduced by 21.0% (p<0.001) in the lovastatin group and by 4.4% (p=0.042) in the placebo group. The between-group difference was significant (p<0.001).

Table 9- Analysis of Percent Change From Baseline in Apolipoprotein B at Weeks 24 and 48

	Week 24		Week 48	
Apolipoprotein B (mg/dL)	Lovastatin	Placebo	Lovastatin	Placebo
N	59	58	62	59
Baseline				
Mean	195.1	203.3	195.9	203.9
SD†	40.1	42.0	40.0	41.9
Endpoint				
Mean	147.7	188.8	152.1	191.9
SD	31.6	37.0	36.4	37.7
Percent Change				
Mean	-23.0	-5.5	-21.0	-4.4
SD†	15.1	15.9	17.8	16.3
95% CI‡	(-26.9, -19.0)	(-9.7, -1.3)	(-25.6, -16.5)	(-8.6, -0.2)
p-Value	<0.001	0.011	<0.001	0.042
Between-treatment p-value	<0.001		<0.001	

Assessor's comment: the Apolipoprotein B concentration was reduced by approximately 44 mg/dl after 48 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant and clinically meaningful compared with the placebo group.

This reduction is expected as Apo B is the ligand for LDL receptors in various cells throughout the body, and somewhat a better predictor of coronary heart disease than LDL levels.

Apolipoprotein A-I
At Week 48 (40 mg/day lovastatin), mean apo A-I was increased by 1.6% (p=0.290) in the lovastatin group and by 0.2% (p=0.908) in the placebo group. The between-group difference was not significant (p=0.421). Additional analyses included the percent change from baseline in apo A-I at Week 24 (40 mg/day lovastatin), which did not show a significant difference between the groups.

Apolipoprotein A-II
At Week 48 (40 mg/day lovastatin), mean apo A-II was increased by 2.1% (p=0.323) in the lovastatin group and reduced by 2.2% (p=0.332) in the placebo group. The between-group difference was not significant (p=0.145). Additional analyses included the percent change from baseline in apo A-II at Week 24 (40 mg/day lovastatin), which did not show a significant difference between the groups.

Lipoprotein (a)
At Weeks 24 & 48 (40 mg/day lovastatin), median Lp (a) did not change from baseline for either treatment group.

Assessor's comment: analysis of other circulating lipid parameters showed that Total-C and Apo B concentration have been reduced significantly At Week 48 (40 mg/day) in the lovastatin group compared with the placebo. This result ties in with the primary endpoint result of reduction in LDL-C.

HDL Cholesterol, Triglycerides, Apolipoprotein A-I, Apolipoprotein A-II and Lipoprotein (a), concentration were not affected by lovastatin treatment and the values remained similar to that

of baseline and placebo level.

Of note, the applicant states that: The analysis of percent change in total-C, HDL-C and Triglycerides at Week 48, excluding the 17 patients with missing source documents, yielded similar results.

- **Safety results**

Adverse Events
Clinical adverse experiences were evaluated with regard to the numbers (percentages) of patients with adverse experiences. The most common adverse experiences and adverse experiences determined by the investigator to be drug related (i.e., possibly, probably, or definitely drug related) are listed in Table 10 below:

Table 10- Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Body System

	Lovastatin (N=67)		Placebo (N=65)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	47	(70.1)	49	(75.4)
Patients with no adverse experience	20	(29.9)	16	(24.6)
Body as a Whole—General Disorders	**32**	**(47.8)**	**31**	**(47.7)**
Accidental trauma	12	(17.9)	8	(12.3)
Allergy	5	(7.5)	3	(4.6)
Fatigue	2	(3.0)	1	(1.5)
Fever	3	(4.5)	4	(6.2)
Headache	10	(14.9)	10	(15.4)
Influenza-like symptoms	7	(10.4)	12	(18.5)
Gastrointestinal System Disorders	**11**	**(16.4)**	**11**	**(16.9)**
Abdominal pain	7	(10.4)	5	(7.7)
Diarrhea	1	(1.5)	3	(4.6)
Gastroenteritis	5	(7.5)	2	(3.1)
Musculoskeletal System Disorders	**7**	**(10.4)**	**10**	**(15.4)**
Arthropathy	1	(1.5)	2	(3.1)
Back pain	1	(1.5)	2	(3.1)
Myalgia	3	(4.5)	4	(6.2)
Resistance Mechanism Disorders	**7**	**(10.4)**	**6**	**(9.2)**
Infection	3	(4.5)	2	(3.1)
Otitis media	4	(6.0)	3	(4.6)
Respiratory System Disorders	**33**	**(49.3)**	**30**	**(46.2)**
Bronchitis	3	(4.5)	3	(4.6)
Coughing	3	(4.5)	3	(4.6)
Pharyngitis	8	(11.9)	6	(9.2)
Rhinitis	3	(4.5)	7	(10.8)
Upper respiratory tract infection	27	(40.3)	19	(29.2)
Skin and Appendages Disorders	**5**	**(7.5)**	**7**	**(10.8)**
Contact dermatitis	2	(3.0)	0	(0.0)
Dermatitis	0	(0.0)	2	(3.1)
Rash	3	(4.5)	2	(3.1)
Vision Disorders	**3**	**(4.5)**	**0**	**(0.0)**
White Cell and Resistance Disorders	**2**	**(3.0)**	**0**	**(0.0)**
Lymphadenopathy	2	(3.0)	0	(0.0)

Clinical adverse experiences were coded to body system categories from the WHO dictionary. The most common adverse experiences were upper respiratory tract infection, headache, accidental trauma, influenza-like symptoms, pharyngitis, and abdominal pain.

Assessor's comment: during the 48 weeks of double blind phase, the number of treatment emergent AEs were similar in both lovastatin (70.1%) and in placebo (75.4 %) groups. The most common adverse experiences were upper respiratory tract infection, headache, accidental trauma, myalgia, influenza-like symptoms, pharyngitis, and abdominal pain. However they are mostly common childhood diseases and their incidences were comparable to the placebo group.

Vision disorder (n=3), lymphadenopathy (n=2) and insomnia (n=1) were reported in lovastatin group only. Whilst lymphadenopathy could probably be confounded by other infections, 3 cases of vision disorder should be addressed by the applicant. The applicant should explain what type of vision disorder and if possible compare the frequency of its occurrence between children and adults.

One patient in the lovastatin group had a serious clinical adverse experience consisting of right wrist and left elbow fractures, that probably is not drug related. There were no deaths reported.

The number (percent) of patients with 1 or more clinical adverse experiences that were determined to be drug related by the investigator is in Table 11 by body system. Although a greater number of patients in the placebo group had drug-related adverse experiences, the difference between the 2 treatment groups was not clinically meaningful.

Table 11- Number (%) of Patients with Drug-Related Specific Clinical Adverse Experiences by Body System

	Lovastatin (N=67)		Placebo (N=65)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences	1	(1.5)	6	(9.2)
Patients with no drug-related adverse experience	66	(98.5)	59	(90.8)
Body as a Whole—General Disorders	**0**	**(0.0)**	**1**	**(1.5)**
Allergy	0	(0.0)	1	(1.5)
Gastrointestinal System Disorders	**0**	**(0.0)**	**3**	**(4.6)**
Abdominal pain	0	(0.0)	1	(1.5)
Diarrhea	0	(0.0)	1	(1.5)
Flatulence	0	(0.0)	1	(1.5)
Psychiatric Disorders	**1**	**(1.5)**	**0**	**(0.0)**
Insomnia	1	(1.5)	0	(0.0)
Respiratory System Disorders	**0**	**(0.0)**	**1**	**(1.5)**
Upper respiratory tract infection	0	(0.0)	1	(1.5)
Skin and Appendages Disorders	**0**	**(0.0)**	**2**	**(3.1)**
Dermatitis	0	(0.0)	1	(1.5)
Rash	0	(0.0)	1	(1.5)

Discontinuation

- One patient in the lovastatin group discontinued therapy due to the clinical adverse experiences of petechiae and purpura during the active-treatment phase.
- One patient discontinued due to a respiratory allergy.

- One patient in the placebo group discontinued study medication due to soreness of arm and leg muscles.

Assessor's comment: of the 7 clinical adverse events that were determined by the investigators to be drug related, 6 occurred in the placebo group and 1 in the lovastatin group. The 6 Adverse events in placebo group were allergy, abdominal pain, diarrhoea, flatulence, upper respiratory infection, dermatitis and rash. All of which are common childhood ailments.

One patient in the lovastatin group experienced insomnia, which is a known adverse event associated with lovastatin in adults.

The discontinuations are rather unremarkable. 1 patient in the lovastatin group had a serious clinical adverse experience consisting of right wrist and left elbow fractures, that probably is not drug related. There were no deaths reported.

Overall, the majority of TEAEs in both cohorts were of mild or moderate intensity.

Laboratory Adverse Experiences

The number and percentage of patients with laboratory adverse experiences by laboratory test category is in Table 12 below. Laboratory adverse experiences were coded to laboratory test categories from the WHO dictionary.

Table 12- Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category

	Lovastatin (N=67)		Placebo (N=65)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	4	(6.0)	6	(9.2)
Patients with no adverse experience	63	(94.0)	59	(90.8)
Metabolic and Nutritional Disorders	**3**	**(4.5)**	**2**	**(3.1)**
Creatine kinase increased	3	(4.5)	2	(3.1)
Liver and Biliary System Disorders	**1**	**(1.5)**	**2**	**(3.1)**
Aspartate aminotransferase increased	1	(1.5)	1	(1.5)
Alanine aminotransferase increased	0	(0.0)	1	(1.5)
Bilirubinemia	0	(0.0)	1	(1.5)
Hepatic function abnormal	1	(1.5)	0	(0.0)
Platelet, Bleeding and Clotting Disorders	**0**	**(0.0)**	**1**	**(1.5)**
Thrombocythemia	0	(0.0)	1	(1.5)
Red Blood Cell Disorders	**0**	**(0.0)**	**1**	**(1.5)**
Anemia	0	(0.0)	1	(1.5)
White Cell and Resistance Disorders	**1**	**(1.5)**	**2**	**(3.1)**
Eosinophilia	0	(0.0)	1	(1.5)
Leucopenia	1	(1.5)	1	(1.5)

Serious Laboratory Adverse Experiences & Patient Discontinuation

During the active-treatment phase, 1 patient on placebo had a serious laboratory adverse experience consisting of elevated ALT levels. There were no patients discontinued from therapy due to laboratory adverse experiences.

Assessor's comment: during the 48 weeks of double blind phase, the number of laboratory AEs was similar in both lovastatin (6 %) and in placebo (9.2 %) groups. The most common

laboratory adverse experiences were CK raised (n=3), AST raised (n=1), abnormal hepatic function (n=1) and Leucopoenia (n=1). However these laboratory changes also occurred in the placebo group and their incidences were comparable to the placebo group.

Changes in Growth and Development

Testicular volume: at Week 48, mean testicular volume had increased by 3.4 cm3 ($p<0.001$) in the lovastatin group and by 2.5 cm3 ($p<0.001$) in the placebo group. The between-group difference approached statistical significance ($p=0.074$).

Weight: at Week 48, mean weight had increased by 5.4 kg ($p<0.001$) in the lovastatin group and by 5.2 kg ($p<0.001$) in the placebo group. The between-group difference was not significant ($p=0.820$).

Height: at Week 48, mean height had increased by 5.3 cm ($p<0.001$) in the lovastatin group and by 4.7 cm ($p<0.001$) in the placebo group. The between-group difference was not significant ($p=0.325$).

Body Mass index: at Week 48, mean BMI had increased by 0.7 kg/m2 ($p<0.001$) in the lovastatin group and by 0.9 kg/m2 ($p<0.001$) in the placebo group. The between-group difference was not significant ($p=0.673$).

The number of patients from each treatment group who changed Tanner stage over the course of the study, as measured at Weeks 24 and 48, was similar between treatment groups.

Assessor's comment: in this patient population growth would be expected during the 48 weeks course of the study. It is very difficult comparing growth rates because the magnitude of the pubertal growth spurt varies depending on the timing of the onset of puberty. With small sample sizes, it is quite possible to introduce potential bias in either direction with respect to growth; either concluding that there is no effect or that there is a disadvantage. The data provided for testicular volume, weight, height and BMI measurements, do not allow any firm conclusions in this small sample size.

Endocrine Function Safety Endpoints

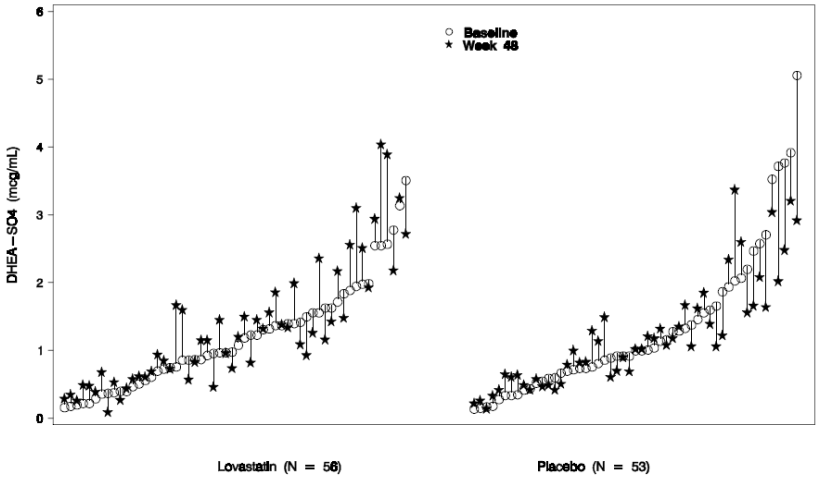
Testosterone: at Week 48, median testosterone had increased by 28.0% ($p<0.001$) in the lovastatin group and by 39.3% ($p<0.001$) in the placebo group. The between-group difference was not significant ($p=0.674$).

Cortisol: At Week 48, median cortisol was reduced by 0.9% ($p=0.316$) in the lovastatin group and by 8.3% ($p=0.466$) in the placebo group. The between-group difference was not significant ($p=0.752$).

Other endocrine parameters: Safety analysis included change from baseline at Week 48 in DHEA-SO4, FSH, LH, T3 resin uptake, TSH, and thyroxine.

For all endocrine parameters other than DHEA-SO_4, there were no significant between-group differences in mean change from baseline at Week 48. At Week 48, mean DHEA-SO_4 increased by 0.14 mcg/mL (p=0.021) in the lovastatin group and was reduced by 0.10 mcg/mL (p=0.194) in the placebo group. The between-group difference was significant (p=0.013). The individual plot of DHEA-SO_4 over time is in shown in figure 1 below.

Figure 1- Individual plot of DHEA-SO4 over time



For the remaining endocrine parameters (FSH, LH, T3 resin uptake, TSH, and Thyroxine), the results at Week 48 of the PP analyses were similar to the results of the ITT analyses. However, for T3 resin uptake, there was a significant between-group difference in the PP analysis (p=0.046).

Assessors comment: at Week 48, mean DHEA-SO4 increased by 0.14 mcg/mL (p=0.021) in the lovastatin group and was reduced by 0.10 mcg/mL (p=0.194) in the placebo group. The between-group difference was significant (p=0.013). That the placebo group did not show this increase, is perhaps more of an issue than the increase observed in boys receiving Lovastatin. With respect to DHEAS itself, it is important to realise that it is an inert compound. Sulfation of DHEA renders DHEA inactive, so the rise in concentration would not necessarily reflect an adverse effect. Sulfation of DHEA largely takes place in the liver and it is possible that the lovastatin influences this particular process.

Liver Function Tests

Table 13- Analysis of Change From Baseline in Liver Function Tests and Creatine Kinase Levels at Weeks 24 and 48

	Week 24		Week 48	
	Lovastatin	Placebo	Lovastatin	Placebo
N	64	61	64	61
Alanine Aminotransferase (mIU/mL)				
Baseline				
Median	9.00	9.00	9.00	9.00
SD†	3.72	3.72	3.72	3.72
Endpoint				
Median	12.00	11.00	13.00	10.00
SD†	4.65	4.65	6.51	4.65
Change				
Median	2.00	1.00	2.50	1.00
SD†	5.58	3.72	5.12	4.65
95% CI‡	(0.61, 3.39)	(0.05, 1.95)	(1.22, 3.78)	(-0.19, 2.19)
p-Value	0.009	0.001	<0.001	0.030
Between-treatment p-value	0.933		0.040	
Aspartate Aminotransferase (mIU/mL)				
Baseline				
Median	17.00	17.00	17.00	17.00
SD†	6.05	4.65	6.05	4.65
Endpoint				
Median	17.00	17.00	17.00	17.00
SD†	4.19	3.72	4.65	4.65
Change				
Median	0.00	0.00	0.00	-1.00
SD†	3.72	4.65	4.65	2.79
95% CI‡	(-0.93, 0.93)	(-1.19, 1.19)	(-1.16, 1.16)	(-1.71, -0.29)
p-Value	0.868	0.678	0.917	0.092
Between-treatment p-value	0.566		0.214	
Creatine Kinase (mIU/mL)				
Baseline				
Median	74.00	74.00	74.00	74.00
SD†	38.60	41.86	38.60	41.86
Endpoint				
Median	78.00	80.00	86.50	82.00
SD†	27.91	46.51	38.60	42.79
Change				
Median	-2.00	8.00	-2.00	5.00
SD†	40.93	37.21	32.09	36.28
95% CI‡	(-12.22, 8.22)	(-1.53, 17.53)	(-10.02, 6.02)	(-4.29, 14.29)
p-Value	0.717	0.134	0.887	0.140
Between-treatment p-value	0.125		0.336	

At Week 48, median ALT had increased by 2.50 mIU/mL (p<0.001) in the lovastatin group and by 1.00 mIU/mL (p=0.030) in the placebo group. The between-group difference was significant (p=0.040). At Week 48, median AST was unchanged (p=0.917) in the lovastatin group and had been reduced by 1.00 mIU/mL (p=0.092) in the placebo group. The between-group difference was not significant (p=0.214). No patients from the lovastatin group had increases in ALT or AST (consecutive >3 x ULN).

At Week 48, median CK was reduced by 2.00 mIU/mL (p=0.887) in the lovastatin group and increased by 5.00 mIU/mL (p=0.140) in the placebo group. The between-group difference was not significant (p=0.336). No patients in the study had myopathy (defined as an unexplained muscle pain or weakness accompanied by elevations in CK to >10 x ULN).

Assessor's comment: the increase in ALT was not consecutively 3 times higher than ULN in any individual patient, but the median ALT has increased by 2.50 mIU/mL (p<0.001) in the lovastatin group. The ALT levels in the lovastatin group are also significantly higher compared to baseline (p<0.001). Although liver enzyme elevation is a well known adverse event associated with the statins, the applicant must provide a quantitative, tabulated comparison with the ALT rise in adult studies, with the view of capturing the possible differences in the section 4.8 of the SmPC.
The CK and AST were not significantly altered after 48 week of lovastatin treatment compared with both placebo and base line levels.

Serum Nutritional Parameters

Safety analysis included median change from baseline in serum nutritional parameters at Week 48. The results from these nonparametric analyses are in Table 14.

Table 14- Analysis of Change From Baseline in Serum Nutritional Parameters at Week 48

Parameter (Unit) /Treatment Group	N	Baseline Median	Baseline SD†	Week 48 Median	Week 48 SD†	Change Median	Change SD†	Change 95% CI‡	p-Value	Treatment p-Value
25 Hydroxyvitamin D (ng/mL)										0.234
Lovastatin	62	27.00	13.02	25.50	10.23	-1.50	11.16	(-4.33, 1.33)	0.509	
Placebo	56	28.50	12.09	31.00	12.56	0.50	7.91	(-1.62, 2.62)	0.339	
Albumin (g/dL)										0.550
Lovastatin	63	4.50	0.37	4.50	0.37	0.00	0.37	(-0.09, 0.09)	0.724	
Placebo	61	4.50	0.28	4.60	0.37	0.00	0.37	(-0.10, 0.10)	0.539	
Alpha-Carotene (mcg/mL)										0.049
Lovastatin	58	0.05	0.05	0.04	0.03	-0.01	0.05	(-0.02, 0.00)	0.006	
Placebo	51	0.05	0.04	0.04	0.05	-0.00	0.04	(-0.02, 0.01)	0.705	
Alpha-Tocopherol (mg/dL)										0.003
Lovastatin	63	1.42	0.34	1.10	0.33	-0.29	0.37	(-0.38, -0.20)	<0.001	
Placebo	58	1.37	0.44	1.28	0.49	-0.11	0.41	(-0.22, -0.00)	0.040	
Beta-Carotene (mcg/mL)										0.618
Lovastatin	63	0.21	0.16	0.17	0.13	-0.03	0.15	(-0.07, 0.01)	0.068	
Placebo	58	0.19	0.20	0.20	0.14	-0.02	0.10	(-0.04, 0.01)	0.320	
Ferritin (ng/mL)										0.664
Lovastatin	57	21.00	15.81	23.00	13.02	-1.00	9.30	(-3.47, 1.47)	0.287	
Placebo	55	30.00	21.40	24.00	18.60	0.00	13.02	(-3.52, 3.52)	0.261	
Gamma-Tocopherol (mg/dL)										0.106
Lovastatin	63	0.29	0.15	0.25	0.14	-0.04	0.14	(-0.08, -0.00)	0.001	
Placebo	58	0.28	0.11	0.26	0.13	-0.01	0.09	(-0.03, 0.01)	0.385	
Glucose (mg/dL)										0.131
Lovastatin	64	87.00	12.09	90.00	10.23	1.00	11.16	(-1.79, 3.79)	0.162	
Placebo	61	88.00	8.37	88.00	8.37	-1.00	12.09	(-4.10, 2.10)	0.562	
Lycopene (mcg/mL)										0.362
Lovastatin	63	0.75	0.33	0.71	0.46	-0.08	0.45	(-0.19, 0.04)	0.203	
Placebo	57	0.76	0.39	0.76	0.33	0.05	0.29	(-0.03, 0.13)	0.701	
Retinol (mcg/dL)										0.659
Lovastatin	63	47.00	14.88	43.00	11.08	-2.00	12.09	(-5.05, 1.05)	0.146	
Placebo	58	46.00	14.88	45.00	13.02	-1.50	12.09	(-4.68, 1.68)	0.410	

At week 48, median alpha-carotene (vitamin A) was reduced by 0.01 mcg/mL (p=0.006) in the lovastatin group and unchanged (-0.00 mcg/mL, p=0.705) in the placebo group. The between-group difference was significant (p=0.049). At Week 48, median alpha-tocopherol (vitamin E) was reduced by 0.29 mg/dL (p<0.001) in the lovastatin group and by 0.11 mg/dL (p=0.040) in the placebo group. The between-group difference was significant (p=0.003). Additionally, at Week 48, median gamma-tocopherol was reduced by 0.04 mg/dL (p=0.001) in the lovastatin group and by 0.01 mg/dL (p=0.385) in the placebo group. The between-group difference was not significant (p=0.106).

For the remaining nutritional parameters (25-hydroxyvitamin D, albumin, beta-carotene, ferritin, glucose, lycopene, retinol, and total protein), there were changes from baseline at Week 48, but there were no significant within- or between-group differences in these changes.

Assessor's comment: changes in alpha carotene, and vitamin E metabolite were noted on Lovastatin treatment. Of all the nutritional values tested, alpha-carotene, alpha-tocopherol, gamma-tocopherol levels were significantly reduced after 48 weeks of lovastatin treatment. The reduction in tocopherol levels in the lovastatin group was approximately 20%, which was in proportion to the reduction in LDL-C. These fat-soluble vitamins are carried in LDL particles, and

reductions of this magnitude are expected when LDL-C levels are reduced.

Other Serum Chemistry Parameters
The parameters with the largest percentage of patients from both treatment groups experiencing either a predefined increase or decrease were alkaline phosphatase, calcium, CK cardiac isoenzyme, creatinine, phosphorous, potassium, and total bilirubin. There were no significant between-group differences for any of these serum chemistry parameters.

Coagulation and Hematology Parameters
The parameters with the largest percentage of patients from both treatment groups experiencing either a predefined increase or decrease were basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelet count, PTT, RBC, and WBC. There were no significant between-group differences for any of these coagulation or hematology parameters.

Clinical Safety Measurements
Pulse systolic and diastolic blood pressures were not significantly between groups after 48 weeks of lovastatin treatment. There were no patients with a worsening visual acuity grade of 2 or more.

2.2. Study P040X: An Open, Multicenter, Extension Study of Lovastatin as an Adjunct to Diet in the Treatment of Adolescent Males With Hypercholesterolemia of Familial Basis.

- **Description**

This is a 2-year, open-label extension study in which **57** adolescent males 10-17 years old who completed the base study (P040) without any serious drug-related adverse experiences were treated with lovastatin.

- **Methods**

In Oct-1992, the FDA requested that treatment be stopped immediately on all patients who had entered the extension, as well as those patients below Tanner Stage II who were randomized into the 1-year base study. This resulted in discontinuation of most of the patients prior to completion of the full two years of the extension study.

Assessor's comment: the applicant should state the reason for FDA request for immediate discontinuation of the study.

- Objective(s)

To evaluate the long-term efficacy and safety of lovastatin treatment plus a lipid-lowering diet, in adolescent males with familial hypercholesterolemia.

- Study design

This was a 2-year, open-label extension study in which adolescent males who completed the base study (P040) without any serious drug-related adverse experiences were treated with lovastatin.

All patients continued to follow the AHA Dietary Guidelines for Children, as in the base study. All patients received open label treatment with lovastatin for up to 2 years at the lowest dosage (10, 20, or 40 mg/day) required to maintain their LDL-C ≥130 mg/dL (the 95th percentile for their age). The randomization code was broken for each patient at Week 48 (the last visit of the base study and the first visit of the extension study). Patients randomized to the lovastatin group in the base study continued on 40 mg/day of lovastatin if their average LDL-C remained >130 mg/dL the dose was down titrated to 20 and 10 mg accordingly. Patients randomized to the placebo group in the base study received 10 mg/day of lovastatin, the dose was subsequently increased to 20 or 40 mg/day if LDL-C remained above 130 mg/dL. Table 15 below summarizes the Schedule of Clinical Observations and Laboratory Measurements.

Table 15- Schedule of Clinical Observations and Laboratory Measurements

	← Year 1 Period →						← Year 2 Period →				
	Week						Month				
Week/Month:	48†	54	60	66	72	84	24‡	27	30	33	36
Hematology	X				X		X		X		X
Urinalysis	X				X		X		X		X
Serum chemistry 1	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry 2	X		X		X	X	X	X	X	X	X
Serum chemistry 3	X				X		X		X		X
Thyroid function tests	X						X				X
Lipid profile: partial		X	X	X		X		X		X	
Lipid profile: complete	X				X		X		X		X
Physical examination§	X				X		X		X		X
Height measurement	X				X		X		X		X
Plot height and weight on growth curve	X				X		X		X		X
Ophthalmologic examination	X						X				X
Electrocardiogram	X						X				X
Dietary review: qualitative			X			X		X		X	
Dietary review: quantitative	X				X		X		X		X
Three-day dietary record given to patient				X		X		X		X	

† Week 48 of the extension is the same visit as Week 48 of the base study.
‡ Month 24 is the same as Week 96, the last visit of the first period of the extension study.
§ Included vital signs, height, weight, assessment of pubertal development (Tanner staging), and testicular volume.

Efficacy measurements:
Blood was drawn at Weeks 48, 54, 60, 66, 72, and 84, and at Months 24, 27, 30, 33, and 36 for the analysis of lipids and lipoproteins. The lipid parameters LDL-C, total-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured at each visit. The lipoprotein parameters apo B, apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), and lipoprotein (a) (Lp (a)) were measured at Weeks 48 and 72, and at Months 24, 30, and 36.

Safety Measurements:
The effects of lovastatin on endocrine function, thyroid function test, liver function tests, creatine kinase, serum chemistry, vital signs, and nutritional parameters were assessed by comparing mean changes (or mean percent changes) from baseline at Week 48 and Months 24 and 36 for both treatment groups. The frequency of clinical and laboratory adverse experiences is listed by body system for both treatment groups. In addition, analyses of predefined limits of change in serum chemistry and hematology parameters were performed for both treatment groups.

- Study population /Sample size

57 Patients were carried over to the open label phase, upon completion of the one-year base study without serious drug-related clinical or laboratory adverse experiences.

- Treatments

One lovastatin (10, 20, or 40 mg) tablet was taken once daily immediately before the evening meal.

At the time of the Month 24 lipid measurement, no patients in the lovastatin/lovastatin group and 3 patients (12.0%) in the placebo/lovastatin group were taking lovastatin at 10 mg/day, one patient (3.0%) in the lovastatin/lovastatin group and 4 patients (16.0%) in the placebo/lovastatin group were taking 20 mg/day, and 31 patients (97%) in the lovastatin/lovastatin group and 18 patients (72%) in the placebo/lovastatin group were taking 40 mg/day.

At the time of the Month 36 lipid measurement, no patients from either treatment group were taking lovastatin at 10 mg/day, one patient (8.0%) in the lovastatin/lovastatin group and no patients in the placebo/lovastatin group were taking 20 mg/day, and 11 patients (92.0%) in the lovastatin/lovastatin group and 13 patients (100.0%) in the placebo/lovastatin group were taking 40 mg/day.

- Outcomes/endpoints

- The primary efficacy endpoint was the percent changes from baseline in LDL-C at Months 24 and 36. For LDL-C, summary statistics of the percent change from baseline (mean of Week -2 and Week 0 of the base study) at Months 24 and 36 by baseline Tanner stage were also determined.

- The Secondary efficacy endpoints were the percent changes from baseline (mean of Week -2 and Week 0 of the base study) in total-C, HDL-C, TG, apo B, apo A-I, apo A-II, and Lp (a) at Months 24 and 36.

- The primary safety measures were evaluated by assessing the occurrence and frequency of adverse experiences, and changes in growth, sexual development, vital signs, physical examinations, and laboratory values.

- Statistical Methods

Efficacy: For the lipid parameters LDL-C, total-C, HDL-C, TG, apo B, apo A-I, apo A-II, and Lp (a), a paired t-test was used to compare the mean percent change from baseline (i.e., average of Week -2 and Week 0 values from the base study) within each treatment group at Months 24 and 36. Each lipid parameter was tested for normality using the Shapiro-Wilk test. If a parameter was found to be not normally distributed, a Wilcoxon signed-rank test was applied to that lipid parameter instead of a t-test and median values were reported.

Safety: The effects of lovastatin on growth factors, endocrine function, liver function tests, creatine kinase, vital signs, and nutritional parameters were assessed by comparing mean changes (or mean percent changes) from baseline at Week 48 and Months 24 and 36 for both treatment groups. The frequency of clinical and laboratory adverse experiences is listed by body system for both treatment groups. In addition, analyses of predefined limits of change in serum chemistry and hematology parameters were performed for both treatment groups.

Assessor's comment: no detail regarding the statistical tests carried out in the safety population has been provided.

Results

- Recruitment/ Number analysed

Of the 57 patients entered in the Week 48-to-Month 24 period, 27 (47.4%) completed this first one-year period, including 13 patients in the lovastatin/lovastatin group and 14 patients in the placebo/lovastatin group. The reasons for discontinuation are captured in table 16 below:

Table 16- Patient Accounting by Study Period and Treatment Group

	Treatment Group (Base/Extension)		
	Lovastatin/Lovastatin	Placebo/Lovastatin	Total
Week 48 to Month 24			
ENTERED: (age range)†	32 (10 to 17)	25 (10 to 17)	57 (10 to 17)
COMPLETED:	13	14	27
DISCONTINUED:			
Clinical adverse experience	0	0	0
Laboratory adverse experience	0	0	0
Deviation from protocol	0	0	0
Lost to follow-up	1	1	2
FDA request	18	10	28
Month 24 to Month 36			
ENTERED: (age range)†	12 (11 to 16)	13 (10 to 15)	25 (10 to 16)
COMPLETED:	0	0	0
DISCONTINUED:			
Clinical adverse experience	0	0	0
Laboratory adverse experience	0	0	0
Deviation from protocol	0	0	0
Lost to follow-up	1	0	1
FDA request	11	13	24

† All patients were male. Reported age was the age of the patient at screening.

In Oct-1992, the FDA requested that treatment be stopped immediately on all patients who had entered the extension, as well as those patients below Tanner Stage II who were randomized into the 1-year base study. This resulted in discontinuation of most of the patients prior to completion of the full two years of the extension study. There seem to be 5 patients with missing source data.

Assessor's comment: the applicant should provide the reasons for which the FDA requested that treatment be stopped immediately on all patients who had entered the extension, as well as those patients below Tanner Stage II who were randomized into the 1-year base study.

As with the missing 17 source documents in the base study (P040), the applicant needs to provide further information about the 5 patients with missing source data in the extension study.

- Baseline data

A summary of baseline data by treatment group for age, race, height, weight, BMI, and smoking status is in Table 17 below. There were no clinically meaningful differences between treatment groups for these characteristics.

Table 17 - Baseline Patient Characteristics by Treatment Group

	Treatment Group (Base/Extension)					
	Lovastatin/Lovastatin (N=32)		Placebo/Lovastatin (N=25)		Total (N=57)	
	n	(%)	n	(%)	n	(%)
Race						
Caucasian	28	(87.5)	24	(96.0)	52	(91.2)
Black	2	(6.3)	1	(4.0)	3	(5.3)
Other	2	(6.3)	0	(0.0)	2	(3.5)
Age (Years)						
N	32		25		57	
Mean	13.4		12.8		13.2	
SD	2.3		2.0		2.2	
Median	13.5		13.0		13.0	
Range	10 to 17		10 to 17		10 to 17	
Height (cm)						
N	32		25		57	
Mean	160.6		157.6		159.3	
SD	12.8		11.2		12.1	
Median	160.4		153.7		160.0	
Range	140 to 182		141 to 178		140 to 182	
Weight (kg)						
N	32		25		57	
Mean	56.0		52.1		54.3	
SD	16.5		14.2		15.5	
Median	54.9		54.3		54.3	
Range	35 to 103		33 to 88		33 to 103	
Body Mass Index (kg/m^2)						
N	32		25		57	
Mean	21.4		20.7		21.1	
SD	4.2		3.4		3.9	
Median	19.9		20.3		20.2	
Range	16 to 34		16 to 28		16 to 34	
Smoking Status						
Yes	2	(6.3)	1	(4.0)	3	(5.3)
No	30	(93.8)	24	(96.0)	54	(94.7)

Risk factors for CHD including smoking, drinking, xanthomas, mother/father with Xanthomas, mother/father with Corneal Arcus, Heterozygous Familial Hypercholesterolemia, Familial Combined Hyperlipidemia and mother/father with LDL Cholesterol $\geq$190 mg/dL were analysed. There were no clinically meaningful differences between treatment groups for these risk factors.

- Efficacy results

Primary end point

The primary analyses of the extension study were the percent change from baseline in LDL-C at Months 24 and 36. The results of these parametric analyses are in Table 18 below.

Table 18- Analysis of Percent Change From Baseline in LDL Cholesterol at Months 24 and 36

LDL Cholesterol (mg/dL)	Month 24 Treatment Group (Base/Extension)		Month 36 Treatment Group (Base/Extension)	
	Lovastatin/Lovastatin	Placebo/Lovastatin	Lovastatin/Lovastatin	Placebo/Lovastatin
N	32	25	12	13
Baseline				
Mean	256.2	256.3	248.8	260.2
SD†	38.2	57.8	35.8	66.9
Endpoint				
Mean	185.7	193.3	188.0	183.1
SD†	41.5	59.4	38.5	48.4
Percent Change				
Mean	-27.1	-24.4	-24.7	-29.3
SD†	14.0	16.6	10.1	13.0
95% CI‡	(-32.2, -22.1)	(-31.3, -17.5)	(-31.1, -18.2)	(-37.1, -21.5)
p-Value	<0.001	<0.001	<0.001	<0.001

At Month 36, mean LDL-C was reduced by 24.7% (p<0.001) in the lovastatin/lovastatin group and by 29.3% (p<0.001) in the placebo/lovastatin group compared with baseline values. Similar analyses of percent reduction in LDL-C at Months 24 and 36, excluding the 5 patients with missing source documents, yielded similar results.

Assessor's comment: the LDL concentration was reduced by approximately 60-77 mg/dl after 2 or 3 years of lovastatin treatment. This reduction is both statistically significant and clinically meaningful compared with the baseline LDL concentration. The primary objective has been reached.

At the time of the 2nd and 3rd year lipid measurements, most patients in both lovastatin/lovastatin group and placebo/lovastatin groups were taking 40 mg/day.

Percent Change in LDL Cholesterol by Tanner Stage

Comparisons of mean percent change in LDL-C were made by baseline Tanner stage using the ITT approach. Summary statistics of percent change from baseline in LDL-C at Months 24 and 36 for each baseline Tanner stage are in tables 19 and 20, respectively.

Table 19- Percent Change From Baseline in LDL Cholesterol at Months 24 by baseline Tanner stage

Baseline Tanner Stage/ Treatment Group (Base/Ext)	N	Baseline Mean	Baseline SD	Baseline Median	Month 24 Mean	Month 24 SD	Month 24 Median	Percent Change Mean	Percent Change SD	Percent Change Median
I										
Lovastatin/Lovastatin	1	263.0	.	263.0	152.0	.	152.0	-42.2	.	-42.2
Placebo/Lovastatin	5	220.7	51.8	203.5	168.2	46.6	179.0	-23.1	20.4	-31.7
II										
Lovastatin/Lovastatin	12	263.0	34.6	260.3	186.2	43.9	172.0	-29.1	14.1	-28.5
Placebo/Lovastatin	10	271.5	66.1	250.8	182.3	47.9	183.0	-32.5	11.2	-32.5
III										
Lovastatin/Lovastatin	5	243.0	34.5	248.0	194.8	62.4	202.0	-20.9	18.0	-22.8
Placebo/Lovastatin	1	212.0	.	212.0	157.0	.	157.0	-25.9	.	-25.9
IV										
Lovastatin/Lovastatin	12	255.6	48.2	245.8	185.4	36.7	179.0	-26.4	13.7	-27.7
Placebo/Lovastatin	9	264.1	48.7	251.0	223.4	72.1	189.0	-16.0	17.9	-18.4
V										
Lovastatin/Lovastatin	2	248.8	15.2	248.8	179.0	8.5	179.0	-27.8	7.8	-27.8
Placebo/Lovastatin	0	.	.	.	.	.	.	.	.	.

Table 20- Percent Change From Baseline in LDL Cholesterol at Month 36 by base line Tanner stage

Baseline Tanner Stage/ Treatment Group (Base/Ext)	N	Baseline Mean	Baseline SD	Baseline Median	Month 36 Mean	Month 36 SD	Month 36 Median	Percent Change Mean	Percent Change SD	Percent Change Median
I										
Lovastatin/Lovastatin	0	.	.	.	.	.	.	.	.	.
Placebo/Lovastatin	3	235.3	67.3	263.5	159.3	61.0	192.0	-33.8	9.4	-32.4
II										
Lovastatin/Lovastatin	6	248.5	31.6	246.8	188.5	24.6	196.5	-23.7	9.8	-24.3
Placebo/Lovastatin	8	276.7	73.9	257.0	190.1	50.4	198.5	-30.4	14.6	-28.6
III										
Lovastatin/Lovastatin	2	211.8	32.9	211.8	150.0	52.3	150.0	-30.2	13.9	-30.2
Placebo/Lovastatin	1	212.0	.	212.0	172.0	.	172.0	-18.9	.	-18.9
IV										
Lovastatin/Lovastatin	3	270.7	43.4	250.0	205.3	56.0	204.0	-24.6	13.4	-18.3
Placebo/Lovastatin	1	251.0	.	251.0	209.0	.	209.0	-16.7	.	-16.7
V										
Lovastatin/Lovastatin	1	259.5	.	259.5	209.0	.	209.0	-19.5	.	-19.5
Placebo/Lovastatin	0	.	.	.	.	.	.	.	.	.

These results indicate that baseline Tanner stage was not a factor that influenced LDL-C reduction. However, these results should be interpreted in the context of the small sample size of each subgroup.

Secondary Efficacy

Total Cholesterol

Efficacy analyses included the percent change from baseline in total-C at Months 24 and 36. The results of these parametric analyses are in Table 21 below.

Table 21- Analysis of Percent Change from Baseline in Total Cholesterol at Months 24 and 36

Total Cholesterol (mg/dL)	Month 24 Treatment Group (Base/Extension)		Month 36 Treatment Group (Base/Extension)	
	Lovastatin/Lovastatin	Placebo/Lovastatin	Lovastatin/Lovastatin	Placebo/Lovastatin
N	32	25	12	13
Baseline				
Mean	322.6	321.4	313.3	327.1
SD†	42.3	57.7	36.2	65.6
Endpoint				
Mean	250.9	261.0	251.8	247.3
SD†	43.9	65.1	42.9	45.3
Percent Change				
Mean	-21.8	-18.6	-19.7	-23.7
SD†	11.7	14.7	9.3	10.7
95% CI‡	(-26.1, -17.6)	(-24.7, -12.5)	(-25.6, -13.9)	(-30.2, -17.2)
p-Value	<0.001	<0.001	<0.001	<0.001

At Month 24, mean total-C was reduced by 21.8% ($p<0.001$) in the lovastatin/lovastatin group and by 18.6% ($p<0.001$) in the placebo/lovastatin group compared with baseline values.

At Month 36, mean total-C was reduced by 19.7% ($p<0.001$) in the lovastatin/lovastatin group and by 23.7% ($p<0.001$) in the placebo/lovastatin group compared with baseline values.

Similar analyses of percent reduction in total-C at Months 24 and 36, excluding the 5 patients with missing source documents, yielded similar results.

Assessor's comment: the total cholesterol concentration was reduced by approximately 60-80mg/dl after 2 and 3 years of lovastatin treatment. This reduction is both statistically significant and clinically meaningful compared with the baseline Total cholesterol concentration.

HDL Cholesterol

Efficacy analyses included the percent change from baseline in HDL-C at Months 24 and 36. The results of these parametric analyses are in Table 22 below.

Table 22- Analysis of Percent Change From Baseline in HDL Cholesterol at Months 24 and 36

HDL Cholesterol (mg/dL)	Month 24 Treatment Group (Base/Extension)		Month 36 Treatment Group (Base/Extension)	
	Lovastatin/Lovastatin	Placebo/Lovastatin	Lovastatin/Lovastatin	Placebo/Lovastatin
N	32	25	12	13
Baseline				
Mean	43.4	45.7	41.9	48.6
SD†	10.2	8.5	5.4	7.8
Endpoint				
Mean	42.2	43.4	40.3	45.5
SD†	7.3	8.4	8.4	8.7
Percent Change				
Mean	-0.5	-4.5	-3.7	-6.5
SD†	16.5	11.7	16.7	7.2
95% CI‡	(-6.5, 5.4)	(-9.3, 0.3)	(-14.3, 7.0)	(-10.9, -2.1)
p-Value	0.853	0.067	0.465	0.007

At Month 36, mean HDL-C was statistically significantly reduced by 6.5% (p=0.007) in the placebo/lovastatin group compared with baseline values.

Triglycerides

Efficacy analyses included the percent change from baseline in TG at Months 24 and 36. At Month 24 and 36 months median TG was slightly increased in both groups compared with baseline values. This increase was statistically non significant.

Apolipoprotein B

Efficacy analyses included the percent change from baseline in apo B at Months 24 and 36. The results of these parametric analyses are in Table 23 below.

Table 23- Analysis of Percent Change From Baseline in Apolipoprotein B at Months 24 and 36

Apolipoprotein B (mg/dL)	Month 24 Treatment Group (Base/Extension)		Month 36 Treatment Group (Base/Extension)	
	Lovastatin/Lovastatin	Placebo/Lovastatin	Lovastatin/Lovastatin	Placebo/Lovastatin
N	32	23	10	8
Baseline				
Mean	198.4	209.9	210.0	223.6
SD†	37.2	44.1	43.3	53.3
Endpoint				
Mean	154.7	158.8	156.2	150.0
SD†	32.7	44.5	26.0	44.7
Percent Change				
Mean	-21.2	-23.6	-23.9	-33.3
SD†	13.9	16.9	14.9	11.1
95% CI‡	(-26.2, -16.1)	(-31.0, -16.3)	(-34.6, -13.2)	(-42.5, -24.0)
p-Value	<0.001	<0.001	<0.001	<0.001

At Month 24, mean apo B was reduced by 21.2% (p<0.001) in the lovastatin/lovastatin group and by 23.6% (p<0.001) in the placebo/lovastatin group compared with baseline values. At Month 36, mean apo B was reduced by 23.9% (p<0.001) in the lovastatin/lovastatin group and by 33.3% (p<0.001) in the placebo/lovastatin group compared with baseline values.

Assessor's comment: the Apolipoprotein B concentration was reduced by approximately 44-73 mg/dl after 2 to 3 years of lovastatin treatment. This reduction is both statistically significant and clinically meaningful compared with the based line values in both groups.

Apolipoprotein A-I
Efficacy analyses included the percent change from baseline in Apolipoprotein A-I at Months 24 and 36. At Month 24 and 36 months median Apolipoprotein A-I was slightly reduced in both groups compared with baseline values. This reduction was statistically non significant.

Apolipoprotein A-II
Efficacy analyses included the percent change from baseline in Apolipoprotein A-II at Months 24 and 36. At Month 24 and 36 months median Apolipoprotein A-II was slightly reduced in both groups compared with baseline values. This reduction was statistically non significant.

Lipoprotein (a)
Efficacy analyses included the percent change from baseline in Lp (a) at Months 24 and 36. The results of these nonparametric analyses are in Table 27 below.
At Month 24, median Lp (a) was increased by 2.8% (p=0.126) in the lovastatin/lovastatin group and by 12.1% (p=0.045) in the placebo/lovastatin group compared with baseline values.

At Month 36, median Lp (a) was unchanged (p=0.688) in the lovastatin/lovastatin group and increased by 27.6% (p=0.016) in the placebo/lovastatin group compared with baseline values.

Table 24- Analysis of Percent Change From Baseline in Lipoprotein (a) at Months 24 and 36

Lipoprotein (a) (mg/dL)	Month 24		Month 36	
	Treatment Group (Base/Extension)		Treatment Group (Base/Extension)	
	Lovastatin/Lovastatin	Placebo/Lovastatin	Lovastatin/Lovastatin	Placebo/Lovastatin
N	32	22	10	8
Baseline				
Median	17.0	15.0	24.0	14.0
SD†	19.5	46.5	33.5	26.5
Endpoint				
Median	16.5	17.5	22.0	20.5
SD†	23.3	37.2	48.4	29.8
Percent Change				
Median	2.8	12.1	0.0	27.6
SD†	34.0	21.0	52.4	46.4
95% CI‡	(-9.5, 15.0)	(2.8, 21.4)	(-37.5, 37.5)	(-11.2, 66.3)
p-Value	0.126	0.045	0.688	0.016

Assessor's comment: analysis of other circulating lipid parameters showed that Total-C and Apo B concentration have been reduced significantly after 2 to 3 years of lovastatin treatment in both groups compared with the baseline values. This result ties in with the primary endpoint result of reduction in LDL-C. At month 36, mean HDL-C was statistically significantly reduced by 6.5% (p=0.007) in the placebo/lovastatin group compared with baseline values.

Triglycerides, Apolipoprotein A-I, Apolipoprotein A-II and Lipoprotein (a), concentration were not affected by lovastatin treatment and the values remained similar to that of baseline level.
Of note, the applicant states that: The analysis of percent change in total-C, HDL-C and Triglycerides at months 24 and 36, excluding the 5 patients with missing source documents, yielded similar results.

- **Safety results**

Adverse Events

The number and percentage of patients with the most common clinical adverse experiences are listed in Table 25 below.

Table 25- Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥5% in one or More Treatment Groups) by Body System

	Treatment Group (Base/Extension)			
	Lovastatin/Lovastatin (N=32)		Placebo/Lovastatin (N=25)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	22	(68.8)	12	(48.0)
Patients with no adverse experience	10	(31.3)	13	(52.0)
Body as a Whole—General Disorders	**12**	**(37.5)**	**5**	**(20.0)**
Accidental trauma	2	(6.3)	3	(12.0)
Allergy	3	(9.4)	0	(0.0)
Headache	4	(12.5)	1	(4.0)
Influenza-like symptoms	6	(18.8)	1	(4.0)
Gastrointestinal System Disorders	**5**	**(15.6)**	**1**	**(4.0)**
Dyspepsia	3	(9.4)	1	(4.0)
Musculoskeletal System Disorders	**2**	**(6.3)**	**2**	**(8.0)**
Myalgia	1	(3.1)	2	(8.0)
Psychiatric Disorders	**1**	**(3.1)**	**2**	**(8.0)**
Resistance Mechanism Disorders	**5**	**(15.6)**	**1**	**(4.0)**
Infection viral	2	(6.3)	0	(0.0)
Respiratory System Disorders	**7**	**(21.9)**	**6**	**(24.0)**
Pharyngitis	0	(0.0)	2	(8.0)
Rhinitis	2	(6.3)	2	(8.0)
Sinusitis	2	(6.3)	1	(4.0)
Upper respiratory tract infection	3	(9.4)	4	(16.0)
Skin and Appendages Disorders	**3**	**(9.4)**	**2**	**(8.0)**
Dermatitis contact	2	(6.3)	1	(4.0)

Although a patient may have had one or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Serious Clinical Adverse Experiences

During the extension study, 2 patients had serious clinical adverse experiences. One patient (3.1%) in the lovastatin/lovastatin group had a serious clinical adverse experience consisting of mononucleosis and one patient (4.0%) in the placebo/lovastatin group had a serious clinical adverse experience consisting of a psychiatric disorder resulting from a labile psychosocial situation. The investigator determined that the mononucleosis was definitely not drug related and that the psychiatric disorder was probably not drug related. Table 26 lists the patients with serious clinical adverse experiences and is followed by supporting narratives for each.

Table 26- Listing of Patients With Serious Clinical Adverse Experiences

AN†	Study Number	Race	Age‡	Daily Dose	Relative Day of Onset§	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Action Taken	Outcome
Lovastatin/Lovastatin Group											
111	040009	Caucasian	16	40 mg	72	Mononucleosis	64 days	Severe	Definitely not	None	No residual effect
Placebo/Lovastatin Group											
207	040011	Caucasian	10	40 mg	296	Psychiatric disorder	--	Moderate	Probably not	None	Still present

Assessor's comment: after the randomization code was broken at 48 weeks, the placebo patients were also put on lovastatin for the 2 year duration of the open label extension study. The comparison of adverse events between the lovastatin/lovastatin group of 3 years exposure versus the placebo/lovastatin group of 2 years exposure is meaningless.

The applicant must summarise the results of both groups together and present it in a tabulated format.

Assessment of Laboratory Adverse Experiences

Evaluations were based on varying treatment exposure (from 55 weeks to 33 months). Laboratory adverse experiences were coded to laboratory test categories from the WHO dictionary. There were no patients with serious laboratory adverse experiences or discontinued from therapy due to a laboratory adverse experience.

Changes in Growth and Development

Testicular Volume

Safety analyses included change from baseline in testicular volume at Week 48, Month 24, and Month 36. Both treatment groups had similar increases in testicular volume over time.

Weight, Height, Body mass index

Safety analyses included change from baseline in weight, height and body mass index at Week 48,Month 24, and Month 36.

The difference in mean height and BMI between the 2 groups was not clinically meaningful due to the low number of patients in each treatment group.

Tanner Stage

The number of patients from each treatment group who changed Tanner stage over the course of the study, as measured at Months 24 and 36, was similar between treatment groups.

Assessor's comment: after the randomization code was broken at 48 weeks, the placebo patients were also put on lovastatin for the 2 years duration of the open label study. Therefore the comparison of growth parameters of lovastatin/lovastatin versus placebo/lovastatin group is meaningless.

The applicant's argument that *"difference in mean height and BMI between the 2 groups was not clinically meaningful due to the low number of patients in each treatment group"*, may be correct, but does not rule out effect of lovastatin on growth.

The analysis of the probable effect of 36 months of lovastatin treatment on growth should be a comparison of the study group, with children the same age/gender/race unexposed to lovastatin.

Similarly the measurement of sexual maturation parameters ie Testicular Volume and Tanner stage also have to be compared with children the same age/gender/race unexposed to lovastatin.

Endocrine Function Safety Endpoints

Testosterone
Both treatment groups had increases in testosterone. Although the differences in median percent change observed between the 2 treatment groups appear large, they are not clinically meaningful.

Cortisol
Both treatment groups had increases in cortisol. Although the differences in median percent change observed between the 2 treatment groups appear large, they are not clinically meaningful.

Other Endocrine Function Parameters
Safety analyses included change from baseline at Week 48, Month 24, and Month 36 in other endocrine parameters (DHEA-SO_4, FSH, LH, T_3 resin uptake, TSH, and thyroxine).

For all endocrine parameters, there were no clinically meaningful between-group differences in mean change from baseline at Week 48.

Assessor's comment: the same principle as for growth and sexual maturation parameters above applies to the endocrine function parameters; that have to be compared with children the same age/gender/race unexposed to lovastatin.

Elevations in Liver Function Tests
Table 27 provides the number (percent) of patients with clinically meaningful elevations in LFTs at Month 36.

Table 27- Change From Baseline in Liver Function Tests and Creatine Kinase Levels Over Time

	Treatment Group (Base/Extension)					
	Lovastatin/Lovastatin			Placebo/Lovastatin		
	N	Median	SD†	N	Median	SD†
Aspartate Aminotransferase (mIU/mL)						
Baseline	32	16.0	6.0	25	19.0	3.7
Week 48	32	17.0	6.5	25	17.0	4.7
Change from baseline to Week 48	32	1.0	5.1	25	0.0	3.7
Month 24	32	16.0	5.6	25	18.0	3.7
Change from baseline to Month 24	32	-1.0	7.0	25	-1.0	2.8
Month 36	12	13.5	5.1	13	19.0	4.7
Change from baseline to Month 36	12	-1.5	5.1	13	0.0	5.6
Alanine Aminotransferase (mIU/mL)						
Baseline	32	9.0	4.7	25	9.0	3.7
Week 48	32	14.0	7.4	25	11.0	7.4
Change from baseline to Week 48	32	3.0	6.0	25	1.0	5.6
Month 24	32	12.0	3.7	25	13.0	8.4
Change from baseline to Month 24	32	1.5	7.0	25	3.0	4.7
Month 36	12	10.5	7.4	13	15.0	9.3
Change from baseline to Month 36	12	1.0	6.5	13	5.0	7.4
Creatine Kinase (mIU/mL)						
Baseline	32	77.5	36.3	25	63.0	45.6
Week 48	32	91.5	42.8	25	89.0	44.7
Change from baseline to Week 48	32	-1.0	38.1	25	11.0	34.4
Month 24	32	98.5	80.9	25	72.0	35.3
Change from baseline to Month 24	32	17.5	57.2	25	2.0	36.3
Month 36	12	81.0	100.5	13	71.0	31.6
Change from baseline to Month 36	12	-5.0	34.0	13	12.0	32.6

For AST and ALT, there were no clinically meaningful between-group differences in median change from baseline at Week 48, Month 24, or Month 36 based on the ITT analysis. In addition, none of the median changes in AST or ALT for either treatment group was clinically meaningful.

For CK, there were no clinically meaningful between-group differences in median change from baseline at Week 48, Month 24, or Month 36 based on the ITT analysis. In addition, none of the median changes in CK for either treatment group was clinically meaningful. No patients in the study had myopathy (defined as an unexplained muscle pain or weakness accompanied by elevations in CK to >10 x ULN).

Serum Nutritional Parameters
Safety analyses included mean and median change from baseline in serum nutritional parameters at Week 48, Month 24, and Month 36. For all serum nutritional parameters, there were no clinically meaningful between-group differences in change from baseline at Week 48, Month 24, or Month 36 based on the ITT analysis. In addition, none of the changes in serum nutritional parameters for either treatment group was clinically meaningful.

Other Serum Chemistry Parameters
The parameters with the largest percentage of patients from either treatment group experiencing a predefined increase or decrease were alkaline phosphatase, bicarbonate, calcium, CK cardiac isoenzyme, creatinine, phosphorous, potassium, and total bilirubin. There were no clinically meaningful between-group differences for any of these serum chemistry parameters.

Coagulation and Hematology Parameters
The parameters with the largest percentage of patients from either treatment group experiencing a predefined increase or decrease were eosinophils, lymphocytes, monocytes, neutrophils, and RBCs. There were no clinically meaningful between-group differences for any of these coagulation or hematology parameters.

Assessor's comment: The same principle as for growth and sexual maturation parameters above applies to all laboratory parameters; that have to be compared with normal levels in children of the same age/gender/race unexposed to lovastatin.

Clinical Safety Measurements

Systolic Blood Pressure
The results from parametric analyses of change from baseline in systolic blood pressure at Week 48, Month 24, and Month 36 are in Table 28 below. At Week 48, mean systolic blood pressure increased by 1.6 mm Hg in the lovastatin/lovastatin group and by 6.1 mm Hg in the placebo/lovastatin group. At Month 24, mean systolic blood pressure increased by 1.8 mm Hg in the lovastatin/lovastatin group and by 8.0 mm Hg in the placebo/lovastatin group. At Month 36, mean systolic blood pressure increased by 4.8 mm Hg in the lovastatin/lovastatin group and by 7.8 mm Hg in the placebo/lovastatin group.

Diastolic Blood Pressure
The results from parametric analyses of change from baseline in diastolic blood pressure at Week 48, Month 24, and Month 36 are in Table 28 below. At Week 48, mean diastolic blood pressure increased by 2.1 mm Hg in the lovastatin/lovastatin group and by 1.7 mm Hg in the placebo/lovastatin group. At Month 24, mean diastolic blood pressure increased by 1.6 mm Hg in the lovastatin/lovastatin group and by 0.7 mm Hg in the placebo/lovastatin group. At Month 36, mean diastolic blood pressure increased by 4.5 mm Hg in the lovastatin/lovastatin group and by 0.8 mm Hg in the placebo/lovastatin group.

Pulse

Safety analyses included change from baseline in pulse at Week 48, Month 24, and Month 36. The results from these parametric analyses are in Table 28. For pulse, there were no clinically meaningful between-group differences in change from baseline at Week 48, Month 24, or Month 36 based on the ITT analysis. In addition, none of the changes in pulse for either treatment group was clinically meaningful.

Table 28- Summary Statistics of Change From Baseline in Vital Sign Parameters Over Time

	Treatment Group							
	Lovastatin/Lovastatin				Placebo/Lovastatin			
	N	Mean	SD†	Median	N	Mean	SD†	Median
Diastolic Blood Pressure (mm Hg)								
Baseline	32	67.0	8.4	67.0	25	65.7	7.9	68.0
Week 48	32	69.1	8.3	70.0	25	67.4	7.5	70.0
Change from baseline to Week 48	32	2.1	10.1	2.0	25	1.7	8.5	2.0
Month 24	32	68.6	9.0	70.0	25	66.4	6.8	69.0
Change from baseline to Month 24	32	1.6	11.1	1.5	25	0.7	8.0	0.0
Month 36	10	67.4	7.0	67.0	11	64.9	6.6	66.0
Change from baseline to Month 36	10	4.5	7.0	6.0	11	0.8	2.9	0.0
Systolic Blood Pressure (mm Hg)								
Baseline	32	112.2	11.0	111.5	25	107.9	12.7	106.0
Week 48	32	113.8	11.6	112.0	25	114.0	16.7	110.0
Change from baseline to Week 48	32	1.6	12.3	3.0	25	6.1	15.0	4.0
Month 24	32	114.0	11.2	113.0	25	115.9	11.5	118.0
Change from baseline to Month 24	32	1.8	11.0	0.5	25	8.0	12.6	10.0
Month 36	10	114.3	6.9	116.0	11	112.2	12.6	110.0
Change from baseline to Month 36	10	4.8	6.2	2.5	11	7.8	5.9	7.0
Pulse (Beats/Minute)								
Baseline	32	71.0	10.4	72.0	24	71.3	8.3	72.0
Week 48	32	71.9	13.2	70.5	25	70.4	7.3	71.0
Change from baseline to Week 48	32	0.9	14.7	4.0	24	-1.0	8.5	0.0
Month 24	32	67.8	11.3	69.0	25	71.9	7.4	72.0
Change from baseline to Month 24	32	-3.2	11.3	0.0	24	0.6	9.8	2.0
Month 36	10	69.5	10.7	69.0	11	76.6	9.7	80.0
Change from baseline to Month 36	10	0.0	18.9	-3.5	10	7.0	11.9	8.0

For systolic and diastolic blood pressure, there were no clinically meaningful between-group differences in change from baseline at Week 48, Month 24, or Month 36 based on the ITT analysis. In addition, none of the changes in systolic blood pressure for either treatment group was clinically meaningful.

Assessor's comment: there is discrepancy in the values represented in the text and the table (28), for example lovastatin/lovastatin group, diastolic blood pressure, mean baseline= 67.0, mean value at 36 month = 67.4, but the change from baseline to month 36 = 4.5. The applicant must clarify whether this is a typing /calculation error or describe the statistical models that have been used.

Ophthalmologic Examination

There was one patient in the lovastatin/lovastatin group with a worsening visual acuity grade of 2 or more. From Week 48 to Week 84 (Day 258 of the extension study), the best corrected visual acuity in this patient's left eye changed from 20/15 to 20/25. However, at Week 84.1 (follow-up to the Week 84 visit), there was no associated 2- or more-grade worsening of the patient's left eye for the following ophthalmologic categories: water clefts (none), quadrants affected (none), nucleus opacity (absent), nucleus coloration (no color), posterior subcapsular opacity (absent), or anterior subcapsular opacity (absent).

Assessor's comments: It is unlikely that this loss of vision was related to lovastatin usage.

2.3. Study P083: A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lovastatin in Adolescent Girls

➢ Description

A Double-Blind, Randomized, Placebo-Controlled trial to evaluate the efficacy and safety of Lovastatin in adolescent girls aged 10 to 17 years, postmenarchal for at least 1 year, with hypercholesterolemia of familial basis.

➢ Methods

- Objective(s)

Primary: To compare the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of 24 weeks of treatment with lovastatin 20 mg and 40 mg plus diet versus diet plus placebo in girls with familial hypercholesterolemia (FH). Secondary: (1) To determine the effect of 24 weeks of treatment with lovastatin on total cholesterol (total-C), high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and apolipoproteins B (Apo B) and A-I (Apo A-I) in girls with FH. (2) To assess the tolerability of lovastatin in girls with FH.

- Study design

This was a 28 weeks randomized, double-blind, placebo-controlled study in female patients between 10 and 17 years of age postmenarchal for at least 1 year, with familial hypercholesterolemia. Following a 4-week diet/placebo run-in period, eligible patients were randomized to treatment with diet plus lovastatin 20 mg/day for 4 weeks followed by diet plus lovastatin 40 mg/day for 20 weeks or diet plus placebo for 24 weeks. Randomization to the lovastatin and placebo groups was done using a 2:1 ratio. Table 29 summarizes the Schedule of Clinical Observations and Laboratory Measurements.

Table 29- Schedule of Clinical Observations and Laboratory Measurements

Visit Number:	1†	2†	3†	4‡	5‡	6‡	7‡	8‡	9‡
Week:	-4	-1	1	4	8	12	16	20	24
Placebo/diet period	X	------X							
Active-treatment period			X	----------	----------	----------	----------	----------	----------X
Medical history	X								
Monitoring of length of menstrual cycle	X	X	X	X	X	X	X	X	X
Pregnancy risk counseling	X	X	X	X	X	X	X	X	X
β-human chorionic gonadotropin (β-hCG)§	X	X	X	X	X	X	X	X	X
Dietary advice	X								
Dietary monitoring		X	X	X	X	X	X	X	X
Issue of medication	X		X	X	X	X	X	X	
Medication compliance		X	X	X	X	X	X	X	X
Physical examination		X							X
Weight	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X							
Vital signs	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X
Hematology and urinalysis	X		X			X			X
Lipids/lipoproteins	X	X‖	X	X	X	X	X	X	X
Monitor adverse experiences		X	X	X	X	X	X	X	X

Screening history, height, weight, and blood pressure measurements were performed at Visit 1. Weight was measured at each visit. Physical examinations were performed at Visits 2 and 9.

Efficacy measurements:
For lipid measurements, fasting blood (at least 12 hours from the last meal) was drawn at each visit. Quantitative lipid analyses of Total cholesterol, LDL-C, HDL cholesterol, VLDL-C, Triglycerides, Apolipoproteins B, A-I were performed at Weeks 1, 4, 24.

Safety Measurements:
Adverse experiences, ALT, AST, CK , Endocrine function, liver function, hormonal levels (LH, FSH, DHEAS, estradiol, and cortisol), Vital signs, Ophthalmologic and Serum nutritional parameters were measured as detailed in the table 30 below.

Table 30- Laboratory Safety Tests

Hematology
Hemoglobin Hematocrit White blood cells and differential counts Platelet estimate
Urinalysis
Protein Glucose Leukocytes Erythrocytes
Serum Chemistry
Electrolytes (Na, K, Cl, CO_2, blood urea nitrogen at Week -1 only) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Creatine kinase (CK) Creatinine Glucose β-human chorionic gonadotropin (β-HCG) Thyroxine (T4) Thyroid-stimulating hormone (TSH) Estradiol Dehydroepiandrosterone sulfate (DHEAS) Cortisol Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)
Quantitative Lipid Analyses (Performed at Weeks 1, 4, 24)
Total cholesterol LDL-C HDL cholesterol VLDL-C Triglycerides Apolipoproteins B, A-I

Since the patient population in this study consisted of children and adolescents, particular attention was paid to the following parameters related to maturation: hormones (LH, FSH, DHEAS, estradiol, and cortisol), weight, height, and BMI. At Week 24, change (or percent change where appropriate) from baseline for these parameters was analyzed using the above ANOVA model for comparing lovastatin with placebo. For the estradiol analysis, patients were excluded if they were taking an oral contraceptive.

Although not considered an adverse experience, any pregnancy in a patient that occurred during the study or within 14 days of completing the study were reported. All patients who became pregnant were to be followed to the completion/termination of the pregnancy. If the pregnancy

continued to term, the outcome (health of infant) was to be reported to one of the individuals were listed.

- Study population /Sample size

Of the 54 patients randomized, 51 completed the study. Girls postmenarchal for at least 1 year, aged 10 to 17 years, with FH, having LDL-C between 160 mg/dL and 400 mg/dL, TG ≤350 mg/dL, and body mass index (BMI) (kg/m2) between the 10th and 95th percentile for age were included. Patients were considered highly unlikely to conceive as assessed by the investigator, and had a negative pregnancy test at screening.

- Treatments

One lovastatin (20 or 40 mg) or matching placebo tablet was taken each evening without regard to meals. During the active-treatment period, each patient was randomly assigned to receive 1 of 2 treatments: lovastatin 20 mg for 4 weeks, followed by lovastatin 40 mg for 20 weeks or placebo for 24 weeks. The duration of the study (4 weeks on the 20-mg/day dose and 20 weeks on the 40-mg/day dose) allowed time for stabilization of the lipid parameters.

No lipid-lowering medication other than study drug could be taken during the study, including over-the-counter fish oil or niacin in doses >200 mg/day.

- Outcomes/endpoints

- <u>The primary efficacy endpoint</u> To compare the LDL-C-lowering efficacy of 24 weeks of treatment with lovastatin 20 mg and 40 mg plus diet versus diet plus placebo in girls with FH.

- **<u>The Secondary efficacy endpoints</u>** To determine the effect of 24 weeks of treatment with lovastatin on total-C, HDL-C, very-low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and apolipoproteins B (Apo B) and A-I (Apo A-I) in girls with FH.

<u>The primary safety measures</u> Evaluation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), hormones, and frequency of clinical and laboratory adverse experiences and vital signs.

- Statistical Methods

For the primary hypothesis, the sample size of 60 (40 lovastatin and 20 placebo) had 90% power to detect a difference between treatments in LDL-C percent change from baseline of 13.5% (α=0.05, two-tailed). This selection was based upon an estimated pooled between-subject standard deviation (SD) of LDL-C percent change from baseline of 14.9% observed in the LAMS study.

Parametric (or appropriate nonparametric) analysis of variance (ANOVA) for a multicenter, forced titration, parallel design was used to compare the treatment groups for the efficacy and safety parameters. Initially, the ANOVA model contained factors for treatment, center, and treatment-by-center interaction. The interaction term was tested and removed from the model if nonsignificant (p>0.050) or quantitative in nature. A paired t-test or, if appropriate, Wilcoxon signed-rank test was used to test for percent change (change where appropriate) from baseline within each treatment group. A parametric ANOVA was used as the primary analysis for most of the lipid parameters, and the nonparametric ANOVA corroborated the parametric results. For TG and VLDL-C, an ANOVA based on Tukey's normalized ranks, a typical approach for these

parameters to adjust for the large variability and non-normal distribution of the data, was utilized as the primary analysis.

Results

- Baseline data

A summary of baseline characteristics for age and race are in Table 31.

Table 31- Baseline Patient Characteristics by Treatment Group

	Lovastatin (N=35)		Placebo (N=19)		Total (N=54)	
	n	(%)	n	(%)	n	(%)
Age						
10 to 14	14	(40.0)	5	(26.3)	19	(35.2)
15 to 17	20	(57.1)	12	(63.2)	32	(59.3)
18†	1	(2.9)	2	(10.5)	3	(5.6)
Mean	14.9		15.3		15.1	
SD	1.74		1.83		1.76	
Median	15.0		15.0		15.0	
Range	11 to 18		11 to 18		11 to 18	
Race						
Asian	0	(0.0)	2	(10.5)	2	(3.7)
Black	6	(17.1)	2	(10.5)	8	(14.8)
Hispanic	1	(2.9)	0	(0.0)	1	(1.9)
White	28	(80.0)	15	(78.9)	43	(79.6)

There were no clinically meaningful differences between treatment groups for these characteristics.

Assessor's comment: the applicant should provide the baseline data for weight, height, BMI and risk factors for cardiovascular heart disease, in tabulated format.

- Efficacy results

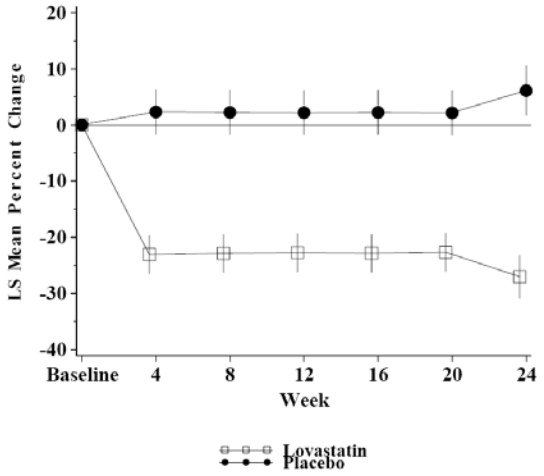
Primary end point

As shown in table 32 and figure 2 below, after 24 weeks of treatment (lovastatin 20 to 40 mg/day versus placebo), LS mean percent changes from baseline in LDL-C of -27.0% and 6.1% were observed for the lovastatin and placebo groups, respectively.

Table 32- Analysis of Percent Changes From Baseline in LDL-C at Week 24

		Mean (mg/dL)		Percent Changes From Baseline			
Treatment	N	Baseline (SD)	Week 24† (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	p-Value for LS Mean
Lovastatin	35	218.3 (49.0)	157.2 (47.0)	-27.7 (15.4)	-27.0	(-34.7, -19.4)	<0.001
Placebo	18	198.8 (39.5)	210.2 (57.5)	5.0 (14.1)	6.1	(-2.7, 15.0)	0.171
Between-Group Comparison			p-Value	LS Mean	95% CI for Difference		
Lovastatin vs. Placebo			<0.001	-33.2	(-43.2, -23.1)		

Figure 2- LS Mean Percent Changes From Baseline in LDL-C (mg/dL) ±SE



The LS mean percent reduction from baseline values for lovastatin was significant (p<0.001). The difference between lovastatin versus placebo was also significant (p<0.001). For LDL-C, after the first 4 weeks of treatment of lovastatin 20 mg/day or placebo, lovastatin 20 mg/day had a significant LS mean percent change from baseline of -23.1% (p<0.001). A significant difference between the lovastatin 20-mg versus placebo groups was also observed at Week 4 (p<0.001).

Assessor's comment: the LDL concentration was reduced by approximately 60 mg/dl after 24 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant and clinically meaningful compared with the placebo group. The primary objective is reached.

A lesser but statistically significant reduction in LDL-C was also seen at 4 weeks with 20 mg daily dose of lovastatin compared to both baseline and placebo.

Secondary endpoints

Total Cholesterol

LS mean percent changes from baseline in total-C after 24 weeks of treatment were -21.8% and 4.5% for the lovastatin and placebo groups, respectively. The corresponding LS mean percent changes from baseline at Week 4 were -17.4% and 2.4% for the lovastatin 20-mg and placebo groups, respectively. The between-treatment difference at Weeks 4 and 24 was significant (p<0.001).

Table 33- Analysis of Percent Changes From Baseline in Total-C for Each Treatment Period

		Mean (mg/dL)		Percent Changes From Baseline			
Treatment	N	Baseline (SD)	Week 4 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	p-Value for LS Mean
Lovastatin 20 mg	35	289.2 (50.3)	237.6 (54.6)	-17.8 (10.5)	-17.4	(-22.5, -12.3)	<0.001
Placebo	18	268.6 (41.1)	275.8 (53.7)	2.5 (9.7)	2.4	(-3.5, 8.3)	0.424
			Week 24[T] (SD)				
Lovastatin 40 mg	35	289.2 (50.3)	223.6 (46.1)	-22.4 (11.2)	-21.8	(-26.9, -16.7)	<0.001
Placebo	18	268.6 (41.1)	277.7 (46.1)	3.6 (9.9)	4.5	(-1.4, 10.5)	0.129

Between-Group Comparison	p-Value	LS Mean	95% CI for Difference
Lovastatin 20 mg vs. Placebo	<0.001	-19.7	(-26.4, -13.0)
Lovastatin 40 mg vs. Placebo	<0.001	-26.3	(-33.0, -19.6)

Assessor's comment: the total cholesterol concentration was reduced by approximately 65 mg/dl after 24 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant and clinically meaningful compared with the placebo group.

A lesser but statistically significant reduction in total cholesterol was also seen at 4 weeks with 20 mg daily dose of lovastatin compared to both baseline and placebo.

HDL Cholesterol
After 24 weeks of treatment, LS mean HDL-C percent changes from baseline of 2.5% and 2.7% were observed for the lovastatin and placebo groups, respectively. No significant between-treatment difference was observed at either Week 4 or Week 24 (p>0.100).

VLDL Cholesterol
Median percent changes from baseline in VLDL-C after 24 weeks of treatment were -6.7% and 0.0% for the lovastatin and placebo groups, respectively. The between-treatment difference was not significant at either Week 4 or Week 24 (p>0.100).

Triglycerides
After 24 weeks of treatment, median TG percent changes from baseline of -22.7% and -3.0% were observed for the lovastatin and placebo groups, respectively. The between-treatment difference was not significant at Week 4 (lovastatin 20 mg versus placebo) (p>0.100), whereas the difference at Week 24 (lovastatin 40 mg versus placebo) was borderline significant (0.050<p≤0.100). Similar to VLDL-C, triglycerides are generally known to have large variability. The large variability and moderate sample size observed in TG also limit the conclusions that can be drawn from the analysis.

Table 34- Analysis of % Changes From Baseline in Triglycerides for Each Treatment Period

		Median (mg/dL)		Percent Changes From Baseline		
Treatment	N	Baseline (SD)	Week 4 (SD)	Median (SD)	95% CI for Median	p-Value
Lovastatin 20 mg	35	106.0 (54.4)	82.0 (44.7)	-10.3 (36.4)	(-22.8, 2.2)	0.002
Placebo	18	103.3 (53.5)	88.0 (45.6)	-11.0 (48.1)	(-34.9, 13.0)	0.304
			Week 24[†] (SD)			
Lovastatin 40 mg	35	106.0 (54.4)	81.0 (43.7)	-22.7 (40.5)	(-36.6, -8.8)	0.003
Placebo	18	103.3 (53.5)	87.0 (80.0)	-3.0 (40.9)	(-23.3, 17.3)	0.734

Between-Group Comparison	p-Value
Lovastatin 20 mg vs. Placebo	0.464
Lovastatin 40 mg vs. Placebo	0.067

Assessor's comment: the percent changes from baseline in triglycerides was reduced significantly at 4 weeks (P= 0.002) and 24 weeks (P=0.003) of lovastatin treatment. There was no statistically significant difference between lovastatin and the placebo groups. The applicant has attributed this to innate large variability in TG levels and moderate sample size.

Apolipoprotein B
Apo B is the major protein constituent of LDL-C, VLDL-C, and chylomicrons. After 24 weeks of treatment, LS mean percent changes from baseline of -23.2% and 6.8% was observed for the lovastatin and placebo groups, respectively. The corresponding LS mean percent changes at

Week 4 were -19.9% and 5.6%, respectively. The between-treatment differences at Weeks 4 and 24 were significant (p<0.001) as shown in table 34 below:

Table 34- Analysis of Percent Changes From Baseline in Apolipoprotein B

		Mean (mg/dL)		Percent Changes From Baseline			
Treatment	N	Baseline (SD)	Week 4 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	p-Value for LS Mean
Lovastatin 20 mg	34	186.7 (36.8)	149.9 (41.3)	-19.6 (13.9)	-19.9	(-27.1, -12.7)	<0.001
Placebo	18	168.0 (33.6)	179.8 (46.8)	6.8 (14.1)	5.6	(-2.6, 13.8)	0.173
			Week 24† (SD)				
Lovastatin 40 mg	34	186.7 (36.8)	141.1 (37.9)	-24.4 (13.2)	-23.2	(-29.9, -16.4)	<0.001
Placebo	18	168.0 (33.6)	176.3 (31.6)	6.4 (15.2)	6.8	(-0.9, 14.4)	0.080

Between-Group Comparison	p-Value	LS Mean	95% CI for Difference
Lovastatin 20 mg vs. Placebo	<0.001	-25.5	(-34.9, -16.2)
Lovastatin 40 mg vs. Placebo	<0.001	-29.9	(-38.6, -21.2)

Assessor's comment: the Apolipoprotein B concentration was reduced by approximately 45 mg/dl after 24 weeks of lovastatin treatment at 40 mg daily dose. This reduction is both statistically significant and clinically meaningful compared with the baseline values and placebo group.

Apolipoprotein A-I
LS mean percent changes from baseline in Apo A-I at Week 24 for the lovastatin and placebo groups were 3.3% and 11.5%, respectively. The between-treatment difference was not significant at Week 4 or 24.

Subgroup Analyses for Primary and Secondary Endpoints
Prespecified subgroup interactions (age group, ethnic group, and study centre) for the primary and secondary efficacy parameters after 24 weeks of treatment were examined in the intention-to-treat population using an ANOVA model. None of the treatment-by-subgroup interaction terms was significant (p>0.100).

- **Safety results**

The most common AEs and AEs determined by the investigator to be drug related (i.e., possibly, probably, or definitely drug related) are in table 35 below.

Table 35- Number (%) of Patients With Specific Clinical Adverse Experiences possibly, probably drug related

	Lovastatin (N=35)		Placebo (N=19)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	23	(65.7)	13	(68.4)
Patients with no adverse experience	12	(34.3)	6	(31.6)
Body As A Whole/Site Unspecified	**17**	**(48.6)**	**11**	**(57.9)**
Abdominal Pain	3	(8.6)	0	(0.0)
Asthenia/Fatigue	0	(0.0)	1	(5.3)
Body Ache	1	(2.9)	0	(0.0)
Contusion	0	(0.0)	1	(5.3)
Dizziness	1	(2.9)	0	(0.0)
Food Poisoning	0	(0.0)	1	(5.3)
Fungal Infection	1	(2.9)	0	(0.0)
Influenza-Like Disease	4	(11.4)	0	(0.0)
Postoperative Pain	1	(2.9)	0	(0.0)
Soft Tissue Infection	0	(0.0)	1	(5.3)
Upper Respiratory Infection	10	(28.6)	9	(47.4)
Viral Syndrome	0	(0.0)	1	(5.3)
Cardiovascular System	**0**	**(0.0)**	**1**	**(5.3)**
Systolic Murmur	0	(0.0)	1	(5.3)
Digestive System	**5**	**(14.3)**	**4**	**(21.1)**
Aphthous Stomatitis	1	(2.9)	0	(0.0)
Constipation	1	(2.9)	0	(0.0)
Dental Pain	2	(5.7)	1	(5.3)
Diarrhea	2	(5.7)	0	(0.0)
Epigastric Discomfort	1	(2.9)	1	(5.3)
Gastritis	1	(2.9)	0	(0.0)
Infectious Gastroenteritis	1	(2.9)	0	(0.0)
Nausea	1	(2.9)	1	(5.3)
Vomiting	0	(0.0)	1	(5.3)
Eyes, Ears, Nose, And Throat	**12**	**(34.3)**	**3**	**(15.8)**
Cerumen Impaction	1	(2.9)	0	(0.0)
Epistaxis	1	(2.9)	0	(0.0)

Eyes, Ears, Nose, And Throat (Cont.)	**12**	**(34.3)**	**3**	**(15.8)**
Nasal Congestion	2	(5.7)	0	(0.0)
Otic Pain	2	(5.7)	0	(0.0)
Otitis	1	(2.9)	1	(5.3)
Pharyngitis	6	(17.1)	2	(10.5)
Sinus Disorder	1	(2.9)	0	(0.0)
Sinusitis	1	(2.9)	0	(0.0)
Streptococcal Pharyngitis	4	(11.4)	0	(0.0)
Hemic And Lymphatic System	**1**	**(2.9)**	**0**	**(0.0)**
Lymphadenitis	1	(2.9)	0	(0.0)
Immune System	**1**	**(2.9)**	**1**	**(5.3)**
Hypersensitivity Reaction	1	(2.9)	0	(0.0)
Nonspecific Allergy	0	(0.0)	1	(5.3)
Metabolism And Nutrition	**1**	**(2.9)**	**0**	**(0.0)**
Weight Loss	1	(2.9)	0	(0.0)
Musculoskeletal System	**2**	**(5.7)**	**1**	**(5.3)**
Back Pain	0	(0.0)	1	(5.3)
Knee Pain	0	(0.0)	1	(5.3)
Leg Pain	1	(2.9)	1	(5.3)
Traumatic Arthropathy	1	(2.9)	0	(0.0)
Nervous System	**7**	**(20.0)**	**4**	**(21.1)**
Headache	7	(20.0)	4	(21.1)
Psychiatric Disorders	**1**	**(2.9)**	**1**	**(5.3)**
Anxiety Disorder	0	(0.0)	1	(5.3)
Behavioral Disturbance	1	(2.9)	0	(0.0)

	Lovastatin (N=35)		Placebo (N=19)	
	n	(%)	n	(%)
Respiratory System	**1**	**(2.9)**	**3**	**(15.8)**
Asthma	0	(0.0)	1	(5.3)
Cough	1	(2.9)	1	(5.3)
Pulmonary Congestion	0	(0.0)	1	(5.3)
Skin And Skin Appendages	**3**	**(8.6)**	**1**	**(5.3)**
Alopecia	0	(0.0)	1	(5.3)
Desquamation	1	(2.9)	0	(0.0)
Herpes Simplex	2	(5.7)	0	(0.0)
Rash	1	(2.9)	0	(0.0)
Urogenital System	**2**	**(5.7)**	**1**	**(5.3)**
Menstrual Disorder	2	(5.7)	1	(5.3)

Clinical AEs were coded to body system categories from the World Health Organization (WHO) dictionary. There were no patients with serious AEs or who were discontinued from therapy due to an adverse experience and no deaths.

Assessor's comment: during the 28 weeks of the study, the number of treatment emergent AEs were similar in both lovastatin (65.7%) and placebo (68.4%) groups. The most common adverse experiences were upper respiratory infection, pharyngitis, and headache. However pharyngitis occurred almost twice as many in the lovastatin group (17.1%) than in the placebo group (10.5%).

Laboratory Adverse Experiences

In all 54 patients only one in the lovastatin group had a laboratory AE of decreased hematocrit and hemoglobin. Her hematocrit increased from 37.1% on Day 1 to 37.9% on Day 91 (Visit 6)

and then decreased to 33.6% on Day 162 (normal range: 36 to 46%). Her hemoglobin increased from 12.6 g/dL on Day 1 to 12.7 g/dL on Day 91 and decreased to 11.5 g/dL on Day 162 (normal range: 12 to 16 g/dL). No patient experienced a >10 X ULN increase in CK during the study period. No patient had a single or consecutive >3 X ULN elevations for AST and/or ALT during the study.

LH, FSH, and Estradiol

Analyses of LH, FSH & estradiol based upon absolute change from baseline are in table below.

Table -36 Analysis of Changes From Baseline in LH, FSH, and Estradiol at Week 24

			Median		Changes From Baseline			p-Value
Parameter	Treatment	N	Baseline (SD)	Week 24 (SD)	Median (SD)	95% CI for Median	p-Value	Lovastatin vs. Placebo
LH (mIU/mL)	Lovastatin	29	5.0 (5.6)	5.0 (11.2)	1.0 (14.0)	(-4.3, 6.3)	0.336	0.040
	Placebo	17	4.0 (10.2)	3.0 (8.4)	0.0 (6.5)	(-3.3, 3.3)	0.879	
FSH (mIU/mL)	Lovastatin	28	8.0 (6.5)	9.0 (6.5)	-1.0 (4.2)	(-2.6, 0.6)	0.518	0.585
	Placebo	16	6.0 (3.7)	10.0 (6.0)	1.0 (5.6)	(-2.0, 4.0)	0.257	
Estradiol (pg/mL)	Lovastatin	29	61.0 (39.1)	74.0 (80.0)	15.0 (54.0)	(-5.5, 35.5)	0.095	0.249
	Placebo	17	95.0 (44.7)	91.0 (37.2)	-9.0 (79.1)	(-49.7, 31.7)	0.854	

After 24 weeks of treatment, median LH changes from baseline of 1.0 mIU/mL and 0.0 mIU/mL were observed for the lovastatin and placebo groups, respectively. The within-group increase in the lovastatin group was not significant. The difference between lovastatin versus placebo was significant ($p<0.040$).

There was no detectable effect on plasma FH or estradiol, or cycle length, and the single patient in whom a possibly drug-related endocrine adverse experience (amenorrhea) was reported was in the placebo group.

Cortisol

After 24 weeks of treatment, median cortisol percent changes from baseline of -1.6% and 5.7% were observed for the lovastatin and placebo groups, respectively. The difference between lovastatin versus placebo was not significant ($p>0.100$)

DHEAS

After 24 weeks of treatment, the lovastatin and placebo groups had LS mean changes from baseline of -0.1μg/dL and 0.1μg/dL, respectively. The difference between lovastatin versus placebo was not significant ($p>0.100$)

Assessor's comment: There were no critical elevations of transaminases or CK, cortisol, DHEAS and no cases of myopathy. One patient in the lovastatin group had a small reduction in haemoglobin and hematocrit at the end of the study. Other than that, the haematology and urine analysis was rather unremarkable.

With respect to the gonad, the luteinising hormone concentration was significantly ($p<0.04$) higher in the girls receiving lovastatin. Given the small sample size, it is extremely difficult to interpret and the increase in concentration was well within normal limits. There are possible explanations for this, which come out in the small sample size that has been studied. The LH concentration does vary considerably through the menstrual cycle, so that it would have been important to know, if possible, what steps were taken to minimise this particular variable. Overall, the changes in the hypothalamo pituitary gonadal axis are not of particular concern.

Vital Signs
LS mean changes from baseline at weeks 4 & 24 for blood pressure and pulse are in Table 37 below.

Table 37- Analysis of Changes From Baseline in Vital Signs for Each Treatment Period

			Mean		Changes From Baseline				p-Value
Parameter	Treatment	N	Baseline (SD)	Week 4 (SD)	Mean (SD)	LS Mean	95% CI for LS Mean	p-Value for LS Mean	Lovastatin vs. Placebo
Systolic Blood Pressure (mm Hg)	Lovastatin 20 mg	35	109.1 (0.6)	107.2 (10.6)	-1.9 (9.8)	-1.6	(-6.1, 3.0)	0.497	0.291
	Placebo	18	110.4 (10.7)	106.6 (7.4)	-3.9 (8.8)	-4.7	(-10.0, 0.6)	0.079	
				Week 24 (SD)					
	Lovastatin 40 mg	33	108.5 (10.6)	108.4 (9.4)	-0.1 (11.1)	-0.7	(-5.8, 4.3)	0.766	0.034
	Placebo	18	110.4 (10.7)	104.3 (5.9)	-6.2 (9.1)	-7.9	(-13.7, -2.1)	0.009	
Diastolic Blood Pressure (mm Hg)				Week 4 (SD)					
	Lovastatin 20 mg	35	67.2 (8.8)	66.6 (7.2)	-0.6 (8.2)	-0.1	(-4.0, 3.7)	0.952	0.766
	Placebo	18	65.7 (8.3)	65.7 (8.9)	0.0 (9.0)	-0.9	(-5.3, 3.6)	0.698	
				Week 24 (SD)					
	Lovastatin 40 mg	33	66.4 (8.4)	65.4 (7.3)	-1.0 (9.3)	-0.6	(-4.5, 3.4)	0.771	0.548
	Placebo	18	65.7 (8.3)	64.1 (6.6)	-1.6 (8.3)	-2.1	(-6.6, 2.4)	0.350	
Pulse (beats/min)				Week 4 (SD)					
	Lovastatin 20 mg	35	71.7 (11.6)	70.3 (9.4)	-1.4 (10.4)	-1.7	(-7.0, 3.7)	0.533	0.860
	Placebo	18	70.8 (11.4)	69.3 (10.2)	-1.5 (10.9)	-1.0	(-7.3, 5.2)	0.734	
				Week 24 (SD)					
	Lovastatin 40 mg	32	72.0 (11.9)	66.7 (8.4)	-5.3 (11.0)	-4.9	(-10.2, 0.4)	0.071	0.126
	Placebo	18	70.8 (11.4)	70.7 (9.9)	-0.2 (9.5)	0.3	(-5.5, 6.0)	0.919	

Analysis of changes in weight, height, and BMI after 4 and 24 weeks of lovastatin treatment showed no significant differences to the baseline values. There were no significant changes in the growth indicators compared with the placebo group either.

Assessor' comments: Systolic, diastolic blood pressures and pulse were measured. No in between-treatment difference was significant (p>0.100), except for systolic blood pressure at Week 24 (p<0.050). This change is inconsequential as Systolic blood pressure actually decreased in both treatment groups, but the decrease was greater in the placebo group. Systolic blood pressure in children is known to have greater physiological variability among observations within a subject.

In this population of one year post menarche girls, there were no significant changes in the growth indicators compared with the placebo group either after 28 week of lovastatin treatment. In post menarchal girls, by the time menarche has taken place, less than 5% of growth is still likely to take place and, as such, it would be highly unlikely, even with very large sample sizes, to detect a difference between groups.

2.4 Periodic Safety Update Reports

A review of paediatric worldwide use with lovastatin 3-year PSUR covering from 21-Jul-2007 to 20-Jul-2010 was carried out. This review identified 1 report of paediatric use for lovastatin. The patient was a 16-year old female and was treated with lovastatin therapy and developed rhabdomyolysis (listed event) in the context of an undiagnosed genetic disorder of mitochondrial dysfunction. Therefore, no new safety concerns were identified. No reports of paediatric use with lovastatin were identified during the remaining time periods.

3. Discussion on clinical aspects and conclusion

Despite relatively large number of children enlisted, types and duration of the 3 clinical studies, this is a poorly presented application. In particular, there are a number of discrepancies in the present submission as follows:

- There is inconsistency on the values represented in the text and the table (vital signs, boys extension study P040X) and within the table (39), perhaps typing /calculation error however this puts the integrity of all the data under question.

- There are missing 17 source documents in the pivotal boys' study; and the reason that the FDA requested that treatment be stopped immediately on all patients who had entered the extension boys study has not been given.

- In the long term male safety study, the comparison of adverse events, growth, sexual maturation, laboratory parameter and all other safety measurements between lovastatin/lovastatin groups of 3 years exposure versus placebo/lovastatin group of 2 years exposure is meaningless and inconclusive.

However, provided that the data are valid, the following conclusions can be made.

Efficacy
The adolescent males in the pivotal efficacy study had baseline mean levels of LDL-C greater than the 95th percentile for their age (252.6 mg/dL for the lovastatin group, 248.7 mg/dL for the placebo group) consistent with the diagnosis of heterozygous familial hypercholesterolemia. After 48 and 24 weeks of lovastatin treatment at 40 mg daily dose, the LDL concentration was reduced by approximately 60 mg/dL in both boys (10-17 years of age) and girls (one year post menarche), respectively. This reduction is both statistically significant and clinically meaningful compared with the baseline and placebo group. This effective reduction was maintained over the 2 years of open extension period in the boys. The primary objective has been reached.

Changes in total-C and apo B levels (secondary endpoints) with lovastatin treatment were also consistent between adolescent boys and girls studies. In the adolescent male base study, the change from baseline in mean total-C was -21% at Week 24 and -19% at Week 48; the change in mean Apo B was -23% at Week 24 and -21% at Week 48 ($p<0.001$). In adolescent female study at Week 24, the change from baseline in mean total-C was -22% and in apo B was -23% ($p<0.001$).

In the adolescent male pivotal, extension and girls studies, the reductions in median TG and HDL-C levels were no different than those observed in the placebo group. Significant increases in HDL-C and decrease in TG were observed at Weeks 8 and 24 in the lovastatin treated adult patients. In addition to limited sample size available in this cohort of patients, the baseline median TG level was higher in the adult study with less variability in the baseline levels. However, significant reductions in HDL-C were observed in the placebo/lovastatin group at the end of the boys extension phase, month 36 (6.5% placebo/lovastatin group $p=0.007$). This could be due to a natural drop in HDL-C levels in boys during adolescence.

Safety
In the 1 year adolescent boys pivotal study and 6 months girls study the number of treatment emergent AEs were similar in both lovastatin and in placebo groups. The most common adverse events were upper respiratory tract infection, headache, accidental trauma, myalgia, influenza-

like symptoms, pharyngitis, and abdominal pain. However they are mostly common childhood diseases and their incidences were comparable to the placebo group.

In the adolescent boys pivotal study, 3 cases of vision disorder were reported. The applicant should discuss the type of vision disorder and if possible compare the frequency of its occurrence between children and adults. The ALT levels in the lovastatin group were also significantly higher compared to base line ($p<0.001$). Although liver enzyme elevation is well known adverse event associated with the statins, the applicant must provide a quantitative, tabulated comparison with the ALT rise in adult studies.

In the adolescent girls the LH levels in the lovastatin group was significantly reduced ($p<0.04$). This should be captured in section 4.8.

The current safety analysis of the extension phase of adolescent boys is unacceptable. After randomization code was broken at 48 weeks, the placebo patients were also put on lovastatin for the 2 year duration of the open label extension study. The comparison of adverse events, growth, sexual maturation, laboratory parameter and all other safety measurements between lovastatin/lovastatin groups of 3 years exposure versus placebo/lovastatin group of 2 years exposure is meaningless and inconclusive. There is no point in comparison with the baseline levels as this population is expected to grow in a period of 3 years.

The analysis of the probable effect of long term lovastatin treatment on all safety measurements should be carried out by comparing the study group, with children of the same age/gender/race unexposed to lovastatin.

Overall, none of the endocrine or nutrition parameters are of concern in all 3 studies. The conduct of the pubertal assessment, allocation of the randomisation process (small sample size) and the diverse parameters that are likely to be encountered in this age group, make it extremely difficult to assess any effect on growth and pubertal development. The majority of treatment emergent adverse events in both cohorts were of mild or moderate intensity.

V. RAPPORTEUR'S OVERALL CONCLUSION & RECOMMENDATION

- **Overall conclusion** (Day 70)

Autopsy studies, such as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY, 2006)) study and the Bogalusa Heart Study (2002), have demonstrated that the atherosclerotic process begins in childhood and is progressive throughout the life span; therefore pediatricians must initiate the lifelong approach to prevention of CVD in their patients. The general risk benefit of statins for use in children with familial hypercholesterolemia is positive. They are first line of drug therapy after diet and life style changes and have proven to be a useful tool in controlling the circulating LDL levels.

The three paediatric studies submitted here have reached the primary objective and demonstrate lovastatin ability to lower LDL-C. This reduction is both statistically significant and clinically important. However, to obtain an indication the applicant must explain the dose selection, particularly in the absence of paediatric PK data. In the adolescent male base study, the level of LDL-C reduction at 16 weeks 20 mg is 191 mg/dL (24%) similar to 24 weeks, 40 mg reduction of 183 mg/dL (27%).

Overall, the majority of treatment emergent adverse events in both cohorts were of mild or moderate intensity. However the safety analysis of long term lovastatin treatment should be carried out by comparing the study group, with children of the same age/gender/race unexposed to lovastatin.

- **Recommendation** (Day 70)

The data submitted by the applicant demonstrate efficacy in lowering the surrogate markers of lovastatin efficacy in children 10-17 years of age of both gender. However, there are no PK data and the applicant must provide justification for the proposed maximum recommended dose of 40 mg daily, before a paediatric indication could be considered.

The safety analysis of long term lovastatin treatment should be carried out by comparing the study group, with children of the same age/gender/race unexposed to lovastatin. The MAH should also comment on the reduction of LH levels in the lovastatin group of the adolescent girls.

Further risk evaluation after the assessment of responses is required before a conclusive risk/benefit conclusion can be drawn.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Study P040:

Q1. In the title and proposed posology section 4.2 of the SmPC the age group is 10-17, whilst in this table there seem to be some 9 year old children included. The applicant needs to clarify this point.

Company response
As indicated in the Table 8, there were children at time of entry who were 9 years of age. It may be that a subject entered study at age 9 and was near / or became 10 years old at the time of study treatment. Due to the length of time since the study was completed, individual listings are not available and no further explanation can be provided.

Assessor's comment: explanation acceptable.

Issue resolved.

Q2. The applicant must provide the reason for FDA request to withdraw 6 children from the study.

Company Response
On page 33 of the Clinical Study Report (CSR), it states: "All patients (6 patients [2 in the lovastatin group and 4 in the placebo group]) below Tanner Stage II were discontinued at the request of the Food and Drug Administration in October, 1992, due to concerns about pre-pubertal treatment with lovastatin". No additional information is available.

Assessor's comment: resolved in spite unsatisfactory answer.

Issue resolved.

Q3. Regarding the missing 17 source documents, the applicant needs to clarify the following:

a) Was there a complete loss of all records on these 17 patients?

Company response
Table 7 on page 26 of CSR states: "Due to the 7-year time interval between study completion and preparation of this clinical study report, patient charts, worksheets, local laboratory reports, and signed consent forms were identified as missing at these sites." As indicated in footnote of Table 7, investigator certified report forms and central laboratory data for these patients were on file at the MAH at the time of the CSR's publication; the data from the report forms and lab reports was transferred to the clinical database for analysis for the CSR, and the database is on file at the MAH.

b) Have they been included in baseline or any other stages of the study analysis?

Company response
Page 25 of CSR under Deviations from Planned analysis contains the following statement: "Source documents for the study were found to be missing for 17 patients at 4 investigator sites." Thus, additional analysis was performed to exclude these 17 patients for the key efficacy endpoint LDL-C and the secondary endpoints total-C, HDL-C and TG. These sensitivity analyses yielded similar results to the pre-specified analyses.

c) What additional analysis was performed to exclude these 17 patients for the key efficacy endpoint?

Company response
The analysis of percent change in LDL-C, the primary endpoint, was performed as described in the clinical study report excluding the 17 patients.

d) Dose this mean the final number of patients that completed the study and were analyzed is actually 92?

Company response
No, the data was included in the database and therefore in the analysis. It was decided since source documentation was not available that additional analysis excluding them be done for LDL-C and the secondary endpoints for total-C, HDL-C and TG. No differences were found.

e) Of this 17 patients how many were in lovastatin and how many in placebo group?

Company response
A total of 10 subjects was in the lovastatin group and 7 in the placebo.

Assessor's comment: this entire section does not address the issue of missing data, the age of the study and unavailability of the source document are to some extent valid arguments, but the entire response is short and does not shed any light on the missing data.

Issue unresolved

Q4. The additional analysis of LDL-C at Week 8 (10 mg/day), Week 16 (20 mg/day), and Week 24 (40 mg/day), shows that the reduction in LDL concentration reached a plateau at around 20 mg on16 weeks. In the absence of a PK study, the applicant must clarify the dose selection and the reasoning behind the 40 mg dose.

Company response
The initial selection of the 10 to 40 mg dose range for simvastatin in protocol 040 was based on the adult dose range at the time the study was initiated. The adult dose range was based on numerous clinical trials in a broad group of adult patients demonstrating a clear dose response in LDL-C lowering with simvastatin. This data supported an approximate 6% incremental

reduction in LDL-C with each doubling of the dose. There is no reason to believe that a similar dose response would not be observed in children.
P040 was not designed to establish a dose response for LDL-C in children on simvastatin and was not powered to detect differences between the individual doses. However it is reassuring that there was a numerical increase in the % reduction in LDL-C across the doses utilized.

Assessor's comment: the response does not answer the question.

Issue unresolved.

Q5. In measuring LDL-C and total -C it is unclear whether the applicant was attempting to establish dose/response relationship or not. If so, the applicant must provide the linear regression analysis of dose versus change from baseline levels of LDL.

Company response
P040 was not designed to establish a dose response for total cholesterol and LDL-C in children and was not powered to detect differences in these parameters between the individual doses.

Assessor's comment: explanation acceptable.

Issue resolved.

Q6. 3 cases of vision disorder should be addressed by the applicant. The applicant should explain what type of vision disorder and if possible compare the frequency of its occurrence between children and adults.

Company response
In (P040) Appendix 4.1.14 states that the vision disorder preferred terms were:
• Abnormal vision (1)
• Conjunctivitis (1)
• Mydriasis (1)

Due to the age of the trial, additional information is not available.

Assessor's comment: explanation acceptable.

Issue resolved.

Q7. The applicant must provide a quantitative, tabulated comparison with the ALT rise in adult studies, with the view of capturing the possible differences in the section 4.8 of the SmPC.

Company response
There were no consecutive ALT or AST elevations >3 x ULN and no single ALT elevations >3 x ULN in adolescent patients treated with lovastatin, as shown in Table 1. Based on best comparable data from studies with adolescents and adults (Table 38 and Table 39), the incidence of single ALT or AST elevations >3 x ULN was similar in adolescent and adult patients (1.8% and 1.4%, respectively).

Table 38- Incidence (n/%) of ALT or AST Elevations Treatment of Lovastatin in Adolescent Males and Females with Familial Hypercholesterolemia

Study	Treatment Period	Lovastatin 10-40 mg	Placebo
Adolescent Males	Treatment Period I (Week 1-24) †	0/67 (0.0%)	0/62 (0.0%)
	Treatment Period II (Week 24-48) †	0/67 (0.0%)	1/62§ (1.6%)
	Extension (P040X)‡ (Week 49-Week 152)	1/57 (1.8%)‖	No placebo group in the extension study
Adolescent Females (P083)	20 mg for 4 weeks followed by 40 mg for 20 weeks	0/35 (0.0%)	0/19 (0.0%)

† P040 Base: Period I - 10 mg for 8 weeks, followed by 20 mg for 8 weeks, followed by 40 mg for 8 Weeks. Period II – 40 mg for 24 weeks
‡ P040X (Extension): At week 49, lovastatin dose (40 mg) was adjusted according to LDL-C values obtained at weeks 36 and 42 of the base study. Patients on placebo in the base study were placed on lovastatin 10 mg at Week 49. During the extension, lovastatin dose was adjusted based on averaged LDL-C levels obtained from the 2 most recent clinic visits.
§ Single AST elevation >3 x ULN at Week 30 (85 mIU/mL, normal range: 8-22 mIU/mL)
‖ Single AST elevation >3 x ULN at Week 72 (74 mIU/mL, normal range: 8-22 mIU/mL). The elevation was asymptomatic and associated with exercise-induced CK increases

Table 39- Incidence (n/%) of ALT or AST Elevations EXCEL Study Treatment with Lovastatin in Adult Patients with Primary Hypercholesterolemia

Study	Lovastatin 20 mg (qpm) n=1642	Lovastatin 40 mg (qpm) n=1654	Lovastatin 40 mg (20 mg bid) n=1646	Lovastatin 80 mg (40 mg bid) n=1649	Incidence in Lovastatin treated patients n=6591	Placebo n=1663
Single Elevation >3 x ULN	10 (0.8)	22 (1.9)	21 (1.8)	42 (3.2)	95 (1.4)	15 (1.2)
Consecutive Elevations >3 x ULN	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)	45 (0.7)	2 (0.1)
Duration of treatment was 48 weeks qpm = once daily; bid = twice daily						

Assessor's comment: explanation acceptable.

Issue resolved.

Q8. In the expert overview document, the applicant claims that, there are some minor discrepancies between the published paper and the clinical study report (P040), attributable to corrections to the database after the statistical analysis that formed the basis of the paper was performed. This needs to be further addressed in detail as to the nature and magnitude of the discrepancies.

Company response

As stated in the expert overview document, the discrepancies between the clinical study report and the manuscript are minor and of no clinical import. They occurred as a result of corrections to the data base between the time of authoring the manuscript and the clinical study report.

Assessor's comment: the response is totally inadequate.

Issue unresolved.

Study P040X:

Q9. As with the missing 17 source documents in the base study (P040), the applicant needs to provide further information about the 5 patients with missing source data in the extension study.

Company response

Table 6 on page 25 of P40X CSR states: Due to the 7-year time interval between study completion and preparation of this clinical study report, patient charts, worksheets, local laboratory reports, and signed consent forms were identified as missing at these sites. Three (3) patients were in the lovastatin/lovastatin treatment group and 2 patients were in the placebo/lovastatin group

Assessor's comment: the response does not address the issue of missing data.

Issue unresolved

Q10. The applicant should provide summary description of the statistical tests carried out in the safety population.

Company response

As stated in the CSR Safety Methods Section:

The mean and median changes in testicular volume from baseline at Week 48, Month 24, and Month 36 were analyzed using the ITT approach and are summarized in Table 29. The mean and median changes in the growth and development parameters of height, weight, and body mass index (BMI) from baseline at Week 48, Month 24, and Month 36 were analyzed using the ITT approach and are summarized in Table 30. The change from baseline in testicular volume at Months 24 and 36 by baseline Tanner stage and treatment group were analyzed using the ITT approach and are summarized in [4.1.1] and [4.1.2]. Additionally, the changes from baseline in Tanner stage by treatment group were analyzed using the ITT approach and are summarized in [4.1.3]. For these analyses, the baseline value is defined as the last measurement before or at Week 0 of the base study.

The mean and median (percent) changes in endocrine function parameters from baseline at Week 48, Month 24, and Month 36 were analyzed using the ITT approach and are summarized in Table 31, Table 32, and Table 33.

The number of patients with clinically important elevations in ALT, AST, and CK are summarized in Table 34. For ALT and AST, elevations were defined as an elevation greater than 3 x ULN. For CK, an elevation greater than 10 x ULN was reported. The median changes in liver function tests and CK levels were analyzed using the ITT approach and are summarized in Table 35. Summaries for changes from baseline at Week 48, Month 24, and Month 36 in serum nutritional parameters are in Table 36. For all laboratory analyses, baseline was defined as the last measurement at or before Week 0 of the base study.

A predefined limit of change analysis was performed for specified serum chemistry, coagulation, and hematology parameters. A patient was classified as "above limit" or "below limit" if his change from the baseline response fell outside of the predefined limits of change at least once during the extension period. Results for these analyses are in Table 37 and Table 38.

The mean and median changes in vital signs parameters from baseline at Week 48, Month 24, and Month 36 were analyzed using the ITT approach and are summarized in Table 39. The number of patients who had 2 or more lines worsening in visual acuity during the study was determined. Patients in this category were further assessed for a 2- or more-grade worsening in any of the 7 categories of lens findings in the same eye.

Most tables discussed above show only summary statistics. For any analysis of continuous variables, a t-test was used to compare mean percent change equal to 0 within a treatment group. Since the t-test is based on the normal distribution assumption, each lipid and lipoprotein parameter was tested for normality using the Shapiro-Wilk test. If a parameter was not normally distributed, a Wilcoxon signed-rank test was applied to the parameter.

Assessor's comment: explanation is acceptable.

Issue resolved.

Q11. The comparison of adverse events, growth, sexual maturation, laboratory parameter and all other safety measurements between lovastatin/lovastatin groups of 3 years exposure versus placebo/lovastatin group of 2 years exposure is meaningless and inconclusive. This analysis should be carried out by comparing the study group, with children of the same age/gender/race <u>unexposed</u> to lovastatin.

<u>Company response</u>
This study was conducted many years ago and it is not possible to conduct an analysis of children of the same age/gender/race unexposed to lovastatin at this time.

Assessor's comment: resolved in spite unsatisfactory answer.

Issue resolved.

Q12. There is discrepancy in the values represented in the text and the table (28), for example lovastatin/lovastatin group, diastolic blood pressure, mean baseline= 67.0, mean value at 36 month = 67.4, but the change from baseline to month 36 = 4.5. The applicant must clarify whether this is a typing /calculation error or describe the statistical models that have been used.

<u>Company response</u>
This is neither a typing nor a calculation error. The discrepancy arises in that the summary statistics needed to calculate the change from baseline to month 36 are not available on the table. To do such a calculation from the table, the baseline for the 10 patients with a change from baseline to month 36 needs to be available. The table gives the month 36 mean for these 10 patients and the change for these 10 patients. However, the baseline mean is based on 25 patients, and therefore does not reflect the baseline mean for the subgroup of 10 patients who also had month 36 information and could contribute to the calculation of change.

Assessor's comment: the response is inadequate.

Issue unresolved

<u>Study P083:</u>

Q13. The applicant should provide the baseline data for weight, height, BMI and risk factors for cardiovascular heart disease, in tabulated format.

Company response

A summary analysis of the changes from baseline in weight, height and body mass index for each treatment period, is provided in Table 37, in section 8.6 of the Clinical Study Report. A complete analysis of the study patients and data sets is presented in Section 6 of the CSR. The baseline individual data is no longer readily available for this study, which is over 10 years old.

Assessor's comment: explanation is acceptable.

Issue resolved.

Comments from other Member States:

a) Comment: The data provided do not support mentioning a specific indication for children and adolescents in SPC section 4.1.

b) Comments: The data provided do not support mentioning a specific indication for children and adolescents in section 4.1. of the SmPC. The data provided neither support mentioning a posology in section 4.2 of the SmPC.

Rational:

1. A specific indication in paediatrics is not acceptable for the following reasons:
- The number of treated children with lovastatin is limited (less than 100 patients)
- Precisions should be given in the extension study P040X on discrepancies observed on lipid parameters : between table 16 (page 31) with completed " 0 " patients at M36 and the efficacy results given at M36 in table 18 (page 33), in table 21 (page 34), in table 22 and 23 (page 35), in table 24 (page 36). The applicant should clarify.
- The company should provide long term efficacy data

2. The posology as proposed is unclear and thus cannot support any mention of a specific wording in section 4.2 of the SmPC. In particular, the highest 40 mg dose has not been sufficiently justified.

Thus, we agree with the rapporteur request for supplementary information and questions 4 and 5 related to Study P040; indeed, the rational for a 40 mg dose escalation should be clarified.

In particular, the applicant should clarify whether all patients treated with a 40 mg dosage were really non reponders to a 20 mg dosage.

c) Comments: The National Institute of Pharmacy agrees with the overall conclusion and recommendation of the RMS and has no further comments.

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION

The entire response document is very spare, inadequate and most questions are left unanswered or fail to even address the issue. This is to some extent understandable due to the age of the study, but it is impossible to assess the data. The bases of dose selection were not clear in the initial report and were not clarified in the response document either. On the issue of missing data, the age of the study and unavailability of the source document are to some extent valid arguments, but the entire response is short and does not shed any light on the matter either. The additional questions from other members of states were left unanswered. On the whole the data does not support a paediatric indication, or a posology in 4.2 section of the SmPC.

The safety profile of lovastatin seems to resemble that of adults and no new safety concerns were found as a result of this study. However the MAH omitted to comment on the reduction of LH levels in the lovastatin group of the adolescent girls. This should be captured in section 4.8.

As the study has been carried out in 100 adolescents and despite all short comings, have shown some clear results, it is the Rapporteur's opinion that the summary of it should go in to section 5.1 of the SmPC. The current proposed text for 5.1 is too long and detailed; the applicant is requested to propose much shorter text for this section. No alteration to PIL is required.

IV. RECOMMENDATION

Based on the review of the presented paediatric data on safety and efficacy; and the assessment of responses to the list of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies do not support a paediatric posology. However, the incorporation of summaries of efficacy study in section 5.1, and a cross reference in section 4.2 of the SmPC will be helpful to the prescriber.

The safety profile of lovastatin generally resembles that of adults and no new adverse events in children have emerged as a result of the submitted data. In the adolescent girls the LH levels in the lovastatin group was significantly reduced ($p<0.04$). This should be captured in section 4.8.

The following changes to the SmPC were proposed by the applicant. The assessor's amendments and recommendations on the text are in italics and strike through:

Summary of Product Characteristics

4.2 Posology and method of administration

The safety and efficacy of MEVACOR in children has not yet been established. Currently available data are described in section 4.8, 5.1 but no recommendation on a posology can be made.

4.4 Special warnings and precautions for use

Paediatric Population

In limited controlled studies (See sections 4.8, and 5.1), there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. Adolescent females should be counselled on appropriate contraceptive methods while on lovastatin therapy (see sections 4.3 and 4.6). MEVACOR has not been adequately studied in pre-pubertal children or pre-menarchal girls, nor in patients younger than 10 years of age.

4.8 Undesirable effects

Paediatric population

Safety and effectiveness of lovastatin (10, 20 & 40 mg daily) in 100 children 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and 24 weeks duration in girls who were at least one year post-menarche. Doses greater than 40 mg have not been studied in this population.

The safety profile of MEVACOR obtained from these limited controlled studies was generally similar to adults; with the exception of a statistically significant reduction in LH levels in the adolescent girls treated with lovastatin.
There was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls (See sections 4.4 and 5.1).

5.1 Pharmacodynamic properties

Paediatric population

In a randomized, double-blind, placebo-controlled study, 132 boys, 10-17 years of age with heterozygous familial hypercholesterolemia (baseline LDL-C 189-500 mg/dL) were randomized to lovastatin (n=67) or placebo (n=65) for 48 weeks. The dosage of lovastatin once daily in the evening was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 19.3%, mean LDL-C by 24.2% and mean apolipoprotein B levels by 21%.

Similarly in another randomized, double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least one year post-menarche with heterozygous familial hypercholesterolemia (baseline LDL-C 160-400 mg/dL) were randomized to lovastatin (n=35) or placebo (n=19) for 24 weeks. The dosage of lovastatin once daily in the evening was 20 mg for the first 4 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 22.4%, mean LDL-C by 29.2%, mean apolipoprotein B levels by 24.4% and median triglycerides levels by 22.7%.

The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Package Leaflet:

Children
Lovastatin is not recommended for use in children and adolescents below 18 years of age because safety and efficacy of lovastatin in children has not been established.

VII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

AUSTRIA	Merck Sharp & Dohme GmbH	MEVACOR 10 mg Tabletten	1-21309	LOVASTATIN 10mg
AUSTRIA	Merck Sharp & Dohme GmbH	Mevacor 20 mg-Tabletten	1-18464	LOVASTATIN 20mg
GERMANY	MSD Sharp & Dohme GmbH	Mevinacor 20 mg Tabletten	15971.00.00	LOVASTATIN 20mg
GERMANY	MSD Sharp & Dohme GmbH	Mevinacor 40 mg Tabletten	15971.02.00	LOVASTATIN 40mg
GREECE	MSD (Vianex)	MEVACOR	12726/17-3-2003	LOVASTATIN 40mg
GREECE	MSD (Vianex)	MEVACOR	43218/02/17-3-2003	LOVASTATIN 20mg
PORTUGAL	Merck Sharp & Dohme, Lda.	MEVINACOR	8683748 (20 tab); 8683789 (30 tab); 8683755 (60 tab)	LOVASTATIN 20mg
PORTUGAL	Laboratorios Quimic-Farmaceuticos Chibret, Lda.	MEVLOR	2049799 (20 tab); 2049898 (60 Tab)	LOVASTATIN 20mg
PORTUGAL	Tecnifar Industria Tecnica Farmaceutica S.A.	TECNOLIP	9751131 (20 Tab); 9751172 (60 tab)	LOVASTATIN 20mg
SPAIN	Merck Sharp & Dohme de Espana, S.A.	MEVACOR 20 mg comprimidos	58.517	LOVASTATIN 20mg
SPAIN	Merck Sharp & Dohme de Espana, S.A.	MEVACOR 40 mg tablets	60.281	LOVASTATIN 40mg

Lek Pharmaceuticals

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