U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 20-261 / SE5 036 Lescol
	NDA 21-192 / SE5 011 Lescol XL
Drug Name:	Lescol (fluvastatin sodium) capsules
	Lescol XL extended release tablets
Indication(s):	For use in the treatment of heterozygous familial hypercholesterelimia (heFH) in pediatric patients
Applicant:	Novartis
Date:	October 14, 2005
Review Priority:	Priority
Biometrics Division:	Metabolism and Endocrine Team, HFD-715
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	Jon T. Sahlroot, Ph.D., HFD-715 Team leader
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Keywords: Clinical studies, NDA review, pediatric exclusivity

Introduction

The purpose of this supplemental NDA is to provide the results of the Lescol® and Lescol® XL pediatric study program. The sponsor, Novartis Pharmaceuticals Corporation, submitted this sNDA to support labeling for use in the treatment of heterozygous familial hypercholesterolemia (heFH) in pediatric patients. The Agency determined that this sNDA is responsive to the Agency's Written Request Amendment #1 (WR), dated July 15, 2002. The sNDA includes the results from two studies that characterize the safety and efficacy of fluvastatin sodium on plasma lipids in 114 childrens and adolescents with heFH. Novartis submitted this sNDA to meet their post-marketing commitments for conducting studies in pediatric patients, and to serve as the basis of their request for the pediatric exclusivity extension.

Lescol (fluvastatin sodium) was first approved in 1997 for use in patients with primary hypercholesterolemia and mixed dyslipidemia whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate. Lescol is available as 20 and 40 mg capsules and 80 mg extended release tablets (Lescol XL; approved in 2000). In clinical studies of adult patients, Lescol XL reduced levels of Total-C, LDL-C, TG and Apo B with respect to baseline levels.

The pediatric studies of Lescol involved children and adolescents with heterozygous familial hypercholesterolemia. The prevalence of familial hypercholesterolemia is 1 in 500 in the mild (heterozygous) form and 1 in 100,000 in its severe (homozygous) form. Affected individuals have a higher than average risk of developing atherosclerotic lesions in childhood and adolescence. Children and adolescents with heFH may have elevated levels of total cholesterol (TC) and LDL-C.

Overall Summary

This reviewer confirmed the key statistical results presented in this sNDA. The statistical results from both studies support the sponsor's conclusion that Lescol and Lescol XL lower mean LDL-C concentrations in children and adolescents aged 9-16 years who have heFH.

The sNDA also includes changes to the label to add the pediatric indication and the results of the the pediatric studies. A summary of comments from this reviewer, with respect to the statistical aspects of the proposed label text, is included in TABLE 1.

TABLE 1 Proposed label text for pediatric use and statistical review comments, based on Study ZA01 and Study B2301

Proposed label text for pediatric use	Statistical review comments
CLINICAL STUDIES **Heterozygous Familial Hypercholesterolemia in Pediatric Patients**	
[redacted] (b) (4)	

Proposed label text for pediatric use	Statistical review comments
(b) (4)	
(b) (4)	(b) (4)

INDICATIONS AND USAGE **Heterozygous Familial Hypercholesterolemia in Pediatric Patients**	
(b) (4) (b) (4) with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present: 1. LDL-C remains ≥ 190 mg/dL or 2. LDL-C remains >160 mg/dL and: • there is a positive family history or premature cardiovascular disease or • two or more other cardiovascular disease risk factors are present	Study 1 (ZA01): The results provide statistical support for the conclusions about Total-C and LDL-C. The study did not report results for Apo B. The statistical support is provided by the 95% confidence interval (CI) of the mean percentage change from baseline. For both Total-C and LDL-C, the 95% CI is entirely in the region that represents a percentage reduction from baseline, and does not include 0%. Study 2 (B2301): The results provide statistical support for the conclusions about Total-C, LDL-C and Apo B. As in Study ZA01, the statistical support is provided by the 95% CI of the mean percentage change from baseline. For Total-C, LDL-C and Apo B, the 95% CI is entirely in the region that represents a percentage reduction from baseline, and does not include 0%.
PRECAUTIONS **Pediatric Use**	
The safety and efficacy of Lescol and Lescol XL in children and adolescent patients 9-16 years of age with heterozygous familial hypercholesterolemia have been evaluated in (b) (4). The most common adverse events observed were influenza and infections. (b) (4) there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls.	These conclusions are consistent with the information on adverse events, laboratory values, and from the assessments of growth, development and endocrine status, obtained from the report of each study.

ADVERSE REACTIONS **Pediatric Patients**	
In two open-label studies, 114 patients (66 boys and 48 girls) with heterozygous familial hypercholesterolemia, 9-16 years of age, were treated for 2 years with fluvastatin sodium administered as Lescol capsules 20 mg- 40 mg bid or Lescol XL 80 mg extended-release tablets. The most common adverse events observed were influenza and infections.	This information is consistent with the summary of adverse events in each study.

Studies Reviewed

The sponsor submitted two studies of Lescol (fluvastatin sodium) in patients aged 9 to 17 with heterozygous familial hypercholesterolemia (heFH) in response to an FDA Written Request (WR) for pediatric studies. Study ZA01 was conducted in 29 prepubescent males. Study B2301 involved 70 patients in Tanner stage 2 and above (39 females and 31 males) and 15 patients in Tanner stage 1 (9 females and 6 males). The major design characteristics of the two studies are summarized in TABLE 2.

TABLE 2 Summary of the designs of Study ZA01 and B2301

Study **Number of centers** **Dates**	**Population**	**Number of patients (open label treatment with Lescol 20-80 mg per day)**	**Duration**
• Study ZA01 • One center (Cape Town, South Africa) • January 13, 1994 – August 31, 1999.	Prepubescent boys, aged 9-12 years at study entry, with heterozygous familial hypercholesterolemia	• 29 patients were enrolled; • The majority were treated with Lescol 80 mg per day	• 27 patients received treatment for 24 months • 11 patients were followed for 5 years
• Study B2301 • Two centers: Amsterdam, The Netherlands, and Cape Town, South Africa • October 15, 2001 – March 7, 2005	Female or male patients 10-16 years of age with an established diagnosis of heterozygous familial hypercholesterolemia, Tanner stage 2 or above	• 70 patients, Tanner stage 2 or above (39 females, 31 males), and 15 patients, Tanner stage 1 (9 females and 6 males) entered the active treatment phase.	65 of the 70 Tanner stage 2 patients, and all 15 of the Tanner stage 1 patients completed the study: 18 week titration period followed by a 2-year treatment period (96 weeks)

Study Number of centers Dates	Population	Number of patients (open label treatment with Lescol 20-80 mg per day)	Duration
		• The majority were treated with Lescol 80 mg per day	

The electronic files that this reviewer used to evaluate the efficacy and safety analyses are located in \\CDESUB1\N20261\S_0236\2005-10-14\crt\datasets\ZA01 and \B2301 for studies ZA01 and B2301, respectively.

Review of Individual Studies

Study No. ZA01 "A prospective dose titration study of the efficacy and safety of Lescol (fluvastatin sodium) in the treatment of children with heterozygous familial hypercholesterolemia"

Objective

The primary objective of study ZA01 was to investigate the safety and efficacy of fluvastatin sodium in lowering low-density lipoprotein-cholesterol (LDL-C) during an initial 2-year period in prepubescent boys with heterozygous familial hypercholesterolemia (FH).

Design

Study ZA01 was conducted at one study center in Cape Town, South Africa as a phase 3, open label, dose titration trial in pediatric patients with heterozygous familial hypercholesterolemia. A patient was eligible for enrollment as follows:

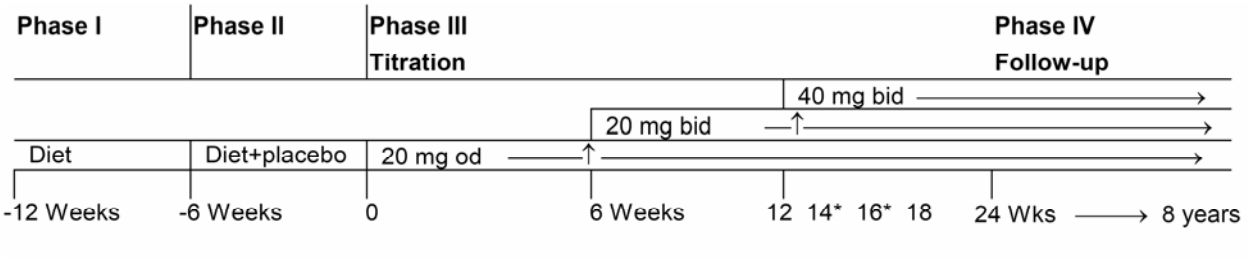
- Prepubertal boys
- Age between 9 and 12 years, inclusive, at study entry [week -12]
- Confirmed familial hypercholesterolemia as follows:
  - Primary hypercholesterolemia above the 90th percentile of their age group
  - A parent with primary hypercholesterolemia
  - Either a family history of premature ischemic heart disease or tendon xanthoma

Exclusion criteria are described in the study protocol.

The study consisted of a 6-week screening/dietary period (Phase I), a 6-week placebo run-in period (Phase II), an 18-week dose titration period (Phase III) and a follow-up phase of up to 5 years (Phase IV). The design of the study is depicted in FIGURE 1.

Fluvastatin sodium was started at 20 mg daily. At approximately 6-week intervals, patients were titrated to fluvastatin sodium 40 mg and then to 80 mg daily, if necessary, to achieve the target cholesterol level (i.e. plasma LDL in the range 2.5-3.2 mM/L, or 96.7 to 123.7 mg/dL). The clinical objective was to maintain LDL-C concentrations within this target range. After the titration phase, the patient entered the follow-up phase (Phase IV), during which the patient was seen at four-monthly intervals. The study protocol reports that Phase IV could last as long as 8 years. The report submitted with sNDA SE5-036 covers the first two years of Phase IV.

FIGURE 1 Design of study ZA01



Source: ZA01 Clinical Study Report, Figure 3.1, p. 14/897

The lipid assessments were obtained at weeks 6, 12, 14, 16, 18 and 24 during the active treatment / titration phase (Phase III), and at months 12, 16, and every four months thereafter during the follow-up period (Phase IV). In addition to LDL-cholesterol, other lipid endpoints were total cholesterol, HDL-cholesterol, triglycerides, and lipoprotein(a). Levels of apolipoprotein A1 were not assessed.

The Tanner stages of growth were assessed at baseline, month 12, 16 and 24, and then annually.

Safety assessments included the recording of all adverse events and serious adverse events. Standard laboratory evaluations were conducted (chemistry, hematology and urinalysis) with special emphasis on liver function (total bilirubin, alkaline phosphatase, ALT, AST, LDH) and on CK. Ophthalmic examinations were also performed.

Patient disposition

After two years, 27 of the 29 patients remained in the study (TABLE 3). One patient dropped out after week 6, and one patient dropped out after month 20.

TABLE 3 Study ZA01: Patient disposition

	N = 29 n (%)
Total no. of patients	29 (100%)
Enrolled and treated	29 (100%)
Completed 12 months (1 year)	28 (96.6%)
Completed 24 months (2 years)	27 (93.1%)
Completed 36 months (3 years)	25 (86.2%)
Completed 48 months (4 years)	19 (65.5%)
Completed 60 months (5 years)	11 (37.9%)
Completed 68 months (5.5 years)	3 (10.3%)

Source: Clinical Study Report, Table 7.1, p. 26/897

Patient demographic and baseline characteristics

A summary of baseline demographic and clinical characteristics is included in TABLE 4. Most patients were between 9 to 11 years of age and Afrikaans. In addition to the ethnic group categories specified in the study protocol and case record forms, patients were also classified according to race and ethnicity categories defined by the FDA.

TABLE 4 Study ZA01: Patient baseline demographic characteristics (ITT population)

	N=29 patients
Age (years)	
9	12 (41.4%)
10	10 (34.5%)
11	6 (20.7%)
12	1 (3.4%)
Average age (SD)	9.9 years (0.9 years)
Race	
White	26 (89.7%)
Native Hawaiian or Pacific Islander	0
Black	0
Asian	0
American Indian or Alaskan Native	0
Other	3 (10.3%)
Ethnicity	
Hispanic/Latino	0
Non Hispanic / Latino	29 (100.0%)
Height (cm)	
Mean (SD)	141.7 (5.0)
Median (min, max)	142 (134, 151)
Weight (kg)	

Mean (SD)	35.5 (7.6)
Median (min, max)	35 (24, 54)
Body Mass Index (kg/m2)	
Mean (SD)	17.6 (3.1)
Median (min, max)	17.3 (13, 26)

Source: Study ZA01 Clinical Study Report, Table 7-3, p. 28/897

Dosage

The sponsor reported that 24 of the 29 patients were exposed to the 80 mg daily dose for a median of 1311 days (range 419 to 1857 days).

Efficacy endpoints and analyses

All 29 patients enrolled were included in the Intent-to-treat as well as in the Safety population. However, the lipid endpoints at month 24 were calculated with the 27 remaining patients, without imputation for the values of the two patients who dropped out prior to month 24.

The primary efficacy parameter was the change from baseline in LDL-cholesterol over an initial period of 2 years of treatment with fluvastatin sodium. Lipid values measured by the Central Laboratory were originally reported in SI units of mmol/L. In order to provide consistent reporting with the study B2301, the sponsor converted the SI units to "conventional" (CV) units of mg/dL.

The study report provides summary statistics of LDL-C at each measurement period, including the primary endpoint, the percentage change from baseline of LDL-C after 24 months of treatment. The baseline value was calculated from the average of measurements taken at week -6 and week 0. In the event that data from one of these weeks was missing, the values at the other week were used as the baseline. In addition, 95% confidence intervals were reported for LDL-C at each measurement period. The sponsor also reported the number of percentage of patients who reached the treatment goal, expressed in SI units as LCL-C between 2.5 and 3.2 mmol/l, inclusive. In addition, the sponsor calculated the percentage of patients who reached the treatment goal expressed in CV units as LDL-C ≤ 130 mg/dL. This latter endpoint was reported in order to provide consistent reporting with the other pediatric trial B2301. The sponsor also provided descriptive measures of the time to achieving an LDL-C goal for the first time and the duration of time spent at the goal level.

This reviewer confirmed the descriptive statistics reported for LDL, HDL, TG and Total-C in TABLE 5. The LDL-C mean reduction was 27.0% at the 2 years of follow-up visit. This reviewer notes that the descriptive statistics for month 24 were calculated without imputation for the two patients who dropped out before month 24.

TABLE 5 Study ZA01: Efficacy endpoints

	N=29 for baseline, N=27 for Month 24*
LDL-(mg/dL)	
Baseline mean	226.0
(min, max)	(137.3, 353.8)
Mean at Month 24	160.6
(min, max)	(73.5, 336.4)
[95% CI]	[138.2, 182.9]
% Change at Month 24	-27.0%
(min, max)	(-57.9%, 10.6%)
[95% CI]	[-34.7%, -19.4%]
Number (%) of patients with LDL ≤ 130 mg/dL at Month 24	8/27 (29.6%)
Total-C (mg/dL)	
Baseline mean	296.2
(min, max)	(203.0, 442.8)
Mean at Month 24	229.0
(min, max)	(158.5, 406.0)
% Change at endpoint	-21.1%
(min, max)	(-50.9%, 6.9%)
[95% CI]	[-26.8%, -15.4%]
HDL-C (mg/dL)	
Baseline mean	53.6
(min, max)	(29.0, 83.1)
Mean at Month 24	53.9
(min, max)	(30.9, 77.3)
% Change at endpoint	1.3%
(min, max)	(-40.7%, 61.5%)
[95% CI]	[-8.0%, 10.7%]
Triglycerides (mg/dL)	
Baseline mean	83.2
Baseline median	70.8
(min, max)	(35.4, 216.8)
Mean at Month 24	72.2
Median at Month 24	61.9
(min, max)	(35.4, 247.8)
% Change at Month 24	-7.0%
(min, max)	(-62.2%, 83.3%)
[95% CI]	[-22.1%, 8.0%]
Sources from ZA01 Clinical Study Report:	
Baseline	Table 7.4-29 p. 90/897
Month 24	Table 9.1-1 pp. 103-106/897

* Patient 14 dropped out after week 6 and patient 28 dropped out after month 20. The descriptive statistics for month 24 are based on the remaining 27 patients.

The sponsor reported that 20 out of a total of 29 (69%) patients reached the study target of LDL-C ≤ 130 mg/dL at least once during the first two years of the study.

The results from this study support the sponsor's conclusions about fluvastatin sodium, with respect to male patients aged 9-12 with an established diagnosis of familial hypercholesterolemia. This reviewer calculated the 95% oconfidence interval (CI) of the percentage change in LDL at endpoint from baseline. This 95% CI is entirely in the region that represents a percentage reduction from baseline, and the CI does not include 0% (TABLE 5). This provides statistical support to the sponsor's conclusions about LDL. Similarly, the 95% CI for percentage change in TC is also entirely in the region that represents a percentage reduction from baseline (TABLE 5).

Safety

The four adverse events (AEs) that were reported by the largest number of patients were: (1) influenza-like symptoms, (2) rhinitis, (3) upper respiratory tract infection and (4) bronchitis (see the Clinical Study Report, Table 10-2 p. 34/897). The sponsor reported that most AEs were of mild or moderate intensity, and severe AEs were observed only in two patients. No AEs leading to discontinuation of study medication occurred.

The WR requested an evaluation of the effects of fluvastatin sodium on liver and muscle as monitored by serum transaminase and creatinine kinase levels. The sponsor reported that the median and mean creatinine kinase (CK) values at baseline were 82.5 and 84.3 U/L, respectively. Increased median and mean values were observed at all post-baseline visits, and at month 24 they were 117 and 134 U/L, respectively. On patient had a notable elevation in CK at month 32 of 2216 U/L (i.e. >10 fold the upper limit of normal 195 U/L, which the investigator suspected to be most likely due to trauma. The sponsor also reported that means for serum transaminases ASAT and ALAT tended to be slightly higher than baseline at all post-baseline visits, but that the means and median values were within normal ranges at all visits.

The WR also requested an evaluation of the effects on growth and sexual maturation as assessed by stadiometry and Tanner staging. Twenty-four of the 29 patients had complete data for week -6 and month 24. All of these patients were Tanner stage 1 at week -6. At month 24, 8 were Tanner stage 1, 8 were Tanner stage 2, 4 were Tanner stage 3 and 4 were Tanner stage 4. Three cases were Tanner stage 1 at baseline, but had no Tanner staging at month 24. Two cases had no Tanner staging at week -6; one case was Tanner stage 3 and one case was Tanner stage 5 at month 24.

The sponsor reported that an external consultant reviewed the data on growth, development and endocrine status ((b) (4) (b) (4) reported that the Tanner's score, the skeletal maturation assessed by X-ray, measurements of testicular size, testosterone, DHEAS, LH and FSH revealed no laboratory or clinically significant and relevant abnormalities.

Study B2301: "Open label, dose titration, multicenter study to assess the efficacy and safety of fluvastatin capsules and fluvastatin extended release (XL) tablets (20, 40 and 80 mg) given orally at bedtime for 114 weeks in pediatric patients with heterozygous familial hypercholesterolemia."

Objective

The primary objective of study B2301 was to evaluate the safety and efficacy (i.e. lipid modulating effects) of fluvastatin sodium in pediatric patients with heterozygous familial hypercholesterolemia.

Design

Study B2301 was conducted at two centers as a phase 3, open label, dose titration trial in pediatric patients with heterozygous familial hypercholesterolemia. A patient was eligible for enrollment as follows:

- Age between 10 and 16 years of age, inclusive, at visit 4 (week 0)
- An established diagnosis of heterozygous familial hypercholesterolemia
- At least one of the following criteria at screening (week -3/visit 2, with the possibility of an additional lipid sampling at week -1/visit 3 if needed to meet the criteria):
    - LDL-C ≥ 190 mg/dL (4.9 mmol/L)
    - LDL-C ≥ 160 mg/dL (4.1 mmol/L) and one or more of the following risk factors: Family history of (parent with) premature coronary heart disease; current cigarette smoking; hypertension; confirmed HDL-C < 35 mg/dL; diabetes mellitus
    - Proven LDL-c receptor DNA defect and LDL-C ≥ 160 mg/dL
- Tanner stage 2 or above[1]
- For males age 12 and above: a testicular volume 3 cc or greater at visit 2 (week -3).
- For menstruating females: a history of at least three regular menstrual cycles.

Additional inclusion and exclusion criteria are described in the study protocol.

After a six-week dietary lead-in period, patients entered an 18-week titration period. Fluvastatin sodium was started at 20 mg daily. At approximately 6-week intervals, patients were titrated to fluvastatin sodium 40 mg and then to 80 mg daily, if necessary, to achieve the LDL-C goal of ≤ 130 mg/dL (3.4 mmol/L). Patients who achieved the LDL-C goal at either the 20 mg or 40 mg

[1] Prior to WR Amendment #1, 15 Tanner stage 1 pediatric patients (pre-pubertal), 9 female and 6 males, had already been enrolled in study B2301. These 15 patients were permitted to continue. However, the clinical study report focused on the results for the pubertal and post-pubertal group. The results for the pre-pubertal patients were reported separately.

dose continued with that dose for the remainder of the 18 week titration period. The titration period was followed by a treatment period of 2 years (96 weeks) at either the highest dose (80 mg/day) or else at the dose that achieved the target LDL-C. Patients were asked to adhere to a fat and cholesterol restrictive diet throughout the entire study. A schedule of the study is shown in TABLE 6.

TABLE 6 Study B2301: Evaluation and visit schedule

	Screening Dietary Run-In			Start of Active Treat-ment	Titra-tion Visit		End of Titration 1st Mainte-nance Visit	Maintenance Visit							End of Study
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week No.	-6	-3	-1	0	6	12	18	30	42	54	66	78	90	102	114

Source: Study B2301 Clinical Study Report, Table 3-1 p. 733/999

Lipids (partial or complete profiles) were measured at each visit shown in the study schedule in TABLE 6. The protocol-specified primary efficacy endpoint was the mean percent change from baseline in LDL-C at "endpoint," i.e., the end of the study (week 114 / visit 15). Secondary efficacy variables included the mean percent change at endpoint from baseline in TC, HDL-C, TG and TC:HDL ratio. Other secondary variables were the mean percent change at endpoint from baseline in Apo A-1 and Apo B and the mean change from baseline in lipoprotein subclasses. Carotid arterial wall thickness and carotid arterial wall distensibility were also included as secondary efficacy variables.

The Tanner stages of growth were assessed at visits 4, 11 and 15.

Safety assessments included the recording of all adverse events and serious adverse events. Safety measurements also came from hematology, blood chemistry, hormonal level, urinalysis assessments, as well as from physical examinations and ECG readings.

Patient disposition

This reviewer evaluated the patient disposition and provided additional clarification in TABLE 7. Of the 85 patients who entered the active treatment phase, 80 patients completed the study. Fifteen of the 85 patients were in the pre-pubertal stage (Tanner stage 1) and their results were reported separately from the 70 patients who were pubertal or post-pubertal (Tanner stage 2 or above). One patient in the pubertal / post-pubertal group was not included in the ITT database (TABLE 7). All 5 of the patients who did not complete the study were in the pubertal / post-pubertal group. There was an additional patient in this group who completed the study up to visit 14 / week 102. This patient was not classified by the sponsor as a non-completer.

TABLE 7 Study B2301: Patient disposition

	Overall	Pubertal and Post-Pubertal (Tanner stage ≥ 2)			Pre-Pubertal[1] (Tanner stage 1)		
	Total	Total	Female	Male	Total	Female	Male
Entered active treatment	85	70	39	31	15	9	6
Completed the study	80	65	37	28		9	6
Did not complete the study[2, 3]	5	5	2	3		0	0
In the ITT analysis		69	38	31		9	6
Not in the ITT analysis		1	---	---		---	---

[1] The pre-pubertal patients were analyzed separately from the pubertal and post-pubertal group.

[2] The following patients were reported by the sponsor as not completing the study:
Patient 1-06, female, last lipid profile on visit 9 / week 42
Patient 1-47, male, last lipid profile on visit 12 / week 78
Patient 1-48, male, last lipid profile on visit 12 / week 78
Patient 2-17, male, last lipid profile on visit 12 / week 78
Patient 2-36, female (not in the ITT database)

[3] In addition, Patient 1-19, female, discontinued with the last lipid profile on visit 14 / week 102. This patient was not classified by the sponsor as "discontinued."

Patient demographic and baseline characteristics

Most patients were between 10 and 16 years of age at the start of the study. The maximum age of 17 years reported in TABLE 8 refers to one patient who turned 17 at week -4.

TABLE 8 Study B2301: Patient baseline demographic characteristics (ITT population, pubertal and post-pubertal)

	Female N=38	Male N=31	Total N=69
Age at week -3 (years)			
Mean (SD)	12.8 (1.8)	13.5 (2.0)	13.1 (1.9)
(Min, Max)	(10, 16)	(10, 17)	(10, 17)
Race			
White	28 (73.7%)	22 (71.0%)	50 (72.5%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	1 (3.2%)	1 (1.4%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	10 (26.3%)	8 (25.8%)	18 (26.1%)

	Female N=38	Male N=31	Total N=69
Ethnicity			
Hispanic/Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non Hispanic / Latino	38 (100%)	31 (100%)	69 (100%)
Height (cm)			
Mean (SD)	160.1 (8.56)	162.0 (11.33)	161.0 (9.86)
Median (min, max)	158.0 (144, 176)	163.0 (138, 184)	160.0 (138, 184)
Weight at week -3 (kg)			
Mean (SD)	54.21 (13.43)	54.52 (11.95)	54.35 (12.69)
Median (min, max)	52.0 (30.9, 83.0)	54.0 (31.0, 74.0)	52.0 (30.9, 83.0)
Body Mass Index (kg/m2)			
Mean (SD)	21.0 (4.15)	20.6 (3.71)	20.8 (3.93)
Median (min, max)	19.9 (15, 32)	19.5 (16, 31)	19.5 (15, 32)

Source: Study B2301 Clinical Study Report, p. 38/999

Dosage

In the ITT group with Tanner ≥ 2, 54 of the 69 patients (78.3%) were taking the 80 mg daily dose at week 18 (the end of the titration period). In subsequent evaluation periods during the maintenance phase, the percentage of patients taking the 80 mg daily dose increased to a maximum of 94.2% (65/69) at week 66. This percentage showed some variation through the remainder of the maintenance phase, due to small changes in the number of patients reported in a given study week.

In the group with Tanner stage of 1, 11 of the 15 patients (73.3%) were taking the 80 mg daily dose at week 18. This percentage increased to 93.3% (14/15) at week 78 and was maintained at this level until week 114.

In the proposed label, the sponsor reports that 89% of patients were titrated to the maximum dose. This represents 62/69 of the patients in the ITT group with Tanner ≥ 2, and this percentage was first reported at week 42. While the rationale for selecting 89% for use in the label is not clear, it is within the range reported during the maintenance period for both the ITT group with Tanner ≥ 2 and the group with Tanner stage 1.

Efficacy endpoints and analyses

The primary efficacy endpoint was the mean percent change from baseline at endpoint in LDL-C. Endpoint was visit 15 / week 114 or earlier for patients who did not complete the study. Baseline was determined from the patient's last 2 measurements prior to active treatment for all lipid variables except Apo A-1 and Apo B. The last 2 measurements prior to active treatment were at week 0 and the last previous value, at week -3 or week -1 as applicable. For LDL-C and the other lipid parameters, the percent changes from baseline were summarized using descriptive

statistics by study week and at endpoint for the ITT population. The sponsor also calculated the number and percentage of patients who achieved the treatment goal of ≤ LDL-C of 130 mg/dL.

This reviewer confirmed the descriptive statistics reported for LDL, HDL, TG, Total-C, and Apo-B in TABLE 9. This reviewer also calculated the 95% confidence intervals for the percentage change from baseline at endpoint for the variables in TABLE 9 and for the LDL at endpoint.

At the end of the study (114 weeks), the sponsor reported that 26.1% of all patients reached the pre-assigned LDL-C concentration goal (≤ 130 mg/dL).

This reviewer believes that the study results are consistent with the sponsor's conclusion that fluvastatin sodium 20-80 (mostly at 80) mg per day for more than 2 years lowered LDL cholesterol levels effectively in female and male patients 10-17 years of age with an established diagnosis of heterozygous familial hypercholesterolemia. This reviewer calculated the 95% confidence interval (CI) of the percentage change in LDL at endpoint from baseline. This 95% CI is entirely in the region that represents a percentage reduction from baseline, and the CI does not include 0%. This provides statistical support to the conclusions about LDL (TABLE 9).

With respect to the secondary lipid variables, the sponsor concluded that fluvastatin sodium lowered other lipid variables such as Tot-C, Apo B and TG and increased HDL-C. In this reviewer's opinion, the statistical results support this conclusion for TC and for Apo B, because the 95% CIs of the percentage change from baseline for these variables are entirely in the region that represents a percentage reduction from baseline, and neither of the CIs include 0% (TABLE 9). However, the statistical results are less supportive for TG, because the 95% CI of the percentage change from baseline includes increases, 0% change and reductions (TABLE 9). Similarly, while the 95% confidence interval for percentage change in HDL is entirely in the region that represents a percentage increase, and the CI does not include 0%, this reviewer notes that the lower bound is very close to 0% (TABLE 9).

TABLE 9 Study B2301: Efficacy endpoints

	ITT Pubertal and post-pubertal group (N=69[a])	ITT Pre-pubertal group (N=15)
LDL-(mg/dL)		
Baseline mean	224.8	266.2
(min, max)	(148, 343)	(164, 390)
Mean at endpoint	158.5	157.3
(min, max)	(90, 295)	(98, 216)
[95% CI]	[147.5, 169.4]	
% Change at endpoint	-28.3%	-40.5%
(min, max)	(-57%, 52%)	(-63%, -25%)
[95% CI]	[-33.3%, -23.4%]	[-46.3%, -34.8%][b]
Number (%) of patients with LDL ≤ 130 mg/dL at endpoint	18/69 (26.1%)	4/15 (26.7%)
Total-C (mg/dL)		
Baseline mean	288.9	334.6
(min, max)	(211, 411)	(241, 441)
Mean at endpoint	221.9	228.7
(min, max)	(139, 342)	(169, 299)
% Change at endpoint	-21.9%	-31.2%
(min, max)	(-49%, 41%)	(-49%, -18%)
[95% CI]	[-26.2%, -17.7%]	
HDL-C (mg/dL)		
Baseline mean	46.6	51.3
(min, max)	(29, 71)	(35, 66)
Mean at endpoint	47.8	55.5
(min, max)	(28, 69)	(42, 72)
% Change at endpoint	4.1%	9.1%
(min, max)	(-36%, 44%)	(-5%, 30%)
[95% CI]	[0.1%, 8.2%]	
Triglycerides (mg/dL)		
Baseline mean	87.1	85.4
(min, max)	(47, 262)	(57, 140)
Mean at endpoint	78.6	79.9
(min, max)	(31, 214)	(49, 105)
% Change at endpoint	-5.5%	-3.9%
(min, max)	(-71%, 187%)	(-46%, 35%)
[95% CI]	[-14.9%, 3.9%]	
Apo-B		
Baseline mean	171.1	198.5
(min, max)	(111, 252)	(125, 284)
Mean at endpoint	134.1	133.3
(min, max)	(81, 233)	(97, 162)
% Change at endpoint	-20.7%	-32.1%

	ITT Pubertal and post-pubertal group (N=69[a])	ITT Pre-pubertal group (N=15)
(min, max) [95% CI]	(-52%, 45%) [-25.2%, -15.8%]	(-54%, -16%)
Sources from BA2301 Clinical Study Report:	Pubertal and post-pubertal Table 9.1-1a p. 210	Pre-pubertal
LDL	Table 9.2-1a, p. 228	Table 9.1-1b p. 214
HDL	Table 9.2-2a, p. 236	Table 9.2-1b p. 232
Tot-C	Table 9.2-4a, p. 249	Table 9.2-2b, p. 252
Triglycerides	Table 9.2-6a, p. 265	Table 9.2-4b, p. 256
Apo-B		Table 9.2-6b, p. 268

Notes:

[a] For the ITT population of 69 pubertal and post-pubertal patients, the last observation carried forward method was used to impute values for five patients who discontinued the study prior to week 114: one patient after week 42, three patients after week 8, and one patient after week 102 (see also TABLE 7)

[b] The 95% CI was calculated for the percent change in LDL from baseline for the pre-pubertal group because of the observation that the pre-pubertal group had a greater mean percent reduction in LDL compared with the ITT puberbal and post-pubertal group. The 95% CI of the difference in means between the two groups, allowing for unequal variances, is [4.9%, 19.6%].

Safety

The four adverse events (AEs) that were reported by the largest number of patients were: (1) influenza, (2) nasopharyngitis, (3) rhinitis and (4) upper respiratory tract infection (see the Clinical Study Report, Table 10-2 p. 55/999). The sponsor reported that most AEs were of mild or moderate intensity. No deaths or treatment discontinuation because of AEs were reported. Three non-fatal serious adverse events (SAEs) were reported: appendicitis, joint injury and depression.

The WR requested an evaluation of the effects of fluvastatin sodium on liver and muscle as monitored by serum transaminase and creatinine kinase levels. The sponsor reported that no notable changes in liver enzymes or creatine kinase were observed.

The WR also requested an evaluation of the effects on growth and sexual maturation as assessed by stadiometry and Tanner staging. The sponsor reported that pubertal patients who were Tanner stage 2 or above continued to have normal pubertal progression based on the Tanner stages. The number of subjects by baseline and study endpoint scores are summarized for the pre-pubertal and the pubertal/post-pubertal groups for genitals/breasts and pubic hair (TABLE 10). The sponsor summarized the progression of puberty in these patients as normal based on the Tanner staging. The sponsor also provided a review of growth, development and endocrine data by an external consultant, (b) (4) (the same consultant as for study ZA01).

(b) (4) concluded that fluvastatin sodium did not have any significant clinical or laboratory effects in study patient.

TABLE 10 Study B2301. Tanner staging scores for genitals/breasts and pubic hair at study endpoint relative to baseline

Baseline Score	Score at Study Endpoint	Pubertal and Post-Pubertal Group (n=70)	Pre-Pubertal Group (n=15)
Genitals[a] / Breasts			
1	1		0 (0.0%)
	2		7 (46.7%)
	3		6 (40.0%)
	4		0 (0.0%)
	5		0 (0.0%)
	(missing)		(2 missing)
			n=15
2	2	3 (10.3%)	
	3	7 (24.1%)	
	4	11 (37.9%)	
	5	6 (20.7%)	
	(missing)	(2 missing)	
		n=29	
3	3	0 (0.0%)	
	4	8 (44.4%)	
	5	9 (50.0%)	
	(missing)	(1 missing)	
		n=18	
4	4	1 (8.3%)	
	5	10 (83.3%)	
	(missing)	(1 missing)	
		n=12	
5	4[b]	1 (9.1%)	
	5	10 (90.9%)	
		n=11	
Pubic Hair			
1	1	1 (14.3%)	1 (6.7%)
	2	1 (14.3%)	7 (46.7%)
	3	2 (28.6%)	5 (33.3%)
	4	3 (42.9%)	0 (0.0%)
	5	0 (0.0%)	0 (0.0%)
	(missing)	(0 missing)	(2 missing)
		n=7	n=15
2	2	2 (10.5%)	
	3	3 (15.8%)	
	4	6 (31.6%)	
	5	6 (31.6%)	

Baseline Score	Score at Study Endpoint	Pubertal and Post-Pubertal Group (n=70)	Pre-Pubertal Group (n=15)
	(missing)	(2 missing) n=19	
3	3 4 5 (missing)	0 (0.0%) 4 (19.0%) 16 (76.2%) (1 missing) n=21	
4	4 5 (missing)	0 (0.0%) 14 (93.3%) (1 missing) n=15	
5	5	8 (100.0%) n=8	

Notes:
[a] For males, the Tanner score for genitals was an average of the Tanner scores for testes and penis.

[b] One male subject had a Tanner score of 5 for testes at week 0 and 4 at study endpoint. The scores of 5 for testes and 4 for penis at week 0 were averaged and then rounded up to 5 for genitals at week 0. The unexpected decrease in Tanner score for testes between week 0 and study endpoint is likely to be due to variability in the assessment process.

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