London, 01 July 2010
Doc.Ref.: EMA/511109/2010
Patient Health Protection

Assessment report for Sortis and associated names

International non-proprietary name: atorvastatin

Procedure number: EMEA/H/A-29 PAD/1253

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 5 November 2009 an application for a new paediatric appropriate pharmaceutical form in accordance with Article 29 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMEA).

The eligibility to the procedure was agreed upon by the EMEA/CHMP in July 2009.

The application was composed of administrative information, quality data and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain test(s) or studies.

Licensing status:

Sortis and associated names are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom, as well as in Iceland and Norway.

Information on Paediatric requirements
Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMEA Decision (P/53/2008) for the following condition(s):

- On the agreement of a paediatric investigation plan (PIP) heterozygous hypercholesterolaemia
- On the granting of a product-specific waiver for homozygous familial hypercholesterolaemia
- On the granting of a product-specific waiver for combined (mixed) hypercholesterolaemia
- On the granting of a product-specific waiver for primary hypercholesterolaemia
- On the granting of a product-specific waiver for prevention of cardiovascular disease

The PIP is completed.
The PDCO issued an opinion on compliance.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Problem statement

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism. It results from the partial or total lack of LDL-C receptors, which inhibits the degradation of LDL-C mainly by the liver and leads to the accumulation of LDL-C in plasma. In the Caucasian population, heterozygous FH (HeFH) affects approximately one in 500 individuals. The affected individual inherits an LDL-C receptor gene with a functionally significant mutation from one parent, resulting in an approximately 50% reduction in the number of functional LDL-C receptors. In some cases the mutations may include defects affecting Apo B. Homozygous FH (HoFH), when both genes are defective leaving all of the LDL-C receptors defective, affects approximately one in a million individuals, and results in LDL-C levels which can be up to 25 mmol/L causing severe atherosclerosis at a very early age. The severity of atherosclerosis can be correlated to the extent and duration of hypercholesterolemia. HeFH is also associated with increased morbidity of coronary heart disease (CHD) and with premature death.

Childhood cholesterol levels have been linked to an elevated incidence of CHD in adulthood. Studies have shown that cholesterol is deposited in the arteries as fatty streaks, including in the aorta at about 3 years of age and in the coronary arteries at about 10 years of age. There is a positive correlation between the plasma levels of TC, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), diastolic blood pressure and the extent of fatty streaks. Some male patients have been known to experience their first coronary event before the age of 30 years. These patients with familial hypercholesterolemia have two to six-fold elevations in LDL-C and lower HDL-C levels compared to the general population. The recent meta-analysis by Wald et al presents the median TC and LDL-C for patients with HeFH across age ranges.

Table 1. Pooled Median Serum TC and LDL-C concentrations in cases and controls according to age

Age Group (years)	Cases/controls	Concentration (mmol/L) (median)	
Total Cholesterol		**Cases**	**Controls**
Newborn	29/46	2.59	1.81
1-9	253/14085	7.80	4.16
10-19	972/360	7.27	4.31
20-39	341/844	8.79	5.12
40-59	237/721	8.68	6.14
>60	75/165	8.42	6.62
LDL Cholesterol			
Newborn	25/46	1.67	0.78
1-9	218/162	5.95	2.59
10-19	804/249	5.45	2.42
20-39	340/839	7.09	3.62
40-59	237/720	6.74	4.82
>60	75/165	6.01	5.28

Reproduced from Wald et al.[13]

Homozygous FH patients display a much more severe clinical phenotype with serum cholesterol levels usually greater than 15 mmol/L and as high as 25-30 mmol/L. Rapid atherosclerotic disease develops with all patients having developed some degree of disease involving the ascending aorta by puberty. When left untreated, sudden death from acute coronary syndrome or myocardial infarction occurs before the age of 30 and frequently considerably earlier (in the first decade of life).

Paediatric guidelines, published in 1992 by the National Cholesterol Education Program (NCEP) Expert Panel, recommend drug treatment of elevated lipid levels in children and adolescents >10 years of age

if, after adequate dietary modification, LDL-C is still ≥190 mg/dL (ie, ≥4.91 mmol/L) or LDL-C is ≥160 mg/dL (≥4.14 mmol/L) with either a positive family history of premature cardiovascular disease or two or more risk factors present.

The most recent scientific statement from the American Heart Association updated the NCEP guidelines, and advocates using statins as the first-line therapy for children and adolescents meeting criteria for starting lipid-lowering drug therapy. The American Heart Association recommends drug therapy in children >10 years of age after a 6 to 12 month trial of fat and cholesterol-restricted dietary management. In case of children and adolescents with high-risk lipid abnormalities that have additional risk factors or high-risk conditions, the recommended LDL-C level for initiation of drug therapy could be lower and in selected cases initiation of therapy could be considered below the age of 10 years.

About the product

Atorvastatin calcium is a synthetic 3 hydroxy-3 methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor. This enzyme is involved in cholesterol biosynthesis by catalyzing the conversion reaction of HMG-CoA to mevalonic acid. The function of lowering the amount of cholesterol leads to the result in clearing the low-density lipoprotein (LDP) receptor upregulation, and increased hepatic clearance of plasma LDL. The calcium salt of atorvastatin is used in the treatment of primary hypercholesterolemia and dyslipidemia.

Sortis and associated names 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets contain atorvastatin calcium as active substance. These medicinal products have been approved via national and/or mutual recognition procedures across EU. In the mutual recognition procedure Germany acted as Reference Member State.

The present application was submitted under Article 29 of Regulation (EC) No 1901/2006, as amended, to obtain approval for a new pharmaceutical form (chewable tablets) intended to be used as a suitable alternative for paediatric patients. Parallel applications have been submitted under Article 29 of Regulation (EC) No 1901/2006 as amended, to obtain approval for a lower strength of the same pharmaceutical form, as well as to extend the indication of the existing film-coated tablets to include treatment of hypercholesterolemia in paediatric patients aged 10 years or older and to update the product information to provide information for use of atorvastatin in the paediatric population.

Type of Application and aspects on development

On October 2007, the Applicant submitted an application for a Paediatric Investigation Plan to the EMEA (EMEA-000073-PIP01-07). The PDCO issued a positive opinion on the request for agreement to the Paediatric Investigation Plan on 4 June 2008. In November 2009 the PDCO adopted a positive opinion that the studies conducted by the applicant are in compliance with the agreed PIP and that the PIP was fully completed**.**

The following studies were included in the PIP:

Table 2. Summary of studies included in the Paediatric Investigation Plan

Study Number	Area	Subarea	Description
#1	Clinical	Bioequivalence	Bioequivalence study of the final age-appropriate oral atorvastatin formulation to the existing atorvastatin formulation in healthy adult volunteers
#2	Clinical	Pharmacokinetic, safety	Steady-state, eight week pharmacokinetic study of atorvastatin in children and adolescents (aged 6 years to less than 18 years) with heterozygous familial hypercholesterol-aemia using sparse PK sampling methodology and including flow-mediated artery dilatation assessments
#3	Clinical	Safety	A 3-year study of the safety and follow-up study of efficacy of atorvastatin treatment of children and adolescents (aged 6 years to less than 18 years) with heterozygous familial hypercholesterolaemia*

*** Study to be initiated by the date of completion of the paediatric investigation plan**

2.2. Quality aspects

Introduction

A new formulation (chewable tablet) has been developed as an alternative treatment option to the current commercial formulation (film-coated tablets).
The chewable tablets contain 10 mg, 20 mg and 40 mg of atorvastatin as active substance (corresponding to 10.85 mg, 21.70 mg and 43.40 mg atorvastatin calcium).
The other ingredients are calcium carbonate, croscarmellose sodium, microcrystalline cellulose, polysorbate 80, hydroxypropyl cellulose, pregelatinized starch, purified water, mannitol, aspartame, sucralose, magnesium stearate and flavour. The chewable tablets are marketed in PA/Alu/PVC blisters packed in cartons.

Active substance

The MAH confirmed that no further changes were made in the documentation already submitted for the active substance. The MAH has taken into account the quality information of active substance which has been assessed previously. In other words, the active substance used in the proposed formulation is identical with the one used in the manufacture of the approved Sortis and associated names film-coated tablets, which are marketed across EU.

Medicinal Product

Pharmaceutical Development

All information regarding the choice of the excipients is sufficiently justified.
The atorvastatin calcium chewable tablets were developed in strengths of 5 mg, 10 mg, 20 mg and 40 mg. These chewable tablets are differentiated by size and debossing. The composition of the commercial atorvastatin calcium chewable tablet formulation is identical to the clinical formulation.

Bioequivalence studies were conducted bracketing at the lowest and highest doses. Results of these studies demonstrated that atorvastatin 10 mg of chewable tablet formulation (administered as two 5 mg tablets) is bioequivalent to the 10 mg film-coated tablet and atorvastatin 80 mg of chewable tablet formulation (administered as two 40 mg tablets) is bioequivalent to the 80 mg film-coated tablet. Dissolution testes results show atorvastatin chewable tablets and atorvastatin film-coated tablets, which were used in the bioequivalence studies, met specifications at the time of release.

Adventitious Agents

Neither the excipients nor the active substance is derived from human or animal origin. It was noticed that Magnesium stearate used in this formulation is of vegetable origin.

Manufacture of the Product

The proposed commercial manufacturing process involves standard manufacturing processes such as wet granulation, blending, sieving and compression. The equipment used is commonly available in the pharmaceutical industry. No critical steps or intermediates have been identified. It was noted that the process validation scheme for the manufacture of the commercial chewable tablets was provided and considered satisfactory.

Product Specification

The proposed release and shelf life specifications provided contain the quality relevant characteristics required for this new formulation. Furthermore, the specifications were established according to the ICH guidelines and include the following tests: appearance, identification (TLC & HPLC), assay , impurities (HPLC), uniformity of dosage units (Ph.Eur.), dissolution (Ph.Eur.), hardness (Ph.Eur.) and microbial quality (Ph Eur).
The potential degradation products in chewable tablets are the same as those listed for the approved film-coated tablets. All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis data for five pilot scale batches of each strength confirm that the tablets can be manufactured reproducibly according to the agreed finished product specification.

Stability of the Product

Three batches of 5 mg, 40 mg chewable tablets and one batch of 10 mg and 20 mg chewable tablets packed in intended market containers were placed on stability under ICH conditions 25º C/60% RH for12 months, 30º C/65% RH for 12 months and 40º C/75% RH for 6 months. It was verified that the following parameters were controlled: appearance, assay, impurities, water content, dissolution (Ph.Eur.), hardness (Ph.Eur.) disintegration, and microbial quality (Ph Eur).
Photostability study was performed on one batch of each strength stored according to Note of Guidance on photostability test. No significant change was observed in the finished product as result of direct exposure to light. It was noticed that one batch of each strength was stored under stress conditions (thermal; humidity and light).
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substances manufacture and control is essentially the same as that reviewed for the already authorised strength.
Information on development, manufacture, and control of the new formulation (chewable tablet) have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. In this context, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

During the elaboration of the Paediatric Investigation Plan, it was agreed with the PDCO that no further pre-clinical studies were deemed necessary due to the substantial experience in terms of patient exposure.

Therefore, the application did not include any non-clinical data, but crossed-referred to the original Marketing Authorisation Application, for which an extensive non clinical program was conducted.

The non submission of an Environmental Risk Assessment was justified by the Applicant. This application is intended to update the product information with relevant information for the paediatric patients, but is not expected to significantly increase the usage of the atorvastatin as most of the paediatric patients included in the target population of this application are already being treated with atorvastatin film-coated tablets.

2.4. Clinical aspects

Introduction

The paediatric development program for the new indication comprises the following studies:

- Two completed bioequivalence studies in healthy volunteers investigating the chewable tablet formulation
- Four completed paediatric studies:
  - one pivotal PK/PD study (Study A2581172), conducted in accordance with the agreed PIP,
  - three supportive studies (Study 981-147, Study 981-336, and Study 981-080)
- An on-going follow-up study (Study A2581173) initiated in March 2009 to assess the efficacy and safety and tolerability in the long-term, conducted in accordance with the agreed PIP.

Table 3. Studies in paediatric patients providing efficacy data

Study Identification	Study Design	Study Population	Number of Subjects[a]	Study Arms	Duration of Follow-up	Efficacy Endpoints
A2581172	Open-label, multicenter	Children and adolescents with HeFH (Cohort A[b]: 6 to 12 yrs) (Cohort B[c]: 10 to <18 yrs)	39 (Cohort A: 15 subjects; Cohort B: 24 subjects)	Atorvastatin 5 mg/day OR 10 mg/day	8 weeks	LDL-C, TC, TG, HDL-C, LDL-C/ HDL-C, VLDL-C, Apo A-1, Apo B, FMD
981-147	Double-blind, placebo controlled, multicenter	Children and adolescents (10 to 17 yrs) with FH or severe HC	187	Atorvastatin 10 mg/day (n=140) OR Placebo (n=47)	26 weeks in double-blind phase; 26 weeks open-label extension	LDL-C, TC, TG, HDL-C, Apo A-1, Apo B
981-336	Open-label, parallel group, multicenter	Children and adolescents (10 to 18 yrs) with FH and HC	56	Atorvastatin 10 mg/day (n=25) OR Colestipol 5 g/day (n=31)	52 weeks	LDL-C, TC, TG, HDL-C, VLDL-C, TC/HDL-C, LDL-C/ HDL-C
981-080	Open-label, compassionate-use, multicenter	HoFH or SHC	335 (2 to 73 years of age; 46 patients <18 years of age)	Atorvastatin 2.5 mg/day to 160 mg/day	<2 weeks to >2 years	LDL-C, TC, TG, HDL-C

[a] Number of subjects randomized. [b] Tanner Stage 1. [c] Tanner Stage ≥2.
Abbreviations: HeFH=heterozygous familial hypercholesterolemia; FH=familial hypercholesterolemia; HC=hypercholesterolemia; LDL-C= low-density lipoprotein cholesterol; TC=total cholesterol; TG= triglycerides; HDL-C=high-density lipoprotein cholesterol; VLDL-C=very low-density lipoprotein cholesterol; Apo A-1=apolipoprotein A-1; Apo B=apolipoprotein B; FMD= Flow-mediated dilatation; HoFH=homozygous familial hypercholesterolemia; SHC=non homozygous severe hypercholesterolemia; n=number.

Bioequivalence between the chewable tablets and the film-coated tablets have been demonstrated by means of two bioequivalence studies (A2581174 and A25811175).

GCP aspects

The MAH has conducted two bioequivalence studies to support this line extension of chewable tablets for paediatric use:
1.- An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a Paediatric Appropriate Formulation to a 10 mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects, and
2.- An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a New 80 mg (2x40 mg) Paediatric Appropriate Formulation to an 80 mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects.

The MAH has declared that these studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed.

Pharmacokinetics

According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence *CPMP/EWP/QWP/1401/98,* a bioequivalence study investigating only one strength may be acceptable if a new application concerns several strengths of the active substance. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. The two extremes of the strength range have been investigated due to the non-linear kinetics of atorvastatin, and it was concluded that the evidence of bioequivalence demonstrated for the 5 and 40 mg chewable tablets can be extrapolated to the 10 and 20 mg strengths.

Bioequivalence study for the 5 mg strength (study A2581174): An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a Paediatric Appropriate Formulation to a 10 mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects

Objective
Primary objective:
- To determine whether two 5 mg (10 mg) of a new atorvastatin calcium chewable tablets were bioequivalent to one 10 mg commercial atorvastatin calcium tablet formulation.

Secondary objective:
- Assess safety and tolerability of atorvastatin in different formulations in healthy volunteers.

Study design
This was an open label, randomized, single-dose, 2-way crossover study in 74 healthy subjects. Subjects attended a screening visit and participated in 2 treatment periods each of 5 days. The 2 treatment periods were separated by a washout period of at least 14 days and were preceded by an 8-hour overnight fast. Each subject received one 10 mg tablet of a commercial tablet formulation or two 5 mg (10 mg) tablets of the chewable tablet formulation according to a randomization schedule. During treatment period 2, subjects received the study treatment not administered in treatment period 1.

During both treatment periods, blood samples were collected before dosing on Day 1, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after dosing with either the new or commercial atorvastatin tablets. Plasma samples were analyzed for concentrations of atorvastatin and its active hydroxyacid metabolites (ortho-hydroxyatorvastatin and para-hydroxyatorvastatin) using a validated, sensitive, and specific liquid chromatography tandem mass spectrometric (LC/MS/MS) method. The following pharmacokinetic (PK) parameters were calculated for atorvastatin acid, ortho-

hydroxyatorvastatin, and para-hydroxyatorvastatin: Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUClast); area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUCinf); maximum plasma concentration (Cmax), time for Cmax (Tmax), and the terminal elimination half-life (t1/2).

Subject disposition

Seventy-four (74) subjects were planned to be enrolled in this study. Seventy-six (76) subjects were assigned to study treatment. Of the 76 subjects who were assigned to treatment, 2 were replacement subjects for 2 of the 4 subjects who discontinued from the study. Four subjects did not complete the study. In one case the subject discontinued for a reason not related to study treatment (subject was withdrawn because of a positive urine drug test) and 3 subjects discontinued because they were no longer willing to participate in study.

Table 4. Subject disposition

Number (%) of subjects	**Two 5 mg (10 mg) Tablets of New Atorvastatin**	**One 10 mg Tablet of Commercial Atorvastatin**
	n (%)	***n (%)***
Assigned to study treatment N = 76		
Treated	75	76
Completed	75 (100.0)	72 (94.7)
Discontinued	0	4 (5.3)
Not related to study treatment		
Other	0	1 (1.3)
Subject no longer willing to participate in study	0	3 (3.9)

N = number of subjects randomized; n = number of subjects in the indicated category.

Pharmacokinetic Variables

The PK parameter analysis set, which was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period, was used for PK parameter analyses. Primary study endpoints were AUClast, AUCinf (if data permitted), and Cmax from plasma atorvastatin concentration data. Secondary endpoints included Tmax and t1/2 (if data permitted) of atorvastatin; AUClast, AUCinf, Cmax, Tmax, and t1/2 (if data permitted) of ortho-hydroxyatorvastatin and para-hydroxyatorvastatin. AUClast was calculated by the linear/Log trapezoidal method. AUCinf was calculated as AUClast + (Clast*/kel), where Clast was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. Cmax was observed directly from data.

Statistical methods

Natural log transformed AUCinf (if data permitted), AUClast, and Cmax of atorvastatin were analyzed using a mixed effects model with sequence, period, and treatment as fixed effects and subject-within-sequence as a random effect. Estimates of the adjusted mean differences of the Test (new atorvastatin [two 5 mg] tablets) to Reference (commercial atorvastatin [one 10 mg] tablet) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Residuals from the model were examined for normality and the presence of outliers via visual inspection of plots of residuals versus predicted values and normal probability plots of residuals. Bioequivalence of the Test to Reference was concluded if the 90% CIs for the ratios (Test/Reference) of adjusted geometric means for both AUCinf (if data permitted, otherwise AUClast) and Cmax of atorvastatin fell entirely within (80%, 125%).

The statistical model is considered adequate.

Results

After dosing with 10 mg atorvastatin, the pharmacokinetics of both atorvastatin and its ortho-hydroxyatorvastatin metabolite were similar for the new atorvastatin (two 5 mg) and the commercial atorvastatin (one 10 mg) tablet formulations (Table 5).

Table 5. Descriptive Summary of Plasma Atorvastatin and Ortho-Hydroxyatorvastatin Pharmacokinetic Parameters

PK Parameter[a] (units)	Two (5 mg) Tablets of New Atorvastatin (N = 75)		One 10 mg Tablet of Commercial Atorvastatin (N = 76)	
	Atorvastatin	Ortho-Hydroxyatorvastatin	Atorvastatin	Ortho-Hydroxyatorvastatin
AUC_{inf} (ng.h/mL)	22.82 (40)	24.45 (37)	22.14 (41)	24.40 (37)[b]
AUC_{last} (ng.h/mL)	20.51 (43)	21.84 (41)	19.80 (43)	21.62 (42)
C_{max} (ng/mL)	3.799 (52)	1.482 (52)	3.508 (42)	1.519 (53)
T_{max} (h)	0.50 (0.25 – 1.50)	4.00 (0.50 – 9.02)	0.50 (0.40 – 4.00)	3.52 (0.48 – 9.00)
$t_{1/2}$ (h)	10.21 (2.9300)	10.82 (2.3281)	10.34 (2.9983)	11.03 (3.2634)[b]

AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration; AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max} = maximum plasma concentration; N = number of subjects evaluable for pharmacokinetics; PK = pharmacokinetic; T_{max} = time for C_{max}; $t_{1/2}$ = terminal elimination half-life.
[a] Geometric means (coefficient of variation %) for AUC_{inf}, AUC_{last}, and C_{max}; median (range) for T_{max}; and arithmetic mean (standard deviation) for $t_{1/2}$.
[b] Only 75 subjects contributed to these summary statistics.

PK Parameter (units)	Geometric Means		Ratio of Adjusted Geometric Mean[a]	90% CI for Ratio[a]
	Two (5 mg) Tablets of New Atorvastatin (N = 75)	One 10 mg Tablet of Commercial Atorvastatin (N = 76)		
AUC_{inf} (ng.h/mL)	22.78	22.13	102.91	99.02, 106.96
AUC_{last} (ng.h/mL)	20.48	19.80	103.48	99.34, 107.79
C_{max} (ng/mL)	3.80	3.51	108.13	98.75, 118.40

CI = confidence interval; N = number of subjects evaluable for pharmacokinetics; PK = pharmacokinetic.
PK parameters are defined in Table S4.
[a] The ratios (and 90% CI) are expressed as percentages.

The bioequivalence criteria were met for both Cmax and AUCinf of atorvastatin (Table 5). The 90% CIs for the ratio of the adjusted geometric means for both AUCinf and Cmax of atorvastatin lay entirely within the acceptance range for bioequivalence, ie, (80%, 125%).

For both the new and commercial atorvastatin tablet formulations, the plasma concentrations of para-hydroxyatorvastatin were below the limit of quantitation for most samples collected and the PK parameters could not be accurately calculated for the majority of subjects.

Safety data
There were no deaths, serious adverse events (AE), discontinuations due to AEs, or dose reductions due to AEs in this study. A similar percentage of subjects reported all causality AEs after dosing with the new atorvastatin (two 5 mg) tablets (5 [6.7%] subjects) and after dosing with the commercial atorvastatin (one 10 mg) tablet (4 [5.3%] subjects). A higher percentage of subjects reported treatment-related AEs after dosing with the new atorvastatin (two 5 mg) tablets (4 [5.3%] subjects) than after dosing with the commercial atorvastatin (one 10 mg) tablet (1 [1.3%] subject).
The safety profile of both products seems to be comparable although it is obvious that the study design was not powered to compare the safety profile.

Bioequivalence study for the 80 mg strength (study A2581175): An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study comparing a new 80 mg (2x40mg) Paediatric Appropriate Formulation to an 80 mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects

Objectives:
Primary objective:
- Determine whether 80 mg (2x40mg) of the new formulation atorvastatin calcium chewable tablets were bioequivalent to 80 mg of the commercial atorvastatin calcium tablet formulation.

Secondary objective:

- Assess safety and tolerability of atorvastatin in different formulations in healthy volunteers.

Study design
This was an open label, randomized, single-dose, 2-way crossover study in 74 healthy subjects. Subjects attended a screening visit and participated in 2 treatment periods each of 5 days. The 2 treatment periods were separated by a washout period of at least 14 days and were preceded by an 8-hour overnight fast. Each subject received one 80 mg tablet of the commercial atorvastatin tablet formulation or two 40 mg (80 mg) tablets of the new atorvastatin calcium chewable tablet formulation according to a randomization schedule. During Treatment Period 2, subjects received the study treatment not administered in Treatment Period 1.

During both treatment periods, blood samples were collected before dosing on Day 1, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after dosing with either the new or commercial atorvastatin tablets. Plasma samples were analyzed for concentrations of atorvastatin and its active hydroxyacid metabolites (ortho-hydroxyatorvastatin and para-hydroxyatorvastatin) using a validated, sensitive and specific liquid chromatography tandem mass spectrometric (LC/MS/MS) method. The following pharmacokinetic (PK) parameters were calculated for atorvastatin acid, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin: Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUClast); area under the plasma concentration-time profile from time zero extrapolated to infinite time ([AUCinf], if data permitted); maximum plasma concentration (Cmax), time for Cmax (Tmax), and the terminal elimination half-life ([t1/2], if data permitted).

Subject disposition
Seventy-four (74) subjects were planned to be enrolled in this study. Seventy-six (76) subjects were assigned to study treatment: 73 subjects received the new atorvastatin (two 40 mg) tablets and 75 subjects received the commercial atorvastatin (one 80 mg) tablet. Seventy-two (72 [98.6%]) subjects completed treatment with the new atorvastatin (two 40 mg) tablets and 70 (93.3%) subjects completed treatment with the commercial atorvastatin (one 80 mg) tablet. One (1.4%) subject after dosing with the new atorvastatin (two 40 mg) tablets and 5 (6.7%) subjects after dosing with the commercial atorvastatin (one 80 mg) tablet were discontinued from the study. Two subjects were discontinued from the study after dosing with the commercial atorvastatin (one 80 mg) tablet because of treatment-related AEs, and 3 subjects were discontinued from the study after dosing with the commercial (one 80 mg) tablet because of other reasons not related to the study treatment.

Pharmacokinetic Variables
The PK parameter analysis set, which was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period, was used for PK parameter analyses. Primary study endpoints were AUClast, AUCinf (if data permitted), and Cmax from plasma atorvastatin concentration data. Secondary endpoints included Tmax and t1/2 (if data permitted) of atorvastatin; AUClast, AUCinf, Cmax, Tmax, and t1/2 (if data permitted) of ortho-hydroxyatorvastatin and para-hydroxyatorvastatin. AUClast was calculated by the linear/Log trapezoidal method. AUCinf was calculated as AUClast + (Clast*/kel), where Clast was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. Cmax was observed directly from data.

Statistical methods
Bioequivalence of PK parameters of atorvastatin was to be determined by constructing 90% CIs around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model was implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.
Natural log transformed AUCinf (if data permitted), AUClast, and Cmax of atorvastatin were analyzed using a mixed effects model with sequence, period, and treatment as fixed effects and subject-within-sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.
Residuals from the model were examined for normality and the presence of outliers via visual inspection of plots of residuals versus predicted values and normal probability plots of residuals.
Bioequivalence of the Test to Reference was demonstrated if the estimated 90% CIs for the ratios (Test/Reference) of adjusted geometric means for both AUCinf (if data permitted, otherwise AUClast) and Cmax of atorvastatin fell entirely within (80%, 125%).
The statistical model is considered adequate.

Results

After dosing with 80 mg atorvastatin, the pharmacokinetics of atorvastatin were similar for the new atorvastatin (two 40 mg) and the commercial atorvastatin (one 80 mg) tablet formulations (Table 6).

Table 6. Descriptive Summary of Plasma Atorvastatin Pharmacokinetic Parameters

PK Parameter[a] (units)	Two 40 mg (80 mg) Tablets of New Atorvastatin (N=73)	One 80 mg Tablet of Commercial Atorvastatin (N=75)
AUC_{inf} (ng.h/mL)	131.9 (41)	124.5 (40)
AUC_{last} (ng.h/mL)	128.2 (43)	121.3 (41)
C_{max} (ng/mL)	29.23 (49)	28.94 (50)
T_{max} (h)	0.50 (0.25 – 6.02)	0.50 (0.50 – 6.00)
$t_{1/2}$ (h)	6.059 (2.3267)	6.479 (2.0262)

AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration; AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max} = maximum plasma concentration; T_{max} = time for C_{max}; $t_{1/2}$ = terminal elimination half-life; N = number of subjects evaluable for pharmacokinetics; PK = pharmacokinetic.

[a] Geometric mean (coefficient of variation %) for AUC_{inf}, AUC_{last}, and C_{max}; median (range) for T_{max}; and arithmetic mean (standard deviation) for $t_{1/2}$.

The bioequivalence criteria were met for both Cmax and AUCinf of atorvastatin (Table 7). The 90% CIs for the ratio of the adjusted geometric means for both AUCinf and Cmax of atorvastatin lay entirely within the acceptance range for bioequivalence (80%, 125%).

Table 7. Statistical Summary of Treatment Comparisons for Plasma Atorvastatin Pharmacokinetic Parameters

	Adjusted Geometric Mean			
PK Parameter[a] (units)	Two 40 mg (80 mg) Tablets of New Atorvastatin (N=73)	One 80 mg Tablet of Commercial Atorvastatin (N=75)	Ratio of Adjusted Geometric Means[b]	90% CI for Ratio[b]
AUC_{inf} (ng.h/mL)	131.13	124.03	105.73	100.69, 111.02
AUC_{last} (ng.h/mL)	127.49	120.79	105.55	100.34, 111.03
C_{max} (ng/mL)	29.24	28.85	101.37	92.39, 111.23

CI = confidence interval; N = number of subjects evaluable for pharmacokinetics; PK = pharmacokinetic.

PK parameters are defined in **Table S4**.

[a] Geometric mean (coefficient of variation %) for all PK parameters.

[b] The ratios (and 90% CIs) are expressed as percentages.

Geometric mean AUCinf and Cmax, median Tmax, and mean t1/2 of ortho-hydroxyatorvastatin were similar for the new atorvastatin (two 40 mg) and commercial atorvastatin (one 80 mg) tablet formulations (Table S6). Geometric mean Cmax and median Tmax of para-hydroxyatorvastatin were similar for the new atorvastatin (two 40 mg) and commercial atorvastatin (one 80 mg) tablet formulations (Table S6). Geometric mean AUCinf and t1/2 of para-hydroxyatorvastatin were not reported as les s than 50% of subjects were evaluable for these parameters for both the new and commercial atorvastatin tablet formulations.

Safety data

There were no deaths or serious AEs reported in this study. Three subjects were permanently discontinued from the study due to AEs: 2 subjects after dosing with the commercial atorvastatin (one 80 mg) tablet and 1 subject after dosing with the new atorvastatin (two 40 mg) tablets. One subject was temporarily discontinued from the study due to an AE after dosing with the commercial atorvastatin (one 80 mg) tablet.

A higher percentage of subjects reported all causality AEs after dosing with the new atorvastatin (two 40 mg) tablets (19 [26.0%] subjects) than after dosing with the commercial atorvastatin (one 80 mg) tablet (14 [18.7%] subjects). However a similar number of subjects reported treatment-related AEs after dosing with the new atorvastatin (two 40 mg) tablets (9 [12.3%] subjects) and after dosing with the commercial atorvastatin (one 80 mg) tablet (9 [12.0%] subjects).

Overall, the AE profiles for both treatments in this study were consistent with the currently approved product information for commercial atorvastatin. The safety profile of both products seems to be comparable although the study design was not powered to compare the safety profile.

Pharmacokinetics/Pharmacodynamics

PK/PD Pivotal Study (Study A2581172): An 8-Week, Open-Label, Phase 1 Study to Evaluate Pharmacokinetics, pharmacodynamics, Safety and Tolerability of Atorvastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolemia

The study was conducted in three centres, in Canada, Greece, and Norway.

Objectives:
Primary objective:
- To develop population pharmacokinetic (PK) models for atorvastatin and its active metabolites (ortho-hydroxyatorvastatin and para-hydroxyatorvastatin) in children and adolescents with HeFH, and to examine the influence of covariates on the PK parameters.

Secondary objectives:
- To assess the pharmacodynamic (PD) responses of atorvastatin in children and adolescents with HeFH, exploring the relationship between exposure and PD responses. The PD variables were LDL-C, TC, TG, HDL-C, VLDL-C, Apo A-1, and Apo B.
- To assess the safety and tolerability of atorvastatin in children and adolescents with HeFH.

Tertiary objective:
- To provide descriptive information on flow-mediated dilatation (FMD) of the brachial artery at Week 0 and at Week 8 in children and adolescents with HeFH, for whom consent for the procedure was given, at centres with established FMD facilities.

Study Participants:
A total of 39 children and adolescents, aged 6 to 17 years, were enrolled and treated with atorvastatin, with initial doses based on cohort age range. One cohort (Cohort A) included 15 patients, 6 to 12 years of age (mean = 8.7 years) and at Tanner Stage 1. The other cohort (Cohort B) included 24 patients, 10 to 17 years of age (mean = 13.5 years) and at Tanner Stage ≥2. All subjects had genetically confirmed HeFH and LDL-C ≥4 mmol/L at baseline. All subjects were Caucasian. The study included 20 males and 19 females. The mean body mass index (BMI) was 17.1 kg/m2 among Cohort A subjects, and 20.9 kg/m2 among Cohort B subjects. Subjects could take no concomitant medication, including antihyperlipidemic therapy, at study entry.

Treatments:
The initial dose of atorvastatin was 5 mg daily of a chewable tablet for Cohort A and 10 mg daily of a tablet formulation for Cohort B. The starting doses were based on analyses of data from paediatric subjects with hypercholesterolemia (Study 981-147), and from a dose-response study in adult subjects (Study A2581042). The data indicate that a minimally efficacious effect of atorvastatin, defined as a 35% to 40% reduction in LDL-C, occurs within the dose range of 0.1 to 0.3 mg/kg, in both adults and children. World Health Organization (WHO) population height/weight charts show the average weight for 6- and 10-year-olds is approximately 20 kg and 28 kg, respectively. A 5 mg starting dose in 6- to 10-year-old children would correspond to doses between 0.18 to 0.25 mg/kg/day, which are within the effective dose range seen in adults and older children and adolescents.
The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of <3.35 mmol/L based on data at Week 4 and if atorvastatin was well tolerated. Thus, subjects in Cohort A and Cohort B could have received an increased daily dose of atorvastatin 10 mg (two 5-mg tablets) and 20 mg (two 10-mg tablets), respectively.

Variables:

- PK: A sparse PK sampling approach was used in this study. At Weeks 2 and 6, a single blood sample was taken between 4 and 12 hours postdose. At Weeks 4 and 8, blood samples were collected predose and at 1 and 2 hours postdose. There were a total of 310 blood samples from the 39 subjects. Samples were analyzed for atorvastatin and active metabolites (o-hydroxyatorvastatin and p-hydroxyatorvastatin).
- PD variables: percent changes from baseline for the following lipid parameters: LDL-C, TC, TG, HDL-C, LDL-C/HDL-C Ratio, VLDL-C, Apo A-1, and Apo B. These assessments were required to be

performed after a >10-hour fast. Blood samples were taken for the lipid profile assessments at Screening (Visit 1), Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 8 (Visit 6).

- FMD, conducted at centres with established FMD facilities, was used to assess endothelial function in the brachial arteries by means of high-resolution ultrasound to measure arterial diameter responses to increased blood flow. FMD was assessed at Weeks 0 and 8. For each scan, baseline vessel diameter (mm), Peak vessel diameter (mm) and FMD (%) were entered into the FMD database. FMD was calculated from these parameters as:

  Brachial FMD = ([maximum diameter - baseline diameter]/baseline diameter) x 100%.

Statistical analysis:
Population PK analyses were conducted via nonlinear mixed effects modelling. The concentrations of p-hydroxyatorvastatin were generally below the lower limit of quantification (LLQ) at the doses used in this trial, consistent with the results at the lower doses in adults; therefore, p-hydroxyatorvastatin was not included in the PK model. Exposure-response relationships were evaluated between atorvastatin, o-hydroxyatorvastatin, and atorvastatin plus o-hydroxyatorvastatin exposures and the PD endpoints (LDL-C, TC, and TG). Area under the concentration-time curve at steady state (AUCss) was utilized as the exposure metric.

The absolute and percent changes from baseline in the PD endpoints at Week 8 were analyzed for exposure-response relationship. The PD analysis population was defined as all enrolled subjects who received ≥1 dose of study drug and had ≥1 PD parameter measurement (ie, lipid values or FMD). Change and percent change from baseline in the PD lipid parameters (LDL-C, TC, TG, HDL-C, LDLC/ HDL-C Ratio, VLDL-C, Apo A-1, and Apo B) were summarized using descriptive statistics (N, mean, median, SD, minimum, and maximum) by cohort over time. FMD was summarized using descriptive statistics (N, mean, median, SD, minimum, and maximum) by cohort and by centre.

Results
Of the 39 subjects who were treated with atorvastatin, including 15 in Cohort A and 24 in Cohort B, all completed the study. All treated subjects were analyzed for PD (efficacy) variables.

Population PK Results:
The paediatric PK dataset consisted of atorvastatin, o-hydroxyatorvastatin, and p-hydroxyatorvastatin plasma concentrations in 310 blood samples from 39 subjects, with weight ranging from 25 to 99 kg. Age and weight distributions across Tanner Stages were consistent and lower in Tanner Stage 1 when compared to Tanner Stage ≥2 subjects. Renal and hepatic functions were within normal limits for all paediatric subjects. A combined parent-metabolite population PK model was developed, which utilized a 2-compartment model each with first-order absorption to describe atorvastatin PK and a 2-compartment model linked to the parent model to describe the o-hydroxyatorvastatin PK.

Atorvastatin apparent oral clearance (CL/F) was estimated at 699 L/hr (95% CI, 570, 881 L/hr) for the reference covariates Tanner Stage ≥2 and body weight of 70 kg. Given the reference covariates (Tanner Stage ≥2 and 70 kg weight), the population estimates (95% CI) of apparent atorvastatin central volume of distribution (Vc/F), apparent atorvastatin intercompartmental clearance (Q/F), apparent atorvastatin peripheral volume of distribution (Vp/F), absorption rate constant (Ka), apparent o-hydroxyatorvastatin clearance (CLm/fm), apparent o-hydroxyatorvastatin central volume of distribution (Vcm/fm), apparent ohydroxyatorvastatin intercompartmental clearance (Qm/fm), apparent o-hydroxyatorvastatin peripheral volume of distribution (Vpm/fm), and relative bioavailability (F1) were 1020 (209, 2210) L, 227 (80.2, 470) L/hr, 1960 (1390, 2460) L, 0.200 (0.139, 0.304) hr-1, 616 (518, 748) L/hr, 401 (272, 715) L, 368 (248, 562) L/hr, 2040 (1740, 2250) L, and 1 (fixed), respectively. For those subjects at Tanner Stage 1, the typical estimate (95% CI) for relative bioavailability factor (F1) was 0.752 (0.577, 1.01).

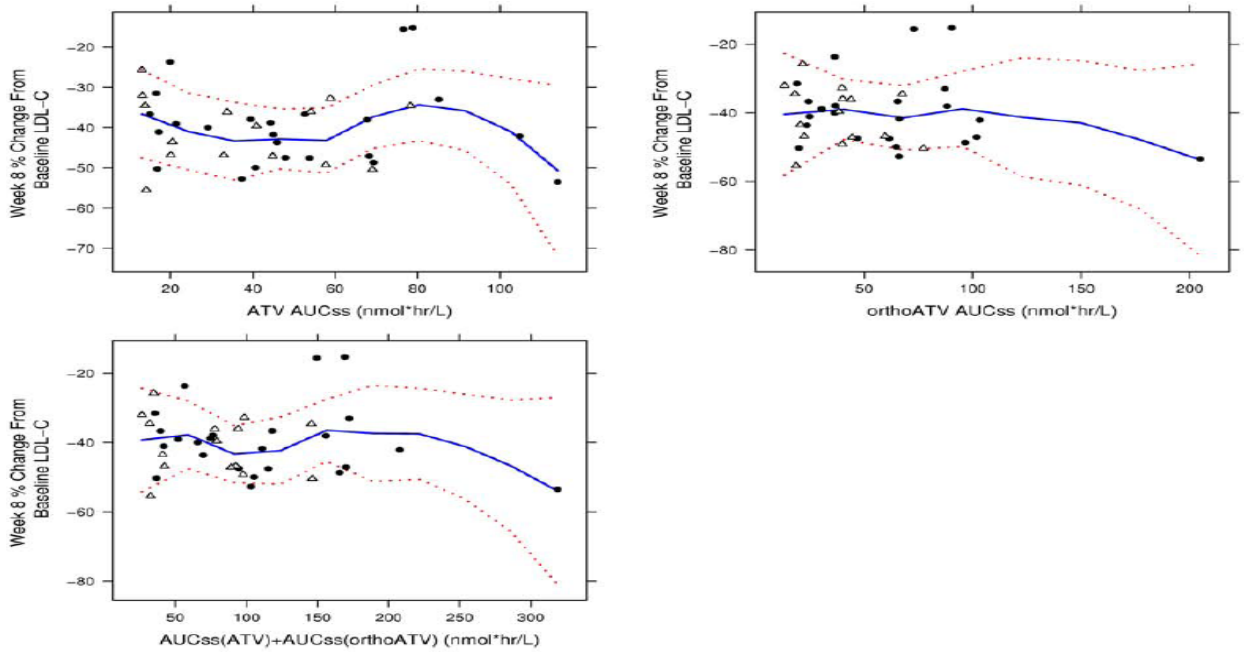
Furthermore, atorvastatin CL/F appears to be similar in paediatric subjects compared to adults when allometrically scaled by subject weight. The estimated typical atorvastatin CL/F was 543 L/hr for subjects with a body weight of 50 kg (approximate group mean for Tanner Stage ≥2 subjects). The estimated typical atorvastatin CL/F was 553 L/hr for subjects with a body weight of 35 kg (approximate group mean for Tanner Stage 1 subjects).
After accounting for the effect of body weight on CL/F (for atorvastatin), Vc/F, Q/F, Vp/F, CLm/fm, Vcm/fm, Qm/fm, and Vpm/fm using an allometric power model, the addition of other covariates resulted in little improvement of the model fit and unexplained interindividual variability. The interindividual variabilities were atorvastatin CL/F (46.3 %CV), Vc/F (106 %CV), and CLm/fm (43.3 %CV). Residual variability in both atorvastatin and o-hydroxyatorvastatin concentrations was approximately 40 %CV.

Exposure-Response Results:

An exploratory exposure-response analysis evaluated the relationship between atorvastatin, o-hydroxyatorvastatin, and atorvastatin+o-hydroxyatorvastatin exposure and the PD endpoints (LDL-C, TC, and TG). *AUCss* was utilized as the exposure metric to explore correlations with the absolute and percent change at Week 8 in the PD endpoints.

The exploratory analysis demonstrated a consistent absolute decrease in LDL-C and TC across all patients and a decrease in TG for most patients. At week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures in the current study. In addition, there did not appear to be any evidence of variations in pharmacodynamic effects between Tanner Stage patients or across the range of atorvastatin and/or o-hydroxyatorvastatin exposures. This is likely due to the Tanner-stage dependent doses and the titration dosing design in this study, wherein the patients were evaluated for dose escalation based on target levels or reduction in LDL.

Table 8. Percent change in LDL-C at week 8 plotted versus atorvastatin, o-hydroxyatorvastatin and atorvastatin+o-hydroxyatorvastatin AUCss. The plot symbol denotes Tanner stage with Tanner stage 1 as open triangles and Tanner stage 2 as solid circles. The blue line is a local regression fit trend line and the dotted red lines represent the 95% confidence interval for the local regression fit.



PD Results:

Results of the parameters measured are presented in the tables below:

Table 9. Descriptive statistics for LDL-C (mmol/L) by visit and final dose assignment.

		Tanner Stage 1			Tanner Stage ≥2		
		Atorvastatin Dose (After Titration Between Weeks 4 and 6) [a]					
Visit	Statistic	Subjects who Stayed at 5 mg	Subjects who Increased to 10 mg	All Tanner 1 Subjects	Subjects who Stayed at 10 mg	Subjects who Increased to 20 mg	All Tanner ≥2 Subjects
N		5	10	15	9	15	24
Baseline	Mean (SD)	4.87 (0.48)	6.37 (1.10)	5.87 (1.18)	5.11 (0.65)	6.23 (1.00)	5.81 (1.03)
	Min, max	4.4, 5.6	4.7, 8.2	4.4, 8.2	4.3, 6.1	4.3, 8.7	4.3, 8.7
Week 2	Mean (SD)	3.12 (0.92)	4.75 (1.02)	4.20 (1.24)	3.16 (0.59)	4.33 (0.83)	3.89 (0.94)
	Min, max	2.1, 4.5	2.9, 6.2	2.1, 6.2	2.2, 4.0	3.1, 5.9	2.2, 5.9
	Mean % change from baseline (SD)	-36.27 (14.72)	-25.70 (7.76)	-29.22 (11.28)	-38.14 (9.35)	-30.27 (9.22)	-33.22 (9.86)
Week 4	Mean (SD)	2.80 (0.40)	4.43 (0.80)	3.89 (1.04)	2.86 (0.43)	3.96 (0.52)	3.55 (0.72)
	Min, max	2.3, 3.2	3.4, 5.7	2.3, 5.7	2.1, 3.6	3.4, 4.9	2.1, 4.9
	Mean % change from baseline (SD)	-42.33 (8.24)	-30.27 (5.72)	-34.29 (8.67)	-43.66 (7.78)	-35.13 (12.01)	-38.33 (11.25)
Week 6	Mean (SD)	2.97 (0.44)	3.80 (0.64)	3.52 (0.69)	2.98 (0.64)	3.68 (0.37)	3.42 (0.59)
	Min, max	2.2, 3.3	3.0, 4.8	2.2, 4.8	2.3, 4.6	3.0, 4.2	2.3, 4.6
	Mean % change from baseline (SD)	-38.87 (7.84)	-40.01 (6.34)	-39.63 (6.61)	-41.22 (11.34)	-39.73 (10.40)	-40.29 (10.54)
Week 8	Mean (SD)	3.06 (0.54)	3.66 (0.80)	3.46 (0.76)	3.12 (0.40)	3.63 (0.43)	3.44 (0.48)
	Min, max	2.3, 3.6	2.7, 4.8	2.3, 4.8	2.6, 3.7	2.9, 4.6	2.6, 4.6
	Mean % change from baseline (SD)	-36.78 (11.16)	-42.70 (6.45)	-40.72 (8.41)	-38.45 (7.84)	-40.39 (11.71)	-39.66 (10.28)

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum.

[a] Upon review of a subject's Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject's dose could be doubled at 3 days (±1 day) after the Week 4 visit.

Table 10. Descriptive statistics for Total Cholesterol (mmol/L) by visit and final dose assignment.

		Tanner Stage 1			Tanner Stage ≥2		
		Atorvastatin Dose (After Titration Between Weeks 4 and 6) [a]					
Visit	Statistic	Subjects who Stayed at 5 mg	Subjects who Increased to 10 mg	All Tanner 1 Subjects	Subjects who Stayed at 10 mg	Subjects who Increased to 20 mg	All Tanner ≥2 Subjects
N		5	10	15	9	15	24
Baseline	Mean (SD)	6.76 (0.46)	8.58 (1.06)	7.97 (1.25)	6.92 (0.71)	8.40 (1.10)	7.84 (1.20)
	Min, max	6.3, 7.3	7.0, 10.4	6.3, 10.4	6.1, 7.9	6.7, 10.7	6.1, 10.7
Week 2	Mean (SD)	4.87 (0.92)	6.55 (1.27)	5.99 (1.39)	4.80 (0.71)	6.12 (0.80)	5.63 (0.99)
	Min, max	4.1, 6.4	4.1, 8.2	4.1, 8.2	3.7, 5.7	5.3, 7.8	3.7, 7.8
	Mean % change from baseline (SD)	-28.06 (11.23)	-24.11 (8.97)	-25.43 (9.57)	-30.60 (7.49)	-26.78 (7.59)	-28.21 (7.63)
Week 4	Mean (SD)	4.49 (0.41)	6.34 (0.84)	5.72 (1.15)	4.55 (0.54)	5.74 (0.55)	5.29 (0.79)
	Min, max	4.0, 5.0	5.0, 7.4	4.0, 7.4	3.7, 5.2	5.0, 6.7	3.7, 6.7
	Mean % change from baseline (SD)	-33.37 (7.81)	-26.12 (4.24)	-28.54 (6.44)	-33.98 (7.13)	-30.54 (11.60)	-31.83 (10.12)
Week 6	Mean (SD)	4.73 (0.60)	5.72 (0.75)	5.39 (0.83)	4.64 (0.71)	5.45 (0.37)	5.15 (0.65)
	Min, max	3.8, 5.2	4.6, 7.0	3.8, 7.0	3.8, 6.2	4.5, 5.9	3.8, 6.2
	Mean % change from baseline (SD)	-29.99 (8.00)	-33.12 (6.83)	-32.08 (7.11)	-32.80 (8.97)	-34.06 (9.94)	-33.59 (9.41)
Week 8	Mean (SD)	4.87 (0.39)	5.39 (0.75)	5.21 (0.69)	4.66 (0.65)	5.18 (0.49)	4.99 (0.60)
	Min, max	4.4, 5.4	4.3, 6.6	4.3, 6.6	3.6, 5.6	4.1, 6.1	3.6, 6.1
	Mean % change from baseline (SD)	-27.80 (5.56)	-37.17 (5.28)	-34.05 (6.90)	-32.43 (8.53)	-37.45 (9.89)	-35.57 (9.54)

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum.

[a] Upon review of a subject's Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject's dose could be doubled at 3 days (±1 day) after the Week 4 visit.

Table 11. Descriptive statistics for Trygliceride (mmol/L) by visit and final dose assignment.

		Tanner Stage 1			Tanner Stage ≥2		
		Atorvastatin Dose (After Titration Between Weeks 4 and 6) [a]					
Visit	Statistic	Subjects who Stayed at 5 mg	Subjects who Increased to 10 mg	All Tanner 1 Subjects	Subjects who Stayed at 10 mg	Subjects who Increased to 20 mg	All Tanner ≥2 Subjects
N		5	10	15	9	15	24
Baseline	Mean (SD)	0.76 (0.15)	0.95 (0.27)	0.89 (0.25)	1.03 (0.37)	1.20 (0.50)	1.14 (0.46)
	Min, max	0.6, 0.9	0.5, 1.4	0.5, 1.4	0.5, 1.6	0.7, 2.3	0.5, 2.3
Week 2	Mean (SD)	0.81 (0.39)	0.87 (0.30)	0.85 (0.32)	1.08 (0.38)	1.21 (0.67)	1.16 (0.57)
	Min, max	0.5, 1.5	0.5, 1.4	0.5, 1.5	0.5, 1.7	0.5, 2.8	0.5, 2.8
	Mean % change from baseline (SD)	5.66 (38.26)	-6.87 (29.08)	-2.69 (31.61)	28.37 (85.32)	-0.56 (32.19)	10.29 (58.03)
Week 4	Mean (SD)	0.71 (0.30)	0.69 (0.17)	0.70 (0.21)	0.93 (0.38)	1.10 (0.55)	1.04 (0.49)
	Min, max	0.4, 1.1	0.5, 1.0	0.4, 1.1	0.5, 1.7	0.5, 2.5	0.5, 2.5
	Mean % change from baseline (SD)	-6.20 (32.55)	-21.43 (30.42)	-16.35 (30.87)	1.27 (50.81)	-7.60 (25.75)	-4.28 (36.34)
Week 6	Mean (SD)	1.17 (0.60)	0.91 (0.27)	1.00 (0.40)	0.91 (0.29)	1.16 (0.52)	1.07 (0.46)
	Min, max	0.5, 2.1	0.6, 1.3	0.5, 2.1	0.6, 1.5	0.4, 2.1	0.4, 2.1
	Mean % change from baseline (SD)	57.06 (78.73)	-1.27 (23.91)	18.18 (54.30)	-4.43 (32.52)	-2.72 (24.80)	-3.36 (27.25)
Week 8	Mean (SD)	0.79 (0.34)	0.79 (0.23)	0.79 (0.26)	0.72 (0.24)	0.92 (0.42)	0.84 (0.37)
	Min, max	0.5, 1.4	0.5, 1.2	0.5, 1.4	0.5, 1.2	0.5, 1.8	0.5, 1.8
	Mean % change from baseline (SD)	1.69 (31.48)	-9.88 (33.31)	-6.02 (32.06)	-20.94 (39.24)	-21.11 (23.85)	-21.05 (29.69)

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum.

[a] Upon review of a subject's Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject's dose could be doubled at 3 days (±1 day) after the Week 4 visit.

Table 12. Descriptive statistics for HDL-C (mmol/L) by visit and final dose assignment.

		Tanner Stage 1			Tanner Stage ≥2		
		Atorvastatin Dose (After Titration Between Weeks 4 and 6) [a]					
Visit	Statistic	Subjects who Stayed at 5 mg	Subjects who Increased to 10 mg	All Tanner 1 Subjects	Subjects who Stayed at 10 mg	Subjects who Increased to 20 mg	All Tanner ≥2 Subjects
N		5	10	15	9	15	24
Baseline	Mean (SD)	1.35 (0.12)	1.45 (0.29)	1.41 (0.25)	1.17 (0.18)	1.18 (0.23)	1.18 (0.21)
	Min, max	1.2, 1.5	0.9, 2.0	0.9, 2.0	0.9, 1.4	0.8, 1.5	0.8, 1.5
Week 2	Mean (SD)	1.43 (0.31)	1.35 (0.36)	1.37 (0.34)	1.12 (0.31)	1.17 (0.31)	1.15 (0.31)
	Min, max	1.1, 1.8	0.8, 1.8	0.8, 1.8	0.8, 1.8	0.7, 1.8	0.7, 1.8
	Mean % change from baseline (SD)	5.38 (17.32)	-6.45 (21.01)	-2.51 (20.07)	-4.11 (19.96)	-0.77 (17.66)	-2.02 (18.20)
Week 4	Mean (SD)	1.32 (0.16)	1.45 (0.20)	1.40 (0.19)	1.18 (0.30)	1.18 (0.25)	1.18 (0.26)
	Min, max	1.1, 1.5	1.1, 1.8	1.1, 1.8	0.8, 1.6	0.9, 1.6	0.8, 1.6
	Mean % change from baseline (SD)	-1.99 (3.90)	1.59 (13.18)	0.40 (10.91)	1.04 (17.38)	1.77 (23.22)	1.50 (20.81)
Week 6	Mean (SD)	1.22 (0.37)	1.43 (0.30)	1.36 (0.33)	1.20 (0.23)	1.15 (0.31)	1.17 (0.28)
	Min, max	0.7, 1.7	0.9, 2.0	0.7, 2.0	0.9, 1.5	0.7, 1.8	0.7, 1.8
	Mean % change from baseline (SD)	-10.18 (22.70)	-0.64 (10.35)	-3.82 (15.42)	3.28 (11.63)	-2.78 (21.49)	-0.51 (18.36)
Week 8	Mean (SD)	1.39 (0.31)	1.38 (0.21)	1.38 (0.24)	1.24 (0.34)	1.11 (0.23)	1.16 (0.28)
	Min, max	1.1, 1.9	1.1, 1.7	1.1, 1.9	0.8, 1.8	0.8, 1.5	0.8, 1.8
	Mean % change from baseline (SD)	2.50 (15.02)	-2.84 (14.49)	-1.06 (14.36)	5.99 (21.02)	-5.19 (17.76)	-1.00 (19.40)

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.
SD = standard deviation; min = minimum; max = maximum.
[a] Upon review of a subject's Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject's dose could be doubled at 3 days (±1 day) after the Week 4 visit.

FMD values for subjects in Cohort A ranged from 0.0% to 11.5% at baseline and from 0.0% to 12.0% at Week 8. Similarly, the FMD values for subjects in Cohort B ranged widely, from 0.0% to 10.0% at baseline and from 2.9% to 9.3% at Week 8.

Discussion of the results

The most important finding in the population PK analysis was that atorvastatin clearance (CL/F) appears similar in paediatric subjects compared with adults when scaled by subject weight and that body weight was the only covariate influencing atorvastatin CL/F. Other covariates such as age, gender and Tanner stage had little influence on the PK parameters tested. The interindividual variability of the main PK parameters in the study was high but this does not invalidate the main conclusions.
Results of the exploratory PK/PD analysis assessing the relationship between AUCss of atorvastatin and PD endpoints (LDL-C, TC, and TG) shows a percent change from baseline in LDL-C and TC of approximately 40% and 30%, respectively, at the exposure level reached with the tested doses.
Study A2581172 demonstrated a clinically relevant reduction in lipid parameters from baseline to the end of week 8 in all cohorts. The measurements of FMD were non-conclusive.
For the efficacy part of the study the number of study subjects is small, especially the number of children below the age of 10 years. As the study is small, open, and not placebo controlled the results regarding efficacy are of limited value. The small number of subjects did not allow for comparative statistical analyses.

The mean % change from baseline for LDL-C (mmol/L) after 8 weeks of treatment was between 35-40% in both cohorts of patients. The mean baseline LDL-C was higher in those patients who needed to double the dose after 4 weeks of treatment vs. those who did not need a dose adjustment (6.37 vs. 4.87 in Cohort A and 6.23 vs. 5.11 in cohort B), but in both subgroups the final mean % change from baseline was similar after the 8 week treatment period. The final absolute value was also of the same range; although in the subgroup of patients who needed an increased dose the final level was slightly higher than the target LDL-C of 3.35 mmol/L. In this patient population with higher LDL-C baseline levels, a higher dose than the ones used in the trial (10mg/20 mg) could be necessary to achieve the LDL-C target, particularly in case of patients with high risk for developing cardiovascular disease. Greater reductions in lipid parameters with increasing doses were observed, but the desirable

treatment goal for LDL according to the AHA guidelines was not reached for the treated groups. The TC changes are also of the same range in both cohorts but the effect over TG and HDL is not so consistent between the low and higher doses.

Clinical efficacy

Three supportive studies have been submitted: Study 981-147, Study 981-336 and Study 981-080.

Study 981-147: A 1-Year Study in Children and Adolescents With Familial or Severe Hypercholesterolemia Comparing Atorvastatin to Placebo (6-Month Double-Blind Treatment), Followed by Atorvastatin Open-Label Treatment for 6 Months

The study was conducted at 20 centres in the following countries: Canada, France, Ireland, Norway, South Africa, Spain, Sweden, the United Kingdom, and the United States.

Objectives:

- To demonstrate the safety and efficacy of atorvastatin in decreasing elevated lipid levels in children and adolescents between 10 and 17 years of age who had familial or severe hypercholesterolemia.

Population:
187 boys and postmenarchal girls 10 to 17 years of age (mean age, 14.1 years) with FH or severe hypercholesterolemia. Subjects qualified for the study were those with known FH or severe hypercholesterolemia and (1) LDL-C ≥4.91 mmol/L (190 mg/dL) or (2) LDL-C ≥4.14 mmol/L (160 mg/dL) and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative.

Treatments:
After a 4-week placebo run-in, subjects were randomized to receive either placebo (n = 47) or atorvastatin 10 mg (n = 140) in a double-blind fashion once daily for 6 months. The study drug could be titrated to 20 mg at Week 4 if the subject's LDL-C was ≥130 mg/dL. The double-blind phase was followed by a 6-month atorvastatin open-label extension. All subjects received atorvastatin 10 mg during the open-label extension phase. Therefore, the 76 subjects in the atorvastatin treatment group who were being treated with atorvastatin 20 mg at Week 26 of the double-blind phase had their dose reduced to 10 mg during the open-label phase. The placebo-treated subjects from the double-blind phase who continued into the open-label phase received 10 mg of atorvastatin.

Variables:
The primary efficacy variable was the percent change from baseline in LDL-C at Week 26 (Endpoint Analysis). The secondary efficacy variables included the percent change from baseline in TC, TG, HDL-C, Apo A-1, and Apo B at Week 4 and Endpoint.

Statistical analysis:
For the Endpoint Analysis the last double-blind observation was carried forward to Week 26 for subjects who did not complete the 6-month double-blind phase of the study. Four subjects (3 [2.1%] atorvastatin, 1 [2.1%] placebo) discontinued early from the double-blind phase. Thus, data were summarized by Endpoint Analysis for all 187 subjects who received atorvastatin and by Week 26 for evaluable subjects enrolled through the end of the double-blind phase. Baseline was defined as the mean of the two values at Weeks -2 and 0. Analysis of covariance (ANCOVA) was performed to compare the effects of atorvastatin and placebo on the primary efficacy variable with a model that included the effects of treatment, centre, sex, baseline Tanner Stage, and the baseline value as a covariate. Each interaction was added separately to the main effects model and the Type III SS F-test *p*-value for each term was presented. The effect of atorvastatin and placebo on the primary efficacy variable was also compared using the Wilcoxon Rank Sum Test. This test was also used to assess the change from baseline in the secondary efficacy variables at Weeks 4 and 26. Data from the open-label phase of the study were analyzed based on length of atorvastatin therapy, and included treatment in the double-blind phase and open-label extension phase. Baseline in these analyses was the last visit before the start of atorvastatin.

Results:

Table 13. Study 981-147: Summary of changes in LDL-C during the double-blind phase.

Statistic[a]	Atorvastatin Treatment Group	Placebo Treatment Group	P Value[b]
Week 4	N=138	N=47	
Baseline (mg/dL)	218.9 ± 3.6	230.0 ± 6.9	
Week 4 (mg/dL)	141.9 ± 3.0	221.8 ± 6.3	
Mean percent change	-35.0 ± 0.9	-2.8 ± 1.6	
LS mean percent change[c]	-35.0 ± 2.6	-2.1 ± 3.0	<0.001
Endpoint[d]	N=140	N=47	
Baseline (mg/dL)	218.6 ± 3.6	230.0 ± 6.9	
Endpoint (mg/dL)	130.7 ± 2.8	228.5 ± 8.0	
Mean percent change	-39.6 ± 1.1	-0.4 ± 1.9	
LS mean percent change[c]	-40.0 ± 3.3	-0.4 ± 3.7	<0.001

[a] Values are mean ± standard error.
[b] Type III SS F-test for percent change controlling for center, sex, baseline Tanner Stage, and baseline LDL-C.
[c] Adjusted for center, sex, baseline Tanner Stage, and baseline LDL-C.
[d] Endpoint = Week 26 data or the last double-blind observation carried forward to Week 26 for subjects who did not complete the 6 month double-blind phase.
Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number; LS=least squares.
Source: Study 981-147 Clinical Study Report.

Table 14. Study 981-147: Summary of changes in secondary efficacy variables at endpoint during the double-blind phase.

Statistic[a]	Atorvastatin Treatment Group	Placebo Treatment Group	P Value[b]
N	140	47	
TC			
Baseline (mg/dL)	285.0 ± 3.8	297.5 ± 7.5	
Endpoint (mg/dL)	194.0 ± 3.1	293.2 ± 8.8	
Mean percent change	-31.4 ± 1.0	-1.5 ± 1.5	
LS mean percent change[c]	-32.3 ± 2.7	-2.0 ± 3.1	<0.001
HDL-C			
Baseline (mg/dL)	45.8 ± 0.8	46.3 ± 1.5	
Endpoint (mg/dL)	46.7 ± 0.9	45.0 ± 1.5	
Mean percent change	2.8 ± 1.3	-1.9 ± 1.9	
LS mean percent change[c]	-2.4 ± 3.4	-8.0 ± 3.9	0.022
TG			
Baseline (mg/dL)	103.2 ± 4.9	106.0 ± 8.3	
Endpoint (mg/dL)	83.2 ± 3.7	98.4 ± 7.8	
Mean percent change	-12.0 ± 2.9	1.0 ± 6.2	
LS mean percent change[c]	-12.0 ± 8.4	1.0 ± 9.5	0.029
Apo A1			
Baseline (mg/dL)	125.4 ± 1.6	124.6 ± 3.1	
Endpoint (mg/dL)	129.0 ± 2.0	125.6 ± 3.1	
Mean percent change	3.3 ± 1.2	1.4 ± 1.7	
LS mean percent change[c]	-2.0 ± 3.3	-4.4 ± 3.7	0.299
Apo B			
Baseline (mg/dL)	186.4 ± 2.8	194.2 ± 5.4	
Endpoint (mg/dL)	121.7 ± 2.2	195.1 ± 6.1	
Mean percent change	-34.0 ± 1.1	0.7 ± 1.6	
LS mean percent change[c]	-32.8 ± 2.9	2.2 ± 3.3	<0.001

[a] Values are mean ± standard error.
[b] Type III SS F-test for percent change controlling for center, sex, baseline Tanner Stage, and baseline LDL-C.
[c] Adjusted for center, sex, baseline Tanner Stage, and baseline LDL-C.
Endpoint = Week 26 data or the last double-blind observation carried forward to Week 26 for subjects who did not complete the 6 month double-blind phase.
Abbreviations: N=number; LS=least squares; TC=total cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides; Apo A1=apolipoprotein A1; Apo B=apolipoprotein B.
Source: Study 981-147 Clinical Study Report.

Table 15. Study 981-147: Summary of change in LDL-Cand percentage of subjects who reached the targeted goal of LDL-C < 130 mg/dL during the open-label phase.

Statistic[a]	Week 26 (End of Double-Blind Phase)	Week 52 (Double Blind + Open Label)
Percent Change in LDL-C[b]		
N	135	132
Baseline (mg/dL)	218.6 ± 3.6	219.9 ± 3.7
Visit Value (mg/dL)	129.1 ± 2.7	143.4 ± 3.3
Mean Percent Change	-40.3 ± 1.1	-34.2 ± 1.3
Percent Subjects at Goal[b]		
N	140	132
Percent Goal	60%	43.9%
95% CI	48.6 – 71.4%	32.8 – 55.1%

[a] Mean ± standard error.
[b] For the subjects who received atorvastatin in the double-blind phase and continued into the open-label phase; 76 of 132 subjects included in the analysis at the end of the open-label period underwent a reduction in dose from atorvastatin 20 mg daily to 10 mg daily.
Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number; CI=confidence interval.
Source: Study 981-147 Clinical Study Report.

Discussion of results
The study population was not entirely homogeneous, being both subjects with HeFH and hypercholesterolemia of other causes. It is not clear what the proportions were between these groups. After week 4, an increase of the dose was necessary in approximately 58% of patients who did not reached the target threshold. At week 26, a statistically significant effect is observed in reducing the LDL-C level with 60% percent of patients reaching the targeted goal of <130 mg/dl. Also a statistically significant effect is observed in the majority of the lipid parameters (TC, HDL-C, TG, Apo-B). The 10 mg dose was administered to all patients during the open-label phase and the target goal was reached in 44% of patients during this period. During the open-label phase the slight lowering of the efficacy was expected because 76 atorvastatin-treated subjects receiving 20 mg daily during the double-blind phase had their dose reduced to 10 mg daily for the open-label phase.
Dosing was not weight adjusted, but a fixed amount of drug was given depending on age, and the dose increased if clinical effect was not adequate. The dose in mg/kg is therefore very variable among study subjects, and ranged between 0.08 mg/kg/day and 0.8 mg/kg/day which makes the evaluation of efficacy more difficult. Even if the efficacy in children at doses of 0.2-0.3 mg/kg/day seems comparable to adults and causes a significant lowering in lipid parameters, the desired target values are not always reached at these doses. Nevertheless, this study provides the strongest evidence for dosing recommendations.

Study 981-336: A 1 Year, Open-Label, Randomized Parallel Group Multicentre Study for the Comparison of Atorvastatin vs. Colestipol on the Treatment of Children and Adolescents with Familial Hypercholesterolemia (FH) and Hypercholesterolemia

Objective:
- To compare the safety and efficacy of atorvastatin versus colestipol in decreasing elevated lipid levels in children and adolescents between 10 and 18 years of age who have FH and hypercholesterolemia.

Population:
The study population consisted of 56 subjects, of whom 25 subjects were randomized to receive atorvastatin and 31 subjects to receive colestipol.

Treatments:
Patients received either atorvastatin 10 mg daily or colestipol 5 g daily according a randomized code, and stratified according to the sex of the patient. The daily dose could have been increased to atorvastatin 20 mg or colestipol 10 g at Week 6 based on a target LDL-C level of ≥130 mg/dL. At Week 12 the doses could have been further increased to atorvastatin 40 mg or colestipol 20 g based on a target LDL-C level of ≤130 mg/dL. Patients were to remain on the dose prescribed at Week 12 through week 52, unless modified for reasons of safety or efficacy.

Variables:
The primary efficacy variable was LDL-C at Week 26. The baseline value was defined as the mean of two values from study Weeks -2 and 0. The secondary efficacy variables were percent change from baseline in LDL-C at Week 52, and percent change from baseline in TC, TG, HDL-C, VLDL-C, TC/HDL-C

Ratio, and LDL-C/HDL-C Ratio at Weeks 26 and 52. In addition, the percentage of patients reaching goal (defined as LDL-C <130mg/dL) was determined at Weeks 26 and 52.

Statistical analysis:
Three subpopulations were used for the analyses: safety population, intent-to-treat (ITT) population, and per protocol (PP) population. The ITT population included subjects who were randomized, received at least one dose of study medication, and had at least one post-baseline efficacy measure. The PP population included subjects in the ITT population who met the following additional criteria:

- Between 10 and 18 years of age;
- Tanner Stage ≥2 at screening visit;
- LDL-C ≥5.2 mmol/L (200 mg/dL) at baseline;
- TG ≤2.25 mmol/L (200 mg/dL; mean of values at two baseline visits); and
- Received no prohibited medication at screening or any time during the study.

The safety population and the ITT population consisted of the 56 randomized subjects, and PP population comprised 45 subjects.

Results:

An overview of the results can be found in the tables below:

Table 16. Study 981-336: Percent change from baseline in LDL-C at week 26.

Statistic[a]	Atorvastatin	Colestipol
Intent-to-Treat Population		
N	25	31
Baseline (mg/dL)	253.8 ± 48.4	232.3 ± 48.4
Week 26 (mg/dL)	146.5 ± 38.3	189.5 ± 38.5
% Change from Baseline	-38.2 ± 16.2	-21.2 ± 16.2
p-value (atorvastatin vs. colestipol)	0.0003	
Per Protocol Population		
N	23	22
Baseline (mg/dL)	260.1 ± 39.0	248.7 ± 39.9
Week 26 (mg/dL)	147.2 ± 40.4	192.6 ± 41.0
% Change from Baseline	-40.7 ± 17.3	-23.0 ±17.3
p-value (atorvastatin vs. colestipol)	0.0012	

[a] Mean ± standard deviation.
Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number.
Source: Study 981-336 Clinical Study Report.

Table 17. Study 981-336: Summary of secondary efficacy variables: LDL-C at week 52, and TC, TG, HDL-C and VLDL-C at weeks 26 and 52.

Variable	Statistic[a]	Atorvastatin	Colestipol
	N	25	31
LDL-C (mg/dL)	Baseline	253.8 (48.4)	232.3 (48.4)
	p-value (atorvastatin vs. colestipol)	0.1024	
	Week 52	139.2 (39.9)	191.7 (40.1)
	% Change from baseline	-40.8 (15.9)	-19.7 (16.0)
	p-value (% change from baseline)	<0.0001	<0.0001
	p-value (atorvastatin vs. colestipol)	<0.0001	
TC (mg/dL)	Baseline	307.1 (49.1)	293.3 (49.1)
	p-value (atorvastatin vs. colestipol)	0.2983	
	Week 26	199.9 (38.7)	247.4 (38.9)
	% Change from baseline	-32.5 (12.9)	-17.0 (12.9)
	p-value (% change from baseline)	<0.0001	<0.0001
	p-value (atorvastatin vs. colestipol)	<0.0001	
	Week 52	194.5 (36.0)	251.1 (36.2)
	% Change from baseline	-34.2 (11.8)	-15.4 (11.9)
	p-value (% change from baseline)	<0.0001	<0.0001
	p-value (atorvastatin vs. colestipol)	<0.0001	
TG (mg/dL)	Baseline	69.9 (27.8)	79.1 (27.8)
	p-value (atorvastatin vs. colestipol)	0.1504	
	Week 26	66.4 (25.7)	84.6 (25.7)
	% Change from baseline	-11.1 (38.0)	13.3 (38.0)
	p-value (% change from baseline)	0.0672	0.0315
	p-value (atorvastatin vs. colestipol)	0.0052	
	Week 52	62.6 (28.5)	84.4 (28.5)
	% Change from baseline	-16.2 (44.8)	12.9 (44.8)
	p-value (% change from baseline)	0.0125	0.0469
	p-value (atorvastatin vs. colestipol)	0.0014	
HDL-C (mg/dL)	Baseline	44.7 (10.2)	48.5 (10.2)
	p-value (atorvastatin vs. colestipol)	0.1646	
	Week 26	46.6 (8.5)	49.6 (8.4)
	% Change from baseline	0.8 (18.6)	7.4 (18.5)
	p-value (% change from baseline)	0.8413	0.0332
	p-value (atorvastatin vs. colestipol)	0.1890	
	Week 52	47.0 (8.9)	47.4 (8.9)
	% Change from baseline	2.2 (18.0)	2.3 (17.9)
	p-value (% change from baseline)	0.5512	0.4850
	p-value (atorvastatin vs. colestipol)	0.9849	
VLDL-C (mg/dL)	Baseline	8.5 (7.4)	10.7 (7.5)
	p-value (atorvastatin vs. colestipol)	0.2364	
	Week 26	6.3 (5.4)	11.4 (5.4)
	% Change from baseline	-34.3 (128.6)	18.7 (128.7)
	p-value (% change from baseline)	0.0015	0.1132
	p-value (atorvastatin vs. colestipol)	0.0004	
	Week 52	7.7 (6.2)	12.8 (6.2)
	% Change from baseline	-19.4 (173.4)	33.7 (173.5)
	p-value (% change from baseline)	0.0592	0.0059
	p-value (atorvastatin vs. colestipol)	0.0011	

[a] Mean (standard deviation).
Abbreviations: LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; VLDL-C=very low-density lipoprotein cholesterol; N=number.
Source: Study 981-336 Clinical Study Report.

Ten of 25 (40%) atorvastatin-treated subjects and five of 31 (16.1%) colestipol-treated subjects had LDL-C ≥130 mg/dL at Week 26 (p = 0.0630). Ten of 25 (40%) atorvastatin-treated subjects and two of 31 (6.5%) of colestipol-treated subjects had LDL-C ≥130 mg/dL at Week 52 (p=0.0024).

Discussion of results

The LDL-C baseline level is slightly higher in this study than in the previous one. Again, it is not clear if the patients included have HeFM, combined (mixed) familial hypercholesterolemia or other diagnosis. The dose of atorvastatin/colestipol was allowed to be increased up to 40 mg atorvastatin/20 g colestipol during the first 12 weeks treatment period in case the targeted goal was not reached but the remained constant until the end of the study. The dose is titrated according to effect on lipid parameters, but the dosing was not weight adjusted. The dose of atorvastatin in mg/kg is therefore very variable among study subject.

At week 26 a statistically significant effect is observed in reducing the LDL-C level with a 40% percent of patients reaching the targeted goal of <130 mg/dl in comparison with a 16% in the colestipol group. The response rate was maintained at week 52.

Study 981-080: A Multicentre, Open-Label, Compassionate-Use Study to Assess the Efficacy and Safety of Atorvastatin in Patients with Severe Hypercholesterolemia Who Have Not Achieved an Adequate Response with Conventional Lipid-Lowering Therapy

Study 981-080 was an 8-week, open-label, compassionate-use study with an optional extension phase of variable length. Subjects were enrolled in 41 centres in the following countries: Belgium, Canada, France, Italy, The Netherlands, Norway, South Africa, Sweden, the United Kingdom, and the United States.

Objective:

- To evaluate the efficacy and safety of atorvastatin in patients with severe hypercholesterolemia refractory to maximally tolerated lipid-lowering therapy.

Population:
Patients with confirmed homozygous familial hypercholesterolemia or nonhomozygous severe hypercholesterolemia (SHC; LDL-C levels >200 mg/dL while receiving maximally tolerated lipid-lowering therapy) were eligible for participation in the study. A total of 335 patients were enrolled; 89 patients were classified as having HoFH and the remaining 246 patients were classified as patients having non-homozygous severe hypercholesterolemia.
Overall patient age ranged from 2 to 73 years, with a mean age of 39 years. Patients with HoFH had a lower mean age than patients with SHC (24 years versus 45 years). Overall, most patients were 18 years or older (86%); the majority of patients under the age of 18 were in the HoFH patient group. Patients were primarily Caucasian (89%), and the percentage of male and female patients was nearly equal (54% male; 46% female).

Treatment:
Most patients enrolled in the study received atorvastatin 40 mg daily for 4 weeks and were then titrated to 80 mg daily for an additional 4 weeks. However, some patients began treatment with doses as low as 2.5 mg daily and titrated as individually appropriate. Patients who responded to atorvastatin during the 8-week initial evaluation period were allowed to continue into the extension phase with safety and efficacy evaluations at regular intervals.

Variables:
The primary efficacy variable was the percent change in LDL-C from baseline levels to Week 8. Secondary efficacy variables included the percent change in TC, TG, and HDL-C from baseline levels to Week 8. Efficacy data were summarized for all patients, HoFH patients, and SHC patients, and data were compared for patients with HoFH versus those with SHC.

Results:

An overview of the results can be found in the table below:

Table 17. Study 981-080: Summary of primary (LDL-C) and secondary (TC, TG and HDL-C) efficacy variables.

Variable	Statistic[a]	All	HoFH	SHC
	N	335	89	246
LDL-C (mg/dL)	N	308	86	222
	Baseline	388.1 (8.8)	525.3 (16.2)	335.0 (8.1)
	Week 8	265.6 (8.6)	410.1 (15.3)	209.6 (7.6)
	Change	-122.6 (5.5)	-115.3 (13.1)	-125.4 (5.7)
	% Change	-32 (1)	-20 (2)	-36 (2)
TC (mg/dL)	N	328	88	240
	Baseline	458.2 (8.4)	585.7 (16.1)	411.5 (7.9)
	Week 8	326.1 (8.0)	462.0 (14.9)	276.2 (7.1)
	Change	-132.1 (5.4)	-123.7 (12.9)	-135.3 (5.6)
	% Change	-28 (1)	-20 (2)	-32 (1)
TG (mg/dL)	N	327	88	239
	Baseline	198.6 (10.2)	139.9 (10.0)	220.2 (13.1)
	Week 8	132.1 (5.5)	106.0 (6.3)	141.7 (7.1)
	Change	-66.5 (7.8)	-33.9 (7.0)	-78.5 (10.3)
	% Change	-22 (2)	-12 (4)	-26 (2)
HDL-C (mg/dL)	N	326	88	238
	Baseline	37.4 (0.7)	32.4 (1.2)	39.2 (0.8)
	Week 8	38.2 (0.7)	32.2 (1.1)	40.4 (0.8)
	Change	0.8 (0.5)	-0.2 (0.9)	1.2 (0.5)
	% Change	5 (2)	5 (4)	6 (1)

[a] Mean (standard error).
Abbreviations: HmFC=homozygous familial hypercholesterolemia; SHC= non homozygous severe hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; N=number.
Source: Study 981-080 Clinical Study Report.

Discussion of results
In this compassionate, open-label study patients with either confirmed homozygous FH or non-homozygous severe hypercholesterolemia were enrolled and were refractory to other lipid-lowering therapies. All patients had LDL>200 mg/dL. Fourteen percent (46) were children and adolescents. 89 patients were classified as having HoFH the majority of them under the age of 18. The LDL-C baseline level is higher in this study than in the previous ones. The % LDL-C change from baseline reached a 36% in the group of patients with non-homozygous hypercholesterolemia and a lower percentage (20%) in the group of patients with HoFH. Atorvastatin seems to have decreased efficacy in the homozygous FH group, so it is possible that patients with this variant may need higher atorvastatin doses.

Clinical safety

Safety data was presented for the four studies involving paediatric patients (pivotal study A2581172, and supportive studies 981-080, 981-147, and 981-336).

Adverse events
Due to the small number of paediatric studies and the non-homogenous coding of adverse events, the adverse event data from these studies has not been pooled. The data is presented by individual study.

Study 981-080 Compassionate use study in paediatric and adult subjects: Twenty-seven of 46 paediatric patients reported AEs, 12 of which were considered treatment related. There were no treatment-related serious AEs. Due to the small number of paediatric patients in the study, all AEs were considered to be common as a single report would constitute an incidence rate of > 2%. There were no meaningful differences in adverse event profiles when the data were stratified by age. One death occurred in study 981-080: a subject with a history of familial hypercholesterolemia was involved in a motor vehicle accident on study day 538 and died on study day 552 due to severe head injuries sustained during the accident. The patient had received 537 days of treatment with atorvastatin 40 to 80 mg QD; no concomitant medications were noted. The event was considered not related to atorvastatin.

Study 981-147 A 52 week efficacy and safety study in patients 10-17 years: The overall incidence of all causality adverse events reported during the double-blind phase was similar for the atorvastatin and placebo treatment groups (62.9% [88/140] and 61.7% [29/47], respectively).

An overview of the results can be found in the tables below:

Table 18. Adverse events (all causality) occurring in ≥ 5% of subjects in either treatment group during the double-blind phase.

	Atorvastatin N (%)	Placebo N (%)
Subjects		
Total number treated*	140 (100.0)	47 (100.0)
Number with adverse events*	88 (62.9)	29 (61.7)
Adverse Events**		
Abdominal pain	6 (4.3)	3 (6.4)
Accidental injury	13 (9.3)	2 (4.3)
Fever	2 (1.4)	3 (6.4)
Flu syndrome	9 (6.4)	6 (12.8)
Headache	13 (9.3)	3 (6.4)
Infection	27 (19.3)	7 (14.9)
Pharyngitis	9 (6.4)	3 (6.4)

*Number given is number of subjects
**Subjects may have had more than one adverse event

In both treatment groups, the most common adverse events were those caused by illness or a sign of illness, such as infection, flu syndrome, pharyngitis or fever. The 88 subjects with adverse events in the atorvastatin group reported 176 events and the 29 subjects in the placebo group reported 58 events. The majority of these events in both the atorvastatin and placebo treatment groups were mild (93 [53%] and 34 [59%], respectively) or moderate (74 [42%] and 20 [34%], respectively), with only a few events severe (9 [5%] and 4 [7%], respectively). Severe events which occurred in both treatment groups included abdominal pain (one event in each treatment group) and vomiting (two and one events, respectively). Severe events that occurred only in the atorvastatin treatment group (incidence of one for each event) included infection, photosensitivity reaction, migraine, syncope, depression and dizziness. Severe events that occurred only in the placebo treatment group (incidence of one for each event) included accidental injury and dyspepsia.

The overall incidence of treatment-related adverse events was small in both the atorvastatin and placebo treatment groups during the double-blind phase (7.1% [10/140] and 4.3% [2/47], respectively). The majority of these events in both the atorvastatin and placebo treatment groups were mild or moderate, with one severe event in each treatment group.

Study 981-336 A 52 week efficacy and safety study in patients 10-18 years: Of the 25 subjects that received atorvastatin, a total of 14 (56.0%) subjects experienced at least one adverse event. Of the 31 subjects that received colestipol, 19 (61.3%) subjects experienced al least one adverse event. The most frequent adverse events in the atorvastatin group were: gastritis, two subjects, 8%; nasopharingitis, two subjects, 8%; and cough, two subjects, 8%. The most frequent adverse events in the colestipol group were: tonsillitis, three subjects, 9.7%; abdominal pain, two subjects, 6.5%; nasopharyngitis, two subjects, 6.5%; pyrexia, two subjects, 6.5%; and ear infection, two subjects, 6.5%. One (4%) subject who received atorvastatin discontinued due to an adverse event of gastritis, and this was the only AE assessed as serious. No subjects who received colestipol experienced serious adverse events. The most frequent clinically significant laboratory abnormalities were in the atorvastatin group: blood bilirubin increased, one subject, 4%, and in the colestipol group: blood bilirubin increased, two subjects 6.5% and alanine aminotransferase increased, one subject 3.2%.

Study A2581172 An 8 week PK/PD and safety study in subjects 6 to 17 years: No deaths, other serious AEs, or severe AEs were reported in this study. In addition, no permanent or temporary discontinuations or dose reductions due to AEs occurred. Overall, all-causality AEs were experienced by 9 of 15 of the cohort A subjects and 13 of 24 of the cohort B subjects treatment-related AEs were observed for two of 15 cohort A subjects and two of 24 cohort B subjects. Overall (including subjects in both cohorts), the most frequently observed AEs in this study were nasopharyngitis (3 subjects), viral upper respiratory tract infection (3 subjects), gastroenteritis (2 subjects), ALT increased (2 subjects), and headache (3 subjects). Four subjects experienced treatment-related AEs, which included abdominal pain, nausea, vomiting, and headache experienced among two cohort A subjects, and ALT increased experienced by two cohort B subjects. Most AEs were mild and the remaining AEs were of moderate severity. Moderate severity AEs, including six AEs among cohort A subjects and three AEs among cohort B subjects, included AEs of viral upper respiratory tract infection, gastroenteritis, nausea, bronchopneumonia, lower respiratory tract infection bacterial, hand fracture, blood creatinine increased, asthma, and urticaria.

Discussion on clinical safety
The safety database in paediatric patients includes data from the pivotal and the three supportive trials. The majority of the paediatric patients received doses from 5 to 20 mg in the pivotal and the two comparative trials and the longer treatment duration was one year. No new adverse events have been described. The specific body systems associated with a high number of events in the paediatric trials include the 'digestive system', the 'respiratory system' and the 'infections and infestations' group, reflecting intercurrent illnesses that are common among paediatric patients or other AES already described in the product information.

Two cases of ALAT elevation in Study A2581172 are a potential concern. In adult studies the overall incidence of ALAT elevation is only 0.5%. Larger treatment numbers are needed to address this issue. Hopefully, the ongoing A2581173 study (a 3-year study of the safety and follow-up study of efficacy of atorvastatin treatment of children and adolescents (aged 6 years to less than 18 years) with heterozygous familial hypercholesterolemia) will provide supportive safety data in this regard.

Another potential concern, not addressed in the trial cohorts, is the effect of off label use in children and adolescents with dietary (secondary) hypercholesterolemia and possible underlying fatty liver.

The majority of the paediatric patients were treated with 10 mg to 20 mg doses and the patient population exposed to the higher doses is small. Although the safety profile of atorvastatin is well-known, the safety information for paediatric patients treated with the higher doses is scarce. In particular, some adverse events are dose related, and data for paediatric exposure to the 80 mg dose is limited to the compassionate use study (in which only 14% of the patient populations were children and not all of them were treated with this higher dose).

It is also noted that there is no information on the effect of long-term atorvastatin treatment on long-term growth or maturation parameters. Previous experience with other statins does not suggest any detrimental effect. The ongoing study A2581173 is expected to provide useful information also with respect to long-term growth and maturation.

Short term safety is adequately addressed but long term safety is unknown as of yet, especially for children below the age of 10 years.

2.5. Pharmacovigilance

- **Risk Management Plan**

A consolidated version of a Risk Management Plan (RMP) was submitted for atorvastatin.

Safety Specification
Limitations of the human safety database:
Data of overall exposure to atorvastatin in clinical trials is presented. The only information that refers to population ≤18 years is number of persons (154 male and 80 female) and person-days of exposure (1745.35 male and 969.49 female), also differenced by indication and design of the study. Other information (exposure by cumulative duration, by dose of maximum duration, by ethnic origin, in patients with renal disorders and in patients with cardiac impairment), is provided for overall population.
It has been estimated a total of 220.000 prescriptions for patients ≤17 years in post-marketing exposure (0.09%).
Safety and effectiveness of atorvastatin have been studied in a small number of patients younger than 18 years old, and have not been established for pregnant or lactating women.

Table 19. Clinical trial exposure for paediatric patients by age group*

Patient age	Persons	Person Months (mean)
< 6 years	7	13.87
6 - <10 years	14	4.76
10 - <18	228	7.69
All < 18	**249**	**7.70**

*Data generated 02 February 2010 to include patients from newly completed paediatric study A2581172

Table 20. Demographics for paediatric patients in clinical trials (n=249)*

Demographic	Number of Patients
Gender	
Male	149
Female	100
Race	
White	221
Black	5
Asian	6
Other	17

*Data generated 02 February 2010 to include patients from newly completed paediatric study A2581172

Adverse events:
From the results of the clinical trials and the post marketing information submitted, the paediatric safety profile is not foreseen to be significantly different from that of adults. Nevertheless, it is recognised that the information currently available is limited.
The following risks have been listed as identified and potential risks for overall population, taking into account the last PSUR generated for atorvastatin:

Table 21. Safety concerns and planned pharmacovigilance actions.

Safety Concern	Planned action(s)
Important Identified risks	
Rhabdomyolysis and potential rhabdomyolysis-related events	Routine pharmacovigilance
Important potential risks	
Anger, aggression and irritability	Routine pharmacovigilance
Cardiac arrhytmias	Routine pharmacovigilance
Interstitial lung disease / pneumonitis-related events	Routine pharmacovigilance
Selected autoimmune events / Antinuclear antibody positive	Routine pharmacovigilance
Hepatic failure-related events	Routine pharmacovigilance

Pharmacovigilance Plan
The MAH will evaluate all paediatric cases reported through the post marketing systems and perform cumulative reviews of paediatric cases on a quarterly basis.
The MAH will also monitor closely all safety data generated from the ongoing study A2581173 (3-year study of the safety and follow-up study of efficacy of atorvastatin treatment of children and adolescents aged 6 years to less than 18 years with heterozygous familial hypercholesterolaemia) that is part of the approved PIP and is expected to be completed in 2014. Results should be available in the first quarter of 2015.

Evaluation of the need for a Risk Minimisation Plan
Wording has been agreed for inclusion in the SPC to reflect the limited paediatric data available and advise the prescriber on appropriate starting doses and titration considerations in paediatric patients.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

The above mentioned changes to the RMP should be submitted to the Competent Authorities of the Member States.

2.6. Benefit-Risk Balance

Benefits

The efficacy of atorvastatin in reducing lipid parameters in children is analogous to the proved in the adult population. The effect observed in the percentage of change from baseline in LDL-C in paediatric patients is of same magnitude than in the adult population (35% to 40%) with the exception of patients with homozygous familial hypercholesterolemia (20%), although the same pattern is observed in the adult population given the high baseline LDL-C levels. The effect is consistent in both Tanner stage 1 and ≥ 2 and the exploratory PK/PD analysis shows that a similar effect is observed over the ranges of exposures although the efficacy and safety data in children between the ages of 6-9 years are limited.

The safety profile in children appears to be similar to that described in adults. The AEs observed in the paediatric studies are similar to those included in the SPC for the adult population and no new AEs have been described.

The development of a paediatric specific pharmaceutical form promotes treatment compliance and facilitates the administration of doses appropriate to the paediatric patients.

Risks

The experience with the higher recommended doses and in the younger population is scarce and limited to patients with severe disease included in the compassionate use programme. Only 14 patients between 6 and <10 were exposed to the atorvastatin during clinical trials which is insufficient to consider safety and efficacy adequately demonstrated in this age group. Taking into account that some AEs are dose related, especially the hepatic and musculoskeletal disorders, there are safety concerns regarding the use in the population between 6 and <10 years.

Even in the paediatric patients over 10, information on the long-term safety profile is limited. No information is available on the effect of atorvastatin treatment on long-term growth or maturation parameters, although previous experience with other statins does not suggest any detrimental effect. The ongoing study A2581173 is expected to provide useful information with respect to long-term growth and maturation, as well as lipid parameters and safety profile in approximately 250 patients.

Experience with doses higher than 20 mg is limited, and therefore so is the knowledge of the safety profile at high doses. It is appropriate that paediatric use should be restricted to this dose range and only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia.

Benefit-Risk Balance

In conclusion, the efficacy of atorvastatin in reducing lipid parameters in children is analogous to the proved in the adult population and the effect is consistent with the proposed posology. The safety profile in children appears to be similar to that described in adults, although long term safety is unknown, particularly for children below the age of 10 years and with the higher doses.

Risk management plan

The CHMP, having considered the data submitted, including the fact that a 3-year safety and efficacy study is already ongoing as agreed in the approved PIP, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Sortis and associated names chewable tablets 10 mg, 20 mg and 40 mg as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate was favourable, and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is fully completed and that the PDCO issued an Opinion on Compliance. The CHMP reviewed the paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SPC) and, as appropriate, the Package Leaflet.