CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-445

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-445/N_000
Name of drug:	Zetia (ezetimibe) 10 mg tablets
Applicant:	MSP Singapore Co., LLC
Indication:	(3) Homozygous Sitosterolemia (*Separate reviews for the two other indications ((1) Hypercholesterolemia and (2) Homozygous Familial Hypercholesterolemia (HoFH)) have been prepared. An overview of the whole NDA is in the document for Indication (1)*)
Documents reviewed:	Volumes: 1.1, 1.2, 1.512 to 1.695, amendments dated April 2, 2002, April 5, 2002, April 19, 2002, May 9, 2002, and August 23, 2002
	Location of the NDA in EDR (electronic documents room):
	\\CDSESUB1\N21445\N_000\
Project manager:	William Koch, R.Ph.
Clinical reviewer:	Jean Temeck, M.D. (HFD-510)
Dates:	Received 12/27/01; user fee deadline: 10/27/02
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Keywords:	NDA review, clinical studies, analysis of covariance

CONTENTS:

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor conducted one study that provided statistically significant evidence that ezetimibe 10mg reduces sitosterol from baseline to endpoint (primary hypothesis).

Additionally, the sponsor's analyses as well as this reviewer's analyses, generally (some criticism in Section 2.3.3.f), showed statistically significant superiority of ezetimibe 10 mg over placebo in reducing sitosterol from baseline to endpoint.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The specific Phase II/III clinical therapy studies performed to support all three indications (1) Primary Hypercholesterolemia, (2) Homozygous Familial Hypercholesterolemia (HoFH), and (3) Homozygous Sitosterolemia, and the total numbers of patients by treatment per study are shown in Table 0.1.1[1].

An overview of the whole clinical program for all 3 indications as provided by the sponsor is in Section 2.1 of the document for Indication (1), Primary Hypercholesterolemia.

Note: Except where specifically mentioned otherwise, all other results and statements in this document are the sponsor's. In particular, the material in Sections 2.1 to 2.3.2 is almost verbatim from the sponsor's submissions.

Separate reviews for the two other indications have been prepared. This document is the review for the Specific Indication: Elevated sitosterol and campesterol in patients with homozygous

[1] To maintain consistency with the other two documents, in the Appendix Table (or Appendix Figure) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section. Both Tables and Figures are under one unique sequence without any distinction between them.

sitosterolemia (efficacy of ezetimibe as an adjunct to current therapeutic regimens, which generally consisted of a low-plant-sterol diet and, in some subjects, the use of bile-acid-binding resins).

Only one Phase III study, Study P02243/P02257 (U.S. & International Sites), has been conducted for this indication:

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Dumpion and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/N/C)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P02243/P02257	Effect of EZ on plasma sterols and lipids/ lipoproteins	R, DB, PG	Homozygous sitosterolemic subjects with baseline plasma sitosterol concentrations >5 mg/dL	8 weeks QD in AM	37 9/28 13/24 3/3/4	30 9/21 12/18 2/7/3	Placebo EZ 10	7 30

A total of 37 subjects (30 ezetimibe 10 mg and 7 placebo) were randomized into the study. All 37 subjects (100%) completed the study.

Note: In-depth statistical review and analyses have been done only with respect to the primary sitosterol efficacy evaluation.

1.3 PRINCIPAL FINDINGS

The sponsor conducted one study that provided statistically significant evidence that ezetimibe 10mg reduces sitosterol from baseline to endpoint (primary hypothesis).

Additionally, the sponsor's analyses as well as this reviewer's analyses, performed with the data supplied by the sponsor electronically, generally, showed statistically significant superiority of ezetimibe 10 mg over placebo in reducing sitosterol from baseline to endpoint. However, if we perform an alternative analysis comparing ezetimibe with placebo with respect to endpoint sitosterol (instead of change from baseline), the p-value becomes non-significant (p= 0.47 by Wilcoxon 2-sample test done by the reviewer). This analysis with respect to endpoint sitosterol instead of change from baseline was done (to check robustness of results) because one placebo patient had an unusually high 45% increase from baseline. Also, if the baseline sitosterolemia is categorized (<median, ≥median) and then included in the model along with the interaction (with treatment) term, then the treatment comparison p-value is 0.078 (0.003 if not categorized). However, these are not strong points and should not in any way be regarded as clearly negative evidence. Also, the comparison of the two treatment groups was not the criterion for the determination of the sample size.

Some critical comments regarding interaction are presented in the Section 2.3.3.f Efficacy Results. No serious qualitative concerns were seen in the subgroup results.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

In Study P02243/P02257, thirty patients with homozygous sitosterolemia were exposed to ezetimibe 10 mg/day for 8 weeks. This study was conducted in both the United States and at international sites.

2.2 DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room:
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2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions are following. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's Integrated Summary of Efficacy (ISE). The reviewer's findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes). The sponsor has presented a large number of results and conclusions, all of which may not be based on the primary hypotheses (may not even be mentioned in the Protocol or Data Analysis Plans). The p-values stated and the conclusions drawn by the sponsor are without multiple comparison adjustments (although adjustments are needed for the non-primary variables).

This study (P02243/P02257) was designed to evaluate the efficacy of ezetimibe when added to current therapeutic regimens in individuals with Homozygous Sitosterolemia.

Primary Efficacy Analysis: Percent Change From Baseline to Endpoint in Plasma Sitosterol Concentrations

The primary efficacy analysis was within-group percent change in plasma concentration of sitosterol from baseline (mean of values taken in the week prior to and at Visit 3) to endpoint (mean of values taken in the Weeks 6 and 8), and was performed using an ANOVA model that included a

term for stratum according to usage or non-usage of bile-acid-binding resins. As shown in the table below, ezetimibe 10 mg produced significant reductions in the plasma sitosterol concentrations.

Within the ezetimibe group, mean change was -21.0 ± 2.8% and was significant at P= 0.001. A nonsignificant mean change of 4.0 ± 5.3% was observed within the placebo group. The between-group difference in mean change was -25.0% and was significant at p= 0.001.

Percent Change in Sitosterol (mg/dL) Between Baseline and Endpoint (Average of Weeks 6 and 8): Modified Intent-to-Treat Population

Sitosterol(mg/dL)	Placebo	Ezetimibe 10 mg
Baseline	(n= 7)	(n= 29)
Raw Mean Value in mg/dL (mmoL/L)	18.5 (0.4)	21.0 (0.5)
Endpoint	(n= 7)	(n= 29)
Raw Mean Value in mg/dL (mmoL/L)	17.8 (0.4)	16.2 (0.4)
Raw Mean Percent Change from Baseline (Standard Error) For Subjects on Ezetimibe 10 mg/Day	2.4 (8.1)	-22.6 (2.2)
95% Confidence Limits for Raw Mean Percent Change For Subjects on Ezetimibe 1 0 mg/Day	(-17.4, 22.3)	(-27.5, -18.1)
Mean Percent Change from Baseline (Standard Error)[a]	4.0 (5.3)	-21.0 (2.8)
95% Confidence Limits for Mean Percent Change[a]	(-6.9 , 14.8)	(-26.7 , -15.3)
Difference from Placebo in Mean Percent Change from Baseline (95% Confidence Limits)[a]	-25.0 (-36.7 , -13.2)	
[a]: Mean and Standard Error are LS Mean and LS Standard Error based on the ANOVA model		

The Sponsor's Efficacy Conclusions

• In subjects with homozygous sitosterolemia, treatment with ezetimibe 10 mg/d produced clinically important reductions in plasma sitosterol concentrations that continued to fall throughout 8 weeks of therapy, in conjunction with other findings suggesting progressive improvement in this disease.

2.3.2 STATISTICAL METHODOLOGIES

The Sponsor's Statistical Methods for Efficacy Analyses

This was a single study with 2 protocol numbers for administrative convenience only. For this study there were 2 treatment groups, an ezetimibe 10-mg group and an ezetimibe placebo control group. The primary efficacy endpoint was within-group percent change from baseline to endpoint in plasma sitosterol. In this study, endpoint was defined as the last post-baseline measurement during

the 8-week, double-blind period or the average of the last 2 measurements in the Week 6 to Week 8 period, if a patient had more than one measurement in that period. See Section 2.33.f Efficacy Results for more details.

2.3.3 DETAILED REVIEW OF THIS INDIVIDUAL STUDY

The sponsor stated (May 9, 2002) in response to a request for the thorough investigation of covariation and interaction effects, "We have assessed those baseline characteristics that were pre-specified either for the individual protocols or for the ISE. These characteristics were chosen because they were either subgroups that are assessed for all studies (e.g. gender) or those that potentially have a relationship to the primary endpoint (e.g. baseline LDL-C). "

Only one Phase III study, Study P02243/P02257 (U.S. & International Sites), has been conducted for this indication:

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (yr) Sex (# M/F) Race (# C/N/O)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P02243/P02257	Effect of EZ on plasma sterols and lipids/ lipoproteins	R, DB, PG	Homozygous sitosterolemic subjects with baseline plasma sitosterol concentrations >6 mg/dL	8 weeks QD in AM	37 9-72 13/24 33/4	30 9-72 12/18 27/3	Placebo EZ 10	7 30

A total of 37 subjects (30 ezetimibe 10 mg and 7 placebo) were randomized into the study. All 37 subjects (100%) completed the study.

Study P02243/P02257

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 58235 (Ezetimibe) When Added to Current Regimen in Patients Homozygous Sitosterolemia (U.S.)

The synopsis of the report:

Development Phase of Study: III Study

Initiation Date: 12-Feb-2001 Study Completion Date: 18-Sep-2001

Study Centers: U.S. 12 centers; Non-U.S. 11 centers

Objective: The objective of the study was to evaluate the efficacy and safety of SCH 58235 (ezetimibe) 10 mg taken once a day in subjects with homozygous sitosterolemia.

Methodology: Randomized, double-blind, unbalanced-parallel-groups (4:1, ezetimibe 10 mg to placebo) comparison conducted in conformance with Good Clinical Practices.

Number of Subjects: Thirty-seven subjects, 24 women and 13 men, aged 9 to 72 years, received treatment assignment. Thirty received ezetimibe 10 mg/day and 7 received placebo.

Diagnosis and Criteria for Inclusion: Eligible patients included both males and females with sitosterolemia, who are at least 10 years of age, with an elevated plasma sitosterol level (5 mg/dL) on current regimen.

Duration of Treatment: One to 5 weeks no-treatment screening period, 3-week single-blind placebo period, 8-week double-blind investigational treatment period.

Reference Therapy, Dose, Mode of Administration: Ezetimibe 10 mg and matching placebo were provided as an unscored oral tablet.

Criteria for Evaluation: Primary: To assess the percent change relative to baseline in plasma concentration after double-blind treatment with SCH 58235 10 mg/day.

Statistical Methods: The primary objective of this study was to evaluate the efficacy and safety of SCH 10 mg/day in subjects with homozygous sitosterolemia. The primary hypothesis was assessed excluding one subject treated with apheresis therapy. The primary efficacy variable, percent change in sitosterol between baseline (mean of values taken in the week prior to Visit 3 and taken at Visit 3) and the endpoint (average of Visit 6 [Week 6] and Visit 7 [Week 8]) was assessed by using summary statistics and 95% CI.

2.3.3.a. Objectives

Primary

To assess the percent change relative to baseline in plasma sitosterol concentration after double-blind treatment with SCH- 58235 10 mg/ day when added to the current therapeutic regimen of patients with homozygous sitosterolemia who have continued elevation of plasma sitosterol.

2.3.3.b. Disposition of Patients

A total of 37 subjects (30 ezetimibe 10 mg and 7 placebo) were randomized into the study. All 37 subjects (100%) completed the study.

2.3.3.c. Protocol Deviations

Every subject was at least 90% compliant with dosing and there was good compliance with the visit schedule. No subjects discontinued. Since no per-protocol analysis was planned, no predefined protocol deviations were identified.

2.3.3.d. Demographic and Other Baseline Characteristics

Since the primary efficacy is based on within group change from baseline, baseline balance between treatment groups is not important for primary efficacy. The p-values for baseline comparisons provided by the sponsor on request (dated May 9, 2002) were only for baseline variables identified in the protocol and none of them were significant (< .05). For numerical imbalances between treatment groups with respect to categorized baseline variables (e.g., Bile Salt Binding Resin Therapy, Race), we cannot say anything for sure because just a switch of one patient (out of the 7 placebo patients) among the subgroup categories could result in a balance between the treatment groups.

With respect to Gender, there was a numerical imbalance between the two treatment groups with only one male patient in the placebo group (percents are given in parentheses):

	Placebo	ezetimibe 10mg
Female	6 (86)	18 (60)
Male	1 (14)	12 (40)

Placebo patients had a mean body weight of 63.0 kg compared with 67.5 kg for ezetimibe 10mg patients.

Detailed descriptive statistics are on pages 67 to 76 of the report.

2.3.3.e. Measurements of Treatment Compliance and Other Factors That Could Affect Response

On the results of measurements of treatment compliance and compliance with the visit schedule, compliance with the diet, changes in body weight and level of physical activity, the sponsor stated, "Overall, the results show good compliance with provisions of the protocol, and no obvious differences among groups that might affect the interpretation of the outcome."

The distribution of days of participation in the Randomization Phase is summarized below. Exposure was consistent with the intended 8-week, double-blind treatment, with most subjects having between 50 days and 62 days of exposure to study drug, and with similar exposures study drug exposures in the ezetimibe and in the placebo (numerically slightly less) treatment groups.

Extent of Exposure (Number of Days of Participation in the Randomization Phase, Intent-to-Treat Data Set):

	Placebo (n=7)	Ezetimibe 10 mg (n=30)
Days in Randomized treatment phase[a]		
Mean (SD)	53.3 (6.7)	55.9 (4.3)
Median	53	56
Min-Max	—	—
Frequency by Interval: Number (%) of Subjects With a Maximum Indicated Number of Days in Randomized treatment phase		
0 days	0	0
1 - 7 days	0	0
8 - 21 days	0	0
22 - 35 days	0	0
36 - 49 days	2 (28.6)	4 (13.3)
50 - 62 days	5 (71.4)	23 (76.7)
>62 days	0	3 (10.0)
Missing	0	0

a: n=7 for placebo treatment group and n=30 for ezetimibe treatment group for summary statistics.
SD=standard deviation.
Source Data: Section 14.5.1.

2.3.3.f. Efficacy Results (Sponsor's Analyses)

The sponsor stated that the Data Analysis Plan was finalized (Aug. 24, 2001) before unblinding data (database lock date 9/27/01). The primary hypothesis was: In patients with homozygous sitosterolemia who have continued elevation of plasma sitosterol on their current therapeutic regimen, treatment with ezetimibe will reduce the level of plasma sitosterol relative to baseline. Further, the "Data Analysis Plan" stated:

> The primary efficacy variable, percent change from baseline in plasma sitosterol after 8 weeks of treatment, will be assessed by an ANOVA model. The initial within- group ANOVA model will include a term for (BSBR, non- BSBR). The stratum term will be tested and removed from ANOVA model if found to be not significant (p>0.100). If the stratum term significant, results will be presented separately for each stratum. ... The parametric method will be the primary approach. The underlying assumptions for the analysis of variance will be checked by Shapiro-Wilk test for normality and Levene's test for homogeneity of variances for the primary and secondary lipid variables. If these assumptions are violated, parametric approach will be corroborated with a nonparametric method based upon Tukey's normalized ranks; the

interpretation of the results will be based on the nonparametric results. The least- squares mean (LS mean) for each treatment, between-treatment difference, and 95% confidence intervals (95% CI) will be estimated from the above ANOVA model. The primary hypothesis will be evaluated using the within- treatment confidence interval and p- value from the within- group ANOVA model.

The study report stated that efficacy results were obtained using a **Modified Intent-to-Treat Data Set**, that included all randomized subjects with at least one post-baseline measurement, but excluded one subject (P02243/08/ 050) who received apheresis therapy. This was pre-specified as the efficacy data set for the analysis of all lipid and plant sterol endpoints.

Treatment with ezetimibe 10 mg/day resulted in a mean change (standard error, SE) in plasma sitosterol concentrations from baseline to endpoint (average of Weeks 6 and 8 values) of -22.6% (2.2%) ($p < 0.001$) (Table below). The least-squares mean change (SE) in sitosterol concentration for subjects treated with placebo and ezetimibe was 4.0% (5.3%) and -21.0% (2.8%), respectively.

Percent Change in Sitosterol (mg/dL) Between Baseline and Endpoint (Average of Weeks 6 and 8): Modified Intent-to-Treat Population

Sitosterol(mg/dL)	Placebo	Ezetimibe 10 mg
Baseline	(n= 7)	(n= 29)
Raw Mean Value in mg/dL (mmoL/L)	18.5 (0.4)	21.0 (0.5)
Endpoint	(n= 7)	(n= 29)
Raw Mean Value in mg/dL (mmoL/L)	17.8 (0.4)	16.2 (0.4)
Raw Mean Percent Change from Baseline (Standard Error) For Subjects on Ezetimibe 10 mg/Day	2.4 (8.1)	-22.6 (2.2)
95% Confidence Limits for Raw Mean Percent Change For Subjects on Ezetimibe 1 0 mg/Day	(-17.4, 22.3)	(-27.5, -18.1)
Mean Percent Change from Baseline (Standard Error)[a]	4.0 (5.3)	-21.0 (2.8)
95% Confidence Limits for Mean Percent Change[a]	(-6.9 , 14.8)	(-26.7 , -15.3)
Difference from Placebo in Mean Percent Change from Baseline (95% Confidence Limits)[a]	-25.0 (-36.7 , -13.2)	
[a]: Mean and Standard Error are LS Mean and LS Standard Error based on the ANOVA model		

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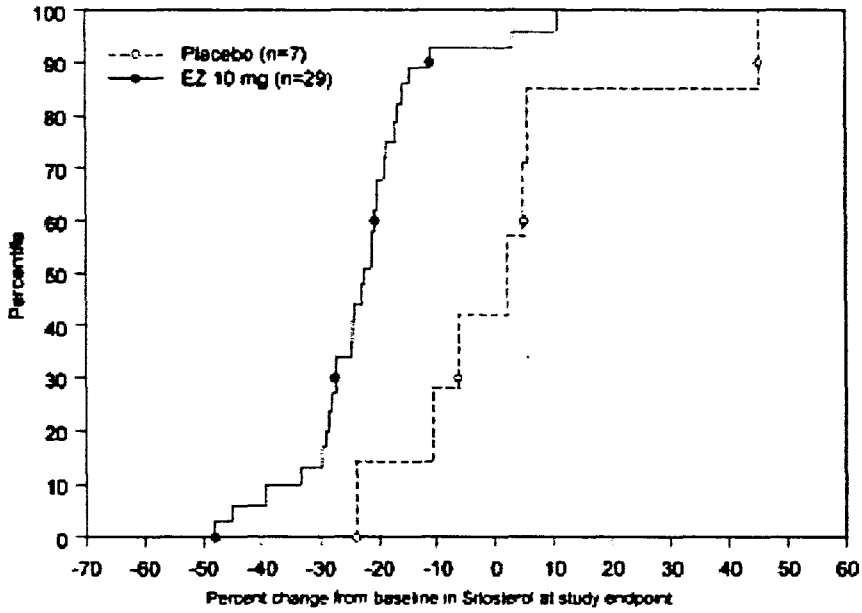
§ Cumulative Distribution Functions of Percent Change from Baseline in Sitosterol at Study Endpoint – P02243/02257:



From this, percent of patients (y-axis value) with a value of Change in Sitosterol from baseline at endpoint, smaller than or equal to a value on the x-axis can be read. For example, 50% of the ezetimibe 10mg patients had a ≤–22.3% change from baseline; whereas, 50% of the placebo patients had a ≤2.1% change from baseline.

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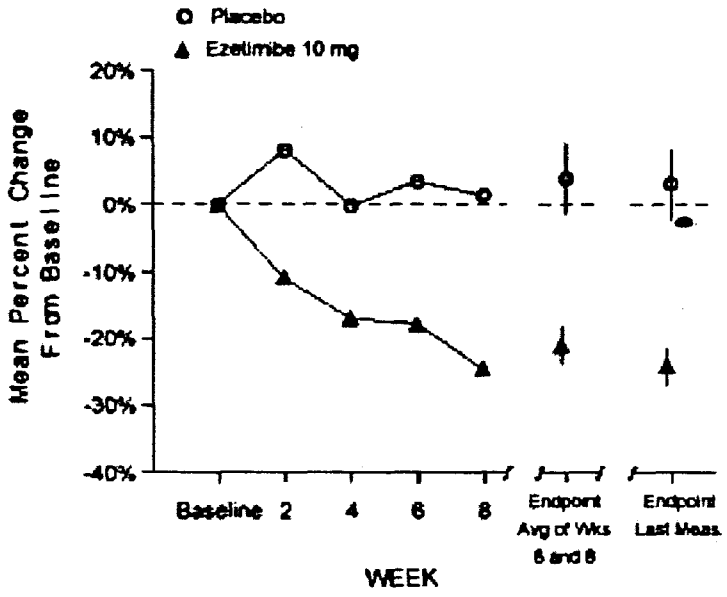
§ The reduction in plasma sitosterol concentration for subjects on ezetimibe during the double-blind period was progressive beginning at Week 2, with numerically greater reduction from baseline observed at each subsequent visit (Figure below).



§ Results for the primary efficacy variable were examined in subgroups defined by subject baseline characteristics: stratum (concomitant usage of bile salt binding resins), concomitant usage of statins, gender, protocol (P02243 or P02257), LDL-C (higher or lower than the baseline median value), and sitosterol (higher or lower than the baseline median value). As stated by the sponsor, the results of the analyses indicate that the response to ezetimibe 10 mg was consistent across subgroups (Figure, below). In particular, neither concomitant bile salt binding resin nor statin treatment meaningfully altered the response to ezetimibe therapy. Subjects with baseline plasma sitosterol concentration above the median had a modestly greater response than that with baseline concentration below the median (among the ezetimibe patients, without any comparison with the placebo group). Too few subjects under 18 years of age were in the study to perform meaningful subgroup analysis by age. Inspection of individual plasma sitosterol responses in the subjects under 18 years of age (see Section 16.2.6.1.) suggests that the effect of ezetimibe on plasma sitosterol concentrations was similar in subjects under 18 years compared to the response in subjects 18 years of age and older.

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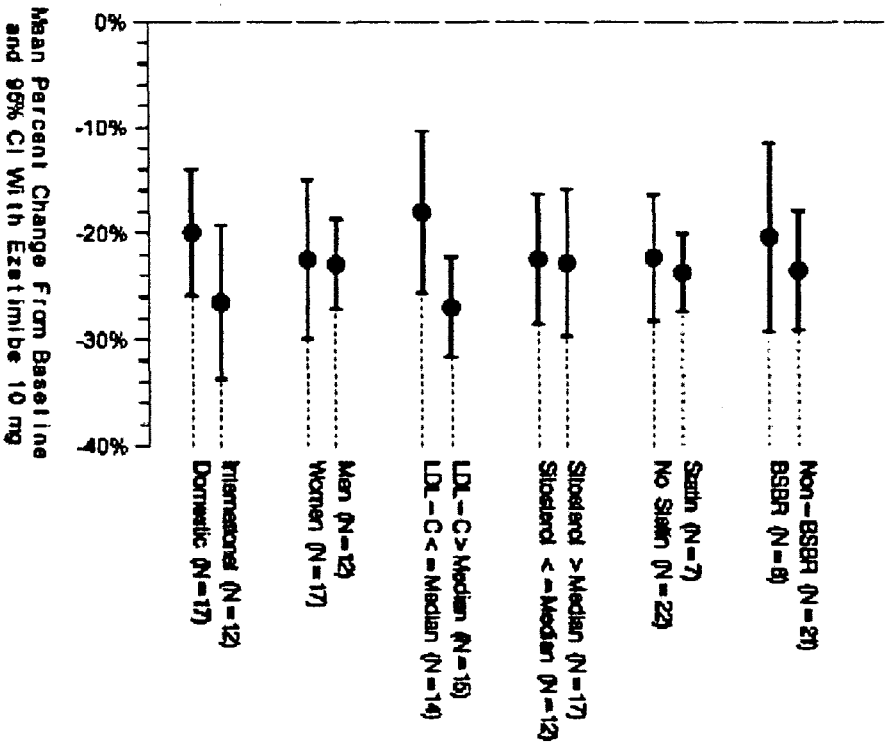
Subgroups – P02243/P02257 – Within Group Change for Ezetimibe



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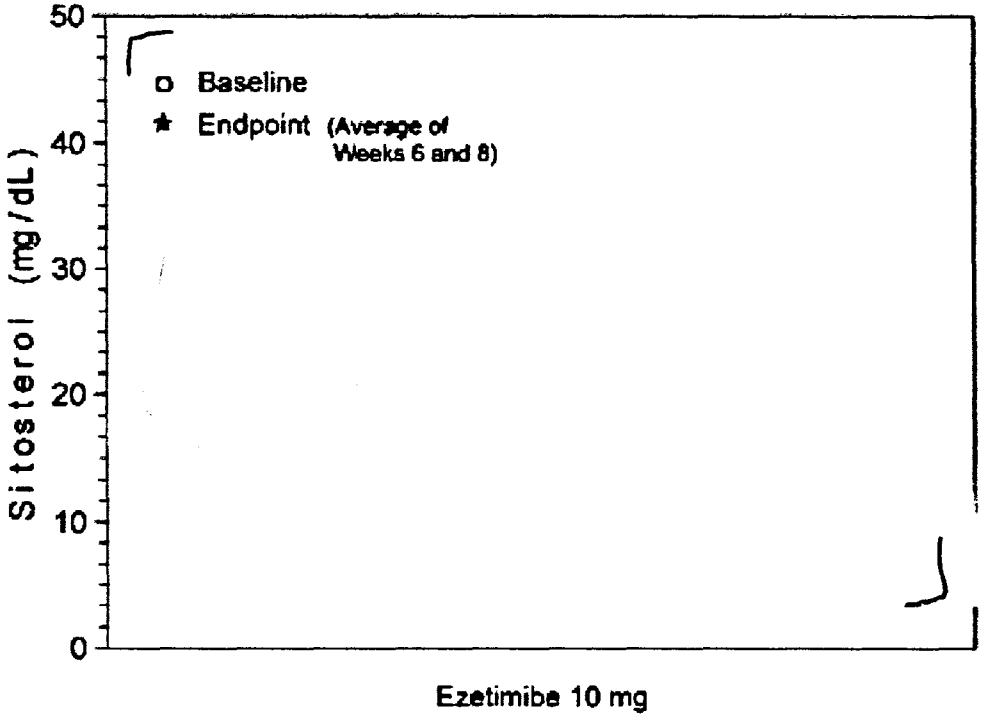
§ Individual changes in plasma sitosterol concentration are shown in Figures below (2nd one when split by concomitant bile salt binding resin use).



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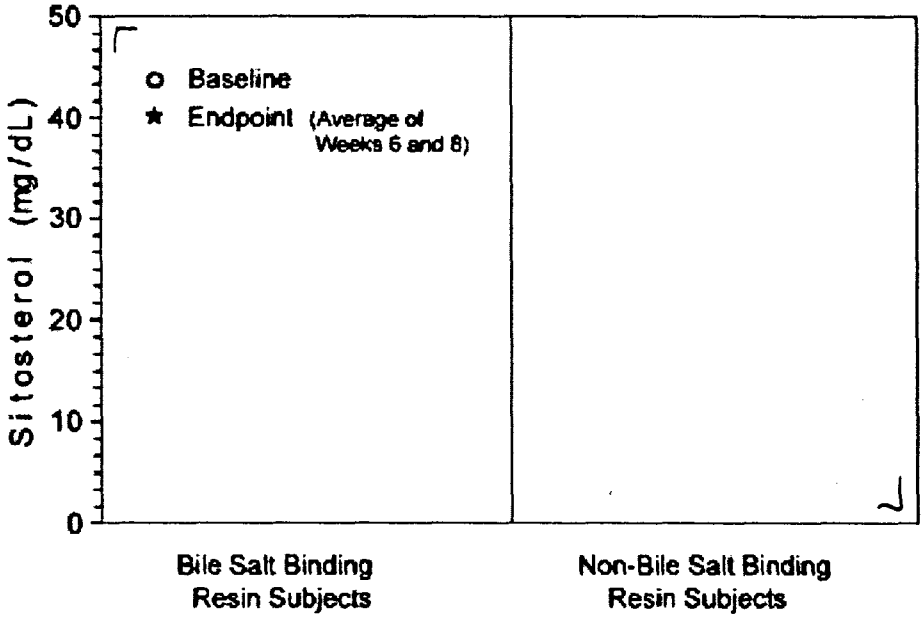
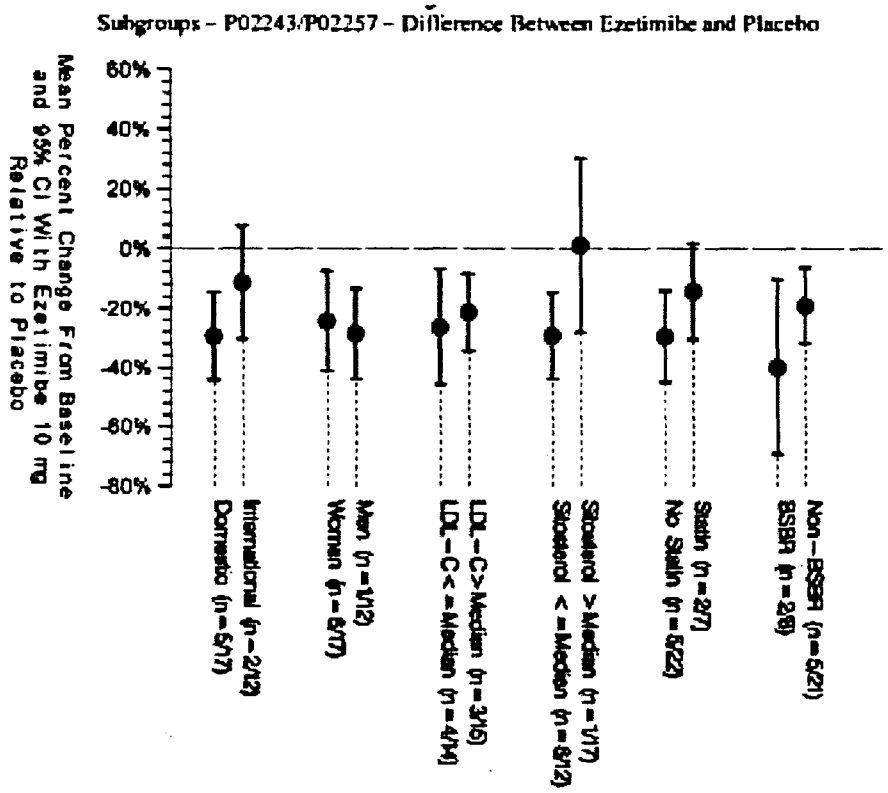


All but 2 subjects on ezetimibe had at least a 5% decrease in plasma sitosterol and all subjects on bile salt binding resins had decreases in plasma sitosterol concentration.

§ The between-group difference (95% CI) was -25.0% (-36.7%, - 3.2%) (p 0.001). If we perform an alternative analysis comparing ezetimibe with placebo with respect to endpoint sitosterol (instead of change from baseline), the p-value becomes non-significant (p= 0.47 by Wilcoxon 2-sample test done by the reviewer). This analysis with respect to endpoint sitosterol instead of change from baseline was done because placebo patients had on average a lower sitosterol level (18.5 vs 21.0 for ezetimibe) at baseline and one placebo patient had an unusually high 45% increase from baseline. Also, we see from Table 4.5 of the May 9, 2000 submission that if the baseline sitosterelemia is categorized (<median, ≥median) and then included in the model along with the interaction (with treatment) term, then the treatment comparison p-value is 0.078 (0.003 if not categorized). However, these are not strong points and should not in any way be regarded as clearly negative evidence. Also, the comparison of the two treatment groups was not the criterion for the determination of the sample size.

§ Subgroup results of ezetimibe 10mg relative to placebo are presented in the Figure below but no definite conclusion (i.e., whether the observed differences were real or not) can be made because there were only 7 patients in the placebo group.

Note: Studies are not, generally, powered to detect differences in subgroup results. In addition, this study was small.



The sponsor stated (May 9, 2002), "Conclusion: This exhaustive assessment of the relationship of baseline characteristics to the primary efficacy variable indicates that the conclusions about the treatment group differences are not altered by consideration of these baseline characteristics."

The following is noted about the covariation and interaction effects of baseline characteristics with treatment response. On the one hand, with multiple comparison adjustments, one or more of the mentioned characteristics may not be significant. On the other hand, it does not mean that the characteristics not providing smaller p-values have no effects; the non-significance (of the p-value) may be because the study was not powered for these purposes.

Covariation p-values:

Baseline LDL-C (continuous)	0.011
Baseline LDL-C (<median, ≥ median)	0.050
Baseline sitosterol (continuous)	0.020
Region (U.S., other)	0.014
Bile Salt Binding Resin (yes, no)	0.040

That is, the above characteristics influence the treatment response statistically significantly.

Interaction p-values:

Baseline sitosterol (<median, ≥ median)	0.058
Baseline sitosterol (continuous)	0.092
Prior surgery (yes, no)	0.060

Since the power of the test of interaction is, generally, poor (and the study was not powered to detect interaction), we, generally, cannot neglect nominal (without multiple-comparison adjustment) interaction p-values < 0.1. On the other hand, we cannot say whether the numerical difference (among subgroups) in superiority of ezetimibe over placebo, seen in the 2nd "subgroup Figure" above, with respect to other characteristics (not providing small interaction p-values) is real or not.

However, these interactions were quantitative and not qualitative (except only the Baseline sitosterol ">median" group, in which there was only one placebo patient with his/her response better than the mean response of the ezetimibe group); i.e., ezetimibe 10 mg was superior to placebo irrespective of the baseline subgroup considered (see the 2nd "subgroup Figure" above for the amount of superiority).

§ For this study (P02243/P02257), the numbers of patients in each center were too small to be presented individually; therefore, the population was divided by U.S. centers and non-U.S. centers. The results are:

P02246/02257 Mean Percent Change from Baseline and 95% CI with Ezetimibe 10 mg

	Group	N	Mean	95% Confidence Interval Lower Bound	Upper Bound	P-Value
Protocol	Domestic	17	-19.90	-25.83	-13.96	<0.001
	International	12	-28.44	-33.66	-19.22	<0.001

§ Parametric/Non-parametric Analysis Results Based on ITT population in P02243/02257 for Percent Change from Baseline in Sitosterol:

	Intent-To-Treat		
	Placebo (n=7)	EZ (n=29)	P-value
Lsmean	4.0	-21.0	<0.001
Median	2.1	-22.3	<0.001

2.3.3.g. Reviewer's Comments and Conclusions on Study P02243/P02257

The sponsor's analyses showed that there was a statistically significant reduction from baseline in sitosterol at endpoint (primary hypothesis).

Additionally, the sponsor's analyses as well as this reviewer's analyses, performed with the data supplied by the sponsor electronically, generally, showed statistically significant superiority of ezetimibe 10 mg over placebo in reducing sitosterol from baseline to endpoint. However, if we perform an alternative analysis comparing ezetimibe with placebo with respect to endpoint sitosterol (instead of change from baseline), the p-value becomes non-significant (p= 0.47 by Wilcoxon 2-sample test done by the reviewer). This analysis with respect to endpoint sitosterol instead of change from baseline was done because placebo patients were on average less sick at baseline and one placebo patient had an unusually high 45% increase from baseline. If the baseline sitosterelemia is categorized (<median, ≥median) and then included in the model along with the interaction (with treatment) term, then the treatment comparison p-value is 0.078 (0.003 if not categorized). However, these are not strong points and should not in any way be regarded as clearly negative evidence. Also, the comparison of the two treatment groups was not the criterion for the determination of the sample size.

Some critical comments regarding interaction are presented in the Section 2.3.3.f Efficacy Results. No serious qualitative concerns were seen in the subgroup results.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Wilson

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CC:
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HFD-510/Dr. Parks
HFD-510/Dr. Temeck
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 09/30/02

This review consists of 20 pages of text and 3 pages of appendices.

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APPENDIX

Table 0.1.1

Description of Phase II/III Clinical Therapy Studies

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase II Ezetimibe Dose Response Studies								
C96-411/345	Effect of EZ on LDL-C and other lipids (dose ranging); safety; PK	R, DB, PC, PG	Primary hyper-cholesterolemic (PHC) subjects on a low-fat diet with LDL-C 160 to 220 mg/dL and TG ≤250 mg/dL	6 weeks; QD before AM meal	124 30 - 71 66/58 13/11	89 30 - 71 46/43 8/1/8	Placebo EZ 1 EZ 5 EZ 10 EZ 20 EZ 40 lovastatin (L) 40	17 17 20 18 16 18 18
C96-810	Effect of EZ on LDL-C and other lipids (dose response); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤300 mg/dL	12 weeks; QD before AM meal	243 28 - 75 139/104 223/20	181 28 - 75 108/83 176/15	Placebo EZ 0.25 EZ 1 EZ 5 EZ 10	62 47 49 49 46
C96-258	Effect of EZ on LDL-C and other lipids (dose regimen [AM vs PM dosing]); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤300 mg/dL	12 weeks; QD before AM meal or at bedtime (PM)	189 22 - 75 89/100 168/21	153 25 - 75 74/79 135/18	Placebo EZ 5 AM EZ 5 PM EZ 10 AM EZ 10 PM	35 36 40 39 38
Phase III Ezetimibe Monotherapy Studies- Primary Hypercholesterolemia								
P00474	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD in AM	827 20 - 86 397/430 746/81	622 20 - 86 302/320 565/57	Placebo EZ 10	205 622
P00475	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD in AM	892 18 - 85 434/458 809/83	666 18 - 85 332/334 588/68	Placebo EZ 10	226 666

(Table 0.1.1 Continued to next page)

Table 0.1.1 Continued

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase III Ezetimibe/Statin Coadministration – Factorial Coadministration Studies								
P00679	Effect of EZ when coadministered with lovastatin (L) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks, QD with PM meal	548 26 - 85 229/319 484/64	284 28 - 85 117/147 227/37	Placebo L 10 L 20 L 40 EZ 10 EZ 10+L 10 EZ 10+L 20 EZ 10+L 40	64 73 74 73 72 65 62 65
P00680	Effect of EZ when coadministered with simvastatin (S) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks, QD in PM	668 25 - 87 291/377 610/58	335 27 - 84 150/185 306/29	Placebo S 10 S 20 S 40 S 80 EZ 10 EZ 10+S 10 EZ 10+S 20 EZ 10+S 40 EZ 10+S 80	70 70 61 65 67 61 67 69 73 65
P00691	Effect of EZ when coadministered with pravastatin (P) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks, QD at bedtime	538 20 - 86 238/300 462/76	268 20 - 86 106/162 236/32	Placebo P 10 P 20 P 40 EZ 10 EZ 10+P 10 EZ 10+P 20 EZ 10+P 40	65 66 69 70 64 71 68 67

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P00692	Effect of EZ when coadministered with atorvastatin (A) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks, QD in AM	628 18 - 86 250/358 533/95	320 26 - 86 136/184 279/41	Placebo A 10 A 20 A 40 A 80 EZ 10 EZ 10+A 10 EZ 10+A 20 EZ 10+A 40 EZ 10+A 80	60 60 60 66 62 65 65 62 65 63
Phase III Ezetimibe/Statin Coadministration– Add-On Study								
P02173	Effect of EZ when added to ongoing therapy with statins on LDL-C and other lipids; safety	R, DB, PC	Subjects with PHC, known CHD, or multiple CVD risk factors who are not at LDL-C targets with a stable regimen of statins and a low-fat diet	8 weeks, QD in AM or PM with statin as per statin label	769 22-85 443/326 693/76	379 25-85 222/157 337/42	Placebo (+ statin) EZ 10 (+ statin)	390 379
Phase III Ezetimibe Therapy in Special Dyslipidemic Populations								
P01030	Effect of EZ when coadministered with A or S on LDL-C and other lipids; safety	R, DB, PG	HoFH subjects with LDL-C ≥100 mg/dL on low-fat diet and taking OL A or S 40 mg/day for 6 weeks	12 weeks, QD in AM with A, QD in PM with S	50 11 - 74 21/29 45/5	33 11 - 74 16/17 29/4	A/S 80 EZ 10+A/S 40 EZ 10+A/S 80	17 16 17

(Table 0.1.1 Continued to next page)

Table 0.1.1 Continued

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P02243/P02257	Effect of EZ on plasma sterols and lipids/ lipoproteins	R, DB, PG	Homozygous sitosterolemic subjects with baseline plasma sitosterol concentrations >5 mg/dL	8 weeks QD in AM	37 9-72 13/24 33/4	30 9-72 12/18 27/3	Placebo EZ 10	7 30
Ongoing, Uncontrolled, Open-label, Long-term Extension Study								
P00476	Long-term safety and efficacy of EZ as monotherapy or when coadministered with L or S	OL; response-based addition and up-titration of L or S (10-40 mg)	PHC subjects on low-fat diet who completed treatment under Protocols P00474 or P00475	24 months QD in AM as monotherapy or coadministered with statin as per statin label	1313 18-86 655/658 1198/115	1313 18-86 655/658 1198/115	EZ 10 EZ 10 + L/S[a]	783 530

A=atorvastatin; CHD=coronary heart disease; DB=double-blind; EZ=ezetimibe; HoFH=homozygous familial hypercholesterolemia; L=lovastatin; OL=open-label; P=pravastatin; PC=placebo-controlled; PG=parallel group; PHC=primary hypercholesterolemia; QD=once per day by mouth; R=randomized; S=simvastatin; UPG=unbalanced parallel groups.

a: at doses of 10, 20, or 40 mg for L, or 10, 20, 40, or 80 mg for S (following a titration procedure).

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/s/

Japobrata Choudhury
9/30/02 05:14:51 PM
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Todd Sahlroot
10/2/02 03:41:27 PM
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Steve Wilson
10/7/02 03:03:36 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-445/N_000
Name of drug:	Zetia (ezetimibe) 10 mg tablets
Applicant:	MSP Singapore Co., LLC
Indication:	(2) Homozygous Familial Hypercholesterolemia (HoFH) (*separate reviews for the two other indications, (1) Hypercholesterolemia and (3) Homozygous Sitosterolemia, have been prepared. An overview of the whole NDA is in the document for Indication (1)*)
Documents reviewed:	Volumes: 1.1, 1.2, 1.512 to 1.695, amendments dated 4-2-02, 4-5-02, 4-19-02, 5-9-02, 7-22-02, and 8-23-2002
	Location of the NDA in EDR (electronic documents room): \\CDSESUB1\N21445\N_000\
Project manager:	William Koch, R.Ph.
Clinical reviewer:	Jean Temeck, M.D. (HFD-510)
Dates:	Received 12/27/01; user fee deadline: 10/27/02
Statistical reviewer:	Japobrata Choudhury, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Concurrence by:	Stephen Wilson, Dr.P.H. (HFD-715)
Keywords:	NDA review, clinical studies, analysis of covariance, interaction

CONTENTS:

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor conducted one study that provided statistical evidence in favor of the superiority of overall co-administration of ezetimibe 10 mg plus Statin 40/80 mg over Statin 80 mg alone, with respect to the primary efficacy variable, Change From Baseline in Direct LDL-C.

There was statistically significant quantitative interaction of "apheresis treatment" with treatments of this study. That is, the superiority of the ezetimibe +Statin 40/80 mg treatment over the Statin 80 mg treatment was statistically larger in the group of patients with no apheresis treatment than that in the group with apheresis treatment.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The specific Phase II/III clinical therapy studies performed to support all three indications, (1) Primary Hypercholesterolemia, (2) Homozygous Familial Hypercholesterolemia (HoFH), and (3) Homozygous Sitosterolemia, and the total numbers of patients by treatment per study are shown in Table 0.1.1[1].

An overview of the whole clinical program for all 3 indications as provided by the sponsor is in Section 2.1 of the document for Indication (1), Primary Hypercholesterolemia.

Note: Except where specifically mentioned otherwise, all other results and statements in this document are the sponsor's. In particular, the material in Sections 2.1 to 2.3.2 is almost verbatim from the sponsor's submissions.

Separate reviews for the two other indications have been prepared. This document is the review for the Specific Indication: (2) Homozygous Familial Hypercholesterolemia (HoFH)

ZETIA, administered with an HMG-CoA reductase inhibitor approved for HoFH, is proposed to be indicated for the reduction of elevated LDL-C (primary) and total-C levels in patients with HoFH,

[1] To maintain consistency with the other two documents, in the Appendix Table (or Appendix Figure) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section. Both Tables and Figures are under one unique sequence without any distinction between them.

as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Only one Phase III study, Study P01030 (U.S. & International Sites), has been conducted for this indication:

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (yr) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase III Ezetimibe Therapy in Special Dyslipidemic Populations								
P01030	Effect of EZ when coadministered with A or S on LDL-C and other lipids, safety	R, DB, PG	HoFH subjects with LDL-C >100 mg/dL on low fat diet and taking OL A or S 40 mg/day for 6 weeks	12 weeks QD in AM with A, QD in PM with S	50 11 - 74 21/29 45/5	33 11 - 74 16/17 29/4	A/S 80 EZ 10+A/S 40 EZ 10+A/S 80	17 16 17

A total of 50 subjects received randomized treatment assignment: 17 subjects received Statin 80 mg and 33 subjects received EZ 10 mg + Statin 40/80 mg; all received at least one dose of study medication. Forty-eight (48) subjects (96%) completed the protocol-specified, double-blind treatment phase, and 2 subjects (4%) discontinued treatment early. The two discontinuations (4% of randomized subjects) were due to adverse events, in one case related to abnormal laboratory results at baseline that failed to meet the Inclusion and Exclusion Criteria.

1.3 PRINCIPAL FINDINGS

The sponsor conducted one study that provided statistical evidence in favor of the superiority of overall co-administration of ezetimibe 10 mg with Statin 40/80 mg over Statin 80 mg alone, with respect to the primary efficacy variable, Percent Change From Baseline in Direct LDL-C.

Results of the protocol-specified primary efficacy (Low-Density-Lipoprotein Cholesterol) analysis demonstrated that the overall treatment effect was significant (i.e., overall co-administration of ezetimibe 10 mg with Statin 40/80 mg was more efficacious than Statin 80 mg alone) in reducing plasma concentrations of direct LDL-C from baseline to endpoint. For this analysis, data from four treatment groups involving co-administration therapy (EZ 10 mg + Ator 40 mg, EZ 10 mg + Ator 80 mg, EZ 10 mg + Sim 40 mg, and EZ 10 mg + Sim 80 mg) were pooled and compared with the two pooled monotherapy treatment groups (Ator 80 mg and Sim 80 mg). Results in none of the 6 treatment arms were in the opposite direction (i.e., worse than baseline), although there were appreciable numerical differences. In fact, ezetimibe co-administartion with 80 mg statin was statistically superior to ezetimibe co-administartion with 40 mg statin (-27.28 vs –13.43). Numerical results cast some doubt that ezetimibe 10mg + Simva 40 mg with a mean percentage change from baseline in LDL-C of –12.03 is statistically superior to Simva 80 mg with a corresponding change of –10.99. Baseline LS means (corresponding to the primary treatment-comparison) were similar (313.17 ± 21.5 vs 338.75 ± 28.6, respectively, p=0.46; page 113 of NDA report). A mean percent change of –20.73% was observed for the EZ 10 mg + Statin 40/80 mg

group compared with –6.65% for the Statin 80 mg group. The difference between the treatment groups was statistically significant based on ANOVA (p=.0072).

There was a statistically significant quantitative interaction (not qualitative) of "apheresis traetment" with the treatments of this study. The superiority of the ezetimibe +Statin 40/80 mg treatment over the Statin 80 mg treatment was much larger in the group of patients with no apheresis treatment than that in the group with apheresis treatment. Ninety-five percent confidence intervals and other details are in Section 2.3.3.f.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Note: In-depth statistical review and analyses have been done only with respect to the primary efficacy variable LDL-C.

The HoFH study (**P01030**) evaluated the efficacy of coadministering ezetimibe 10 mg with simvastatin or atorvastatin (40 mg or 80 mg) as well as with regular LDL apheresis in subjects already stabilized on such treatments.

2.2 DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room:
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2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions follow. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's Integrated Summary of Efficacy (ISE). The reviewer's findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes). The sponsor has presented a large number of results and conclusions, all of which may not be based on the primary hypotheses (may not even be mentioned in the Protocol or Data Analysis Plans). The p-values stated and the conclusions drawn by the sponsor are without multiple comparison adjustments (although adjustments are needed for the non-primary variables).

Homozygous Familial Hypercholesterolemia

The primary efficacy analysis was percent change from baseline to endpoint in plasma concentrations of direct LDL-C in the intention-to-treat data set. As shown in Table below, EZ + statin 40/80 mg produced greater reductions in plasma LDL-C concentrations than did statin 80 mg. Mean changes from baseline to endpoint in direct LDL-C concentrations were -20.7 ± 3.2% and -6.7 ± 4.2%, respectively, and were significantly different at p=0.007. The incremental change in direct LDL-C concentrations attributable to ezetimibe was -14.1%. Results were similar for calculated LDL-C concentrations: Mean changes from baseline to endpoint were -21.4 ± 3.2% for EZ + statin 40/80 mg versus -6.6 ± 4.2% for statin 80 mg (p <0.01). Significant reductions in plasma LDL-C concentrations in the EZ + statin 40/80 mg group occurred within 2 weeks, the earliest measurement taken, and persisted for the full duration of the 12-week study. [*Note: ISE, Section 10.1.5.1.1 (Page 192) incorrectly stated* ——— .]

Mean Percent Changes in Plasma (Direct and Calculated) LDL-C Concentrations From Baseline to Endpoint in Subjects with HoFH (P01030): Primary Comparison Groups

		Direct LDL-C	
		Statin 80 mg (n=17)	EZ + Statin 40/80 mg (n=33)
Baseline			
	Mean value in mg/dL[a] [mmol/L]	338.8 [8.8]	313.2 [8.1]
Endpoint			
	Mean value in mg/dL[a] [mmol/L]	318.5 [8.2]	247.2 [6.4]
	Mean percent change from baseline (SEM)[a]	-6.7 (4.2)	-20.7 (3.2)
	Differences from statin 80 mg in mean percent change from baseline (95% CI)	--	-14.1** (-24.1, -4.01)

**p=0.007.
EZ=ezetimibe.
a: Values presented are LS means and standard errors of LS means (SEM) based on the 2-way ANOVA model extracting treatment and statin effects.

Sponsor's Efficacy Conclusions

- Ezetimibe 10 mg daily coadministered with atorvastatin or simvastatin caused statistically significant and clinically important reductions in LDL-C compared with treatment with atorvastatin or simvastatin administered alone in subjects with Homozygous Familial Hypercholesterolemia.

- The difference in mean percent change from baseline to endpoint for direct LDL-C in the EZ 10 mg + Statin 40/80 mg group relative to the Statin 80 mg group was –14.1%.

- The difference in mean percent change from baseline to endpoint for direct LDL-C in the EZ 10 mg + Statin 80 mg group relative to the Statin 80 mg group was –20.5%[2].

[2] Note: This was not an originally intended comparison.

- The LDL-C lowering effect of ezetimibe coadministered with statin 40/80 mg was seen as early as Week 2 and was maintained for the duration of the study.

- The effect of ezetimibe coadministered with statin 40/80 mg on direct LDL-C was consistent among the subgroups analyzed.

- Ezetimibe coadministered with statin 40/80 mg and ezetimibe coadministered with statin 80 mg also caused statistically significant reductions in calculated LDL-C and TC.

- Coadministration of ezetimibe 10 mg daily with atorvastatin or simvastatin at doses of either 40 or 80 mg daily was well tolerated in subjects with Homozygous Familial Hypercholesterolemia and had a safety profile similar to that of subjects administered 80 mg of these statins alone.

2.3.2 STATISTICAL METHODOLOGIES

Homozygous Familial Hypercholesterolemia (P01030)
This study included 6 blinded randomized treatment groups: ezetimibe 10 mg +atorvastatin placebo, ezetimibe 10 mg +40 mg atorvastatin, ezetimibe placebo +40 mg atorvastatin, ezetimibe 10 mg +simvastatin placebo, ezetimibe 10 mg +40 mg simvastatin, and ezetimibe placebo +40 mg simvastatin. In addition, all patients received either open-label atorvastatin 40 mg or simvastatin 40 mg. The primary efficacy analysis was based on the percent change in direct LDL-C from baseline to study endpoint. The primary comparison was between the statin-alone 80mg combined group (atorvastatin 80 mg, simvastatin 80 mg) versus statin +ezetimibe 10 mg combined group (irrespective of the statin and statin dose). An ANOVA model with terms for treatment group (statin-alone 80mg combined group, statin +ezetimibe 10 mg combined group) and statin (atorvastatin, simvastatin) was used. Owing to the small number of subjects enrolled in each center, center effect and treatment by center interaction effect were not included in the model. Confidence intervals were calculated using the LSMEANS from the ANOVA model. A parametric analysis was the primary analysis; it was corroborated by a non-parametric analysis.

2.3.3 DETAILED REVIEW OF THIS INDIVIDUAL STUDY

The sponsor stated in response (May 9, 2002) to a request for the thorough investigation of covariation and interaction effects, "We have assessed those baseline characteristics that were pre-specified either for the individual protocols or for the ISE. These characteristics were chosen because they were either subgroups that are assessed for all studies (e.g. gender) or those that potentially have a relationship to the primary endpoint (e.g. baseline LDL-C)."

Only one Phase III study, Study P01030 (U.S. & International Sites), has been conducted for this indication:

Protocol	Objectives	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (yr) Sex (# M/F) Race (# C/N/O)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase III Ezetimibe Therapy in Special Dyslipidemic Populations								
P01030	Effect of EZ when coadministered with A or S on LDL-C and other lipids, safety	R, DB, PG	HoFH subjects with LDL-C ≥100 mg/dL on low-fat diet and taking CL A or S 40 mg/day for 6 weeks	12 weeks QD in AM with A, QD in PM with S	50 11 - 74 21/29 45/5	33 11 - 74 16/17 29/4	A/S 80 EZ 10+A/S 40 EZ 10+A/S 80	17 16 17

A total of 50 subjects received at least one dose of study medication. Forty-eight (48) subjects (96%) completed the study.

Study P01030

Title: A Phase III Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia

The synopsis of the report:

Study Centers: 4 Centers in the USA and 13 International Centers

Studied Period: 03 MAY 2000 to 25 MAY 2001

Objectives: The primary objective was to evaluate the efficacy and the safety of ezetimibe 10 mg/day co-administered with atorvastatin or simvastatin in subjects with Homozygous Familial Hypercholesterolemia.

Methodology: Randomized, double-blind, parallel-group study (2:1, ezetimibe 10 mg + statin 40/80 mg to statin 80 mg) comparison conducted in conformance with Good Clinical Practices. Following dietary assessment and a 6- to 14-week atorvastatin or simvastatin 40 mg lead-in period, qualified subjects received randomized assignment to one of the six once-daily treatment arms: Ator 80 mg, EZ 10 mg + Ator 40 mg, EZ 10 mg + Ator 80 mg, Sim 80 mg, EZ 10 mg + Sim 40 mg, or EZ 10 mg + Sim 80 mg. Subjects continued their open-label statin 40 mg from the lead-in period as part of their total dose. Subjects received 12 weeks of double-blind treatment. Visits occurred at 2- to 4-week intervals, at which time lipids and safety variables were measured.

Number of Subjects: 50 subjects, 21 men and 29 women, aged 11 to 74 years, received randomized treatment assignment: 33 ezetimibe 10 mg + statin 40/80 mg and 17 statin 80 mg.

Diagnosis and Criteria for Inclusion: Subjects with Homozygous Familial Hypercholesterolemia (HoFH) (diagnosed by genetic testing or clinically diagnosed by history of LDL-C ≥ 220 mg/dL on

maximally tolerated lipid lowering therapy and a <15% response to that therapy in addition to LDL-C above the 90th percentile in two or more first degree relatives and the presence of tendinous xanthomas within the kindred, and/or premature corneal arcus, and/or manifestations of premature CHD); plasma LDL-C calculated via the Friedewald ≥ equation100 mg/dL (≥ 2.59 mmol/L) while receiving atorvastatin 40 mg or simvastatin 40 mg; and plasma triglyceride level ≤ 350 mg/dL (≤ 3.99 mmol/L); NCEP Step I diet or stricter; adequate washout of previous lipid-lowering medication (fibrates).

Duration of Treatment: 6 to 14 weeks of washout (fibrates only) during the Pre-Randomization/Statin Lead-In Phase and 12 weeks of double-blind investigational treatment during the Randomized Treatment Phase.

Criteria for Evaluation: The primary efficacy variable was percent change from baseline to endpoint in the plasma concentration of direct LDL-C, determined following a [redacted] The primary efficacy analysis was the EZ 10 mg + Statin 40/80 mg treatment group vs. the Statin 80 mg group. Percent change from baseline to endpoint was also determined for calculated LDL-C, high density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG), subfractions HDL2-C and HDL3-C, apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo B), lipoprotein(a) (Lp(a)) and ratios LDL-C:HDL-C and TC:HDL-C.

Statistical Methods: The primary efficacy analysis was performed using a two-way analysis of variance model that extracts source of variation due to treatment and statin for the percent change from baseline in direct LDL-C at endpoint. Safety and tolerability was assessed by clinical review of all safety parameters, including adverse experiences, laboratory safety parameters, and clinical safety parameters.

2.3.3.a. Objectives

Primary

To evaluate the efficacy and the safety of ezetimibe (10 mg/day) co-administered with atorvastatin or simvastatin in patients with homozygous FH. The primary endpoint will be defined as the percent change from Baseline of the direct LDL-C at treatment endpoint.

2.3.3.b. Disposition of Patients

A total of 50 subjects received randomized treatment assignment: 17 subjects received Statin 80 mg and 33 subjects received EZ 10 mg + Statin 40/80 mg; all received at least one dose of study medication. Forty-eight (48) subjects (96%) completed the protocol-specified, double-blind treatment phase, and 2 subjects (4%) discontinued treatment early, as shown below. The two discontinuations (4% of randomized subjects) were due to adverse events (the difference between

the two primary comparison-groups is not statistically significant), in one case related to abnormal laboratory results at baseline that failed to meet the Inclusion and Exclusion Criteria.

Disposition of Subjects Following Randomized Treatment Assignment: Number (%) of Subjects

Disposition of Subjects	Statin 80 mg (n=17)	EZ 10 mg + Statin 40/80 mg (n=33)	Ator 80 mg (n=12)	EZ 10 mg + Ator 40 mg (n=12)	EZ 10 mg + Ator 80 mg (n=12)	Sim 80 mg (n=5)	EZ 10 mg + Sim 40 mg (n=4)	EZ 10 mg + Sim 80 mg (n=5)
Received Randomized Treatment Assignment	17 (100)	33 (100)	12 (100)	12 (100)	12 (100)	5 (100)	4 (100)	5 (100)
Completed Treatment	17 (100)	31 (94)	12 (100)	11 (92)	12 (100)	5 (100)	4 (100)	4 (80)
Discontinued Treatment	0	2 (6)	0	1 (8)	0	0	0	1 (20)
Adverse event	0	2 (6)	0	1 (8)	0	0	0	1 (20)
Treatment failure	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0
Subject did not wish to continue	0	0	0	0	0	0	0	0
Noncompliance with protocol	0	0	0	0	0	0	0	0
Administrative	0	0	0	0	0	0	0	0

Source Data Section 14.4.3.2.

2.3.3.c. Protocol Deviations

All subjects' data were included in the analyses a priori.

2.3.3.d. Demographic and Other Baseline Characteristics

The p-values for baseline comparisons provided by the sponsor on request (dated May 9th, 2002) were only for baseline variables identified in the protocol and none of them were <.05. There were numerical imbalances (not statistically significant) with respect to gender:

Characteristics and Levels	Statin 80 mg (n=17)	EZ 10 mg + Statin 40/80 mg (n=33)	Ator 80 mg (n=12)	EZ 10 mg + Ator 40 mg (n=12)	EZ 10 mg + Ator 80 mg (n=12)	Sim 80 mg (n=5)	EZ 10 mg + Sim 40 mg (n=4)	EZ 10 mg + Sim 80 mg (n=5)
Sex (no. subjects %)	(n=17)	(n=33)	(n=12)	(n=12)	(n=12)	(n=5)	(n=4)	(n=5)
Female	12 (71%)	17 (52%)	8 (67%)	9 (75%)	5 (42%)	4 (80%)	2 (50%)	1 (20%)
Male	5 (29%)	16 (48%)	4 (33%)	3 (25%)	7 (58%)	1 (20%)	2 (50%)	4 (80%)

The sponsor stated:

> Overall, the baseline characteristics of the study population and their distribution across the treatment groups of interest were appropriate for the objectives of the study, with no unusual

findings or imbalances. The data set consisted of 21 male and 29 female subjects, 11 to 74 years of age, with baseline plasma concentrations of direct LDL-C ranging from [redacted] mg/dL. For the primary comparison, the mean ± standard deviation values were 345.9 mg/dL ± 85.2 (Statin 80 mg group), and 321 mg/dL ± 125.8 (EZ 10 mg + Statin 40/80 mg group)[3]. Based on the large standard deviations, the means for these pooled treatment groups were considered to be similar at baseline. Mean baseline plasma concentrations of direct LDL-C ranged from 267.7 mg/dL to 381.6 mg/dL across treatment subgroups. In general, the treatment groups were well balanced with regard to diet, weight, sex, age, race, physical activity, and smoking history. Most subjects were Caucasian (90%).

Approximately 74% of the subjects had a known family history of coronary artery disease and approximately 16% had some degree of hypertension at baseline. Most of the other cardiovascular risk factors were much less frequent (generally less than 20% of subjects in any treatment group) and there was balance between the EZ 10 mg + Statin 40/80 mg and Statin 80 mg treatment groups and among the six individual treatment groups. Baseline general medical history is summarized in Section 14.1.3 (*Reviewer note: of the report for this study in the NDA*).

Twenty-five subjects received concomitant apheresis or plasmapheresis. All of the subjects maintained a stable schedule of apheresis sessions throughout the study as described in the protocol.

Some numerical imbalances were seen in the following characteristics: Diagnosis (e.g., genetic diagnosis), total cholesterol, operation on heart. (Baseline general medical history is summarized in Section 14.1.3 of the NDA.)

2.3.3.e. Measurements of Treatment Compliance and Other Factors That Could Affect Response

On the results of measurements of treatment compliance and compliance with the visit schedule, compliance with the diet, changes in body weight and level of physical activity, the sponsor stated, "Overall, the results show good compliance with provisions of the protocol, and no obvious differences among groups that might affect the interpretation of the outcome."

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[3] Here raw means are given as opposed to LS Means in tables.

Extent of Exposure (Participation in the Randomization Phase, Intent-to-Treat Data Set):

	Statin 80 mg (n=17)	EZ 10 mg + Statin 40/80 mg (n=33)	Ator 80 mg (n=12)	EZ 10 mg + Ator 40 mg (n=17)	EZ 10 mg + Ator 80 mg (n=12)	Sim 80 mg (n=5)	EZ 10 mg + Sim 40 mg (n=4)	EZ 10 mg + Sim 80 mg (n=5)
Days in Randomization Phase								
Mean (SD)	84 (8.3)	83.1 (16.5)	82.1 (9.7)	86.7 (8.3)	87.5 (6.2)	88.6 (2.9)	77 (9.9)	65 (34.1)
Median	84	84	84	86	85	85	81	84
Min–Max	—	—	—	—	—	—	—	—
Frequency by Interval Number (%) of Subjects with a Maximum Indicated Number of Days in Randomization Phase								
0 Day	0	0	0	0	0	0	0	0
1–7 Days	0	0	0	0	0	0	0	0
8–21 Days	0	1 (3%)	0	0	0	0	0	1 (20%)
22–42 Days	0	0	0	0	0	0	0	0
43–70 Days	1 (6%)	2 (6%)	1 (8%)	1 (6%)	0	0	1 (25%)	0
71–101 Days	16 (94%)	30 (91%)	11 (92%)	11 (65%)	12 (100%)	5 (100%)	3 (75%)	4 (80%)
>101 Days	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

SD = standard deviation
Source Data: Section 14.5.

2.3.3.f. Efficacy Results (Sponsor's Analyses)

The sponsor stated that the statistical and analytical plans specified in the protocol and the study Data Analysis Plan (Dated 08 JUN 2001) were done before any outcome result was known (Date of database lock: June 15, 2001). The "Data Analysis Plan" stated:

> The primary efficacy analysis will be based on the percent change from baseline in the direct LDL-C by ———— at study endpoint (last available post-baseline LDL-C value for each subject). The primary comparison will be between the statin alone (80mg) combined group (atorvastatin 80 mg, simvastatin 80 mg) versus statin plus Ezetimibe 10 mg combined group (irrespective of the statin and statin dose). An analysis of variance (ANOVA) model that extracts effects due to treatment group (statin alone combined group, statin plus Ezetimibe 10 mg combined group) and statin (atorvastatin, simvastatin) will be used in the primary analysis. Owing to a small number of subjects expected to be enrolled in each center, center effect and treatment by center interaction effect will not be included in the model.

Data Set Analyzed

Before the database was locked (6-15-01) and treatment identities were unblinded, the study administrator approved a data analysis plan (Section 16.1.9.; date of finalization: 6-7-01) that pre-specified the definition and analysis of efficacy results for the following data set:

Intent-to-Treat Data Set: all subjects who received randomized treatment assignment and had one post-Randomization lipid determination

Results of the protocol-specified primary efficacy (Low-Density-Lipoprotein Cholesterol) analysis demonstrated that the overall treatment effect was significant (i.e., overall co-administration of ezetimibe 10 mg plus Statin 40/80 mg was more efficacious than Statin 80 mg alone) in reducing plasma concentrations of direct LDL-C from baseline to endpoint (Table below). For this analysis, data from four treatment groups involving co-administration therapy (EZ 10 mg + Ator 40 mg, EZ 10 mg + Ator 80 mg, EZ 10 mg + Sim 40 mg, and EZ 10 mg + Sim 80 mg) were pooled and compared with the two pooled monotherapy treatment groups (Ator 80 mg and Sim 80 mg). Baseline LS means were similar (313.17 ± 21.5 vs 338.75 ± 28.6, respectively, p=0.46). A mean percent change of –20.73% was observed for the EZ 10 mg + Statin 40/80 mg group compared with –6.65% for the Statin 80 mg group. The difference between the treatment groups was statistically significant based on ANOVA (p=.0072).

Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set

Direct LDL-C	Statin 80 mg (n=17)	EZ 10 mg + Statin 40/80 mg (n=33)
Baseline	(n=17)	(n=33)
Mean value in mg/dL	338.75	313.17
Endpoint	(n=17)	(n=33)
Mean value in mg/dL	318.53	247.16
Mean percent change from baseline (SEM)	-6.65 (4.21)	-20.73 (3.15)
Difference from Statin 80 mg in mean percent change from baseline (95% confidence limits)	not applicable	-14.1 (-24.1, -4.01)

Note: all means and standard errors are least-square means and standard errors based on the two-way ANOVA model extracting treatment and statin effects.

Source Data: **Section 14.2.2.1.1.1.**

Individual subject data appear in **Section 16.2.6.1.**

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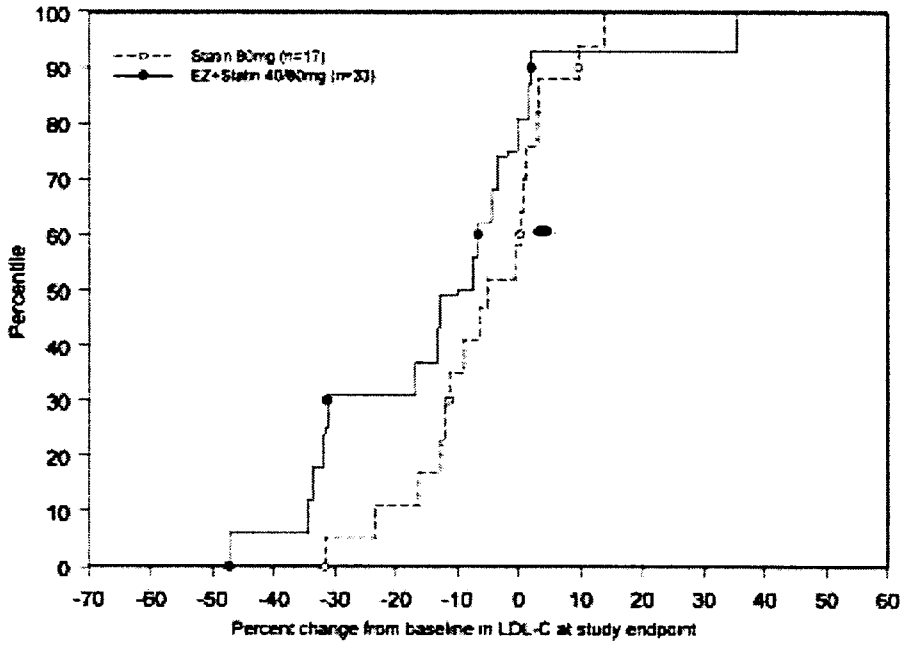
§ The Cumulative Distribution Function of Percent Change from Baseline in LDL-C at Study Endpoint (P01030) is provided below:



From this, percent of patients (y-axis value) with a value of Percent Change from Baseline in LDL-C at Study Endpoint, smaller than or equal to a value on the x-axis can be read. For example, 50% of the ezetimibe + statin 40/80mg patients had a $\leq -18.2\%$ change from baseline; whereas, 50% of the statin 80mg patients had a $\leq -5.0\%$ change from baseline.

§ Results for the individual treatment groups follow:

Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set

Direct LDL-C	Ator 80 mg (n=12)	EZ 10 mg + Ator 40 mg (n=12)	EZ 10 mg + Ator 80 mg (n=12)	Sim 80 mg (n=5)	EZ 10 mg + Sim 40 mg (n=4)	EZ 10 mg + Sim 80 mg (n=5)
Baseline	(n=12)	(n=12)	(n=12)	(n=5)	(n=4)	(n=5)
Mean value (mg/dL)	353.78	381.58	281.56	326.87	324.33	267.73
Endpoint	(n=12)	(n=12)	(n=12)	(n=5)	(n=4)	(n=5)
Mean value (mg/dL)	342.58	321.42	208.00	288.40	285.75	191.20
Mean percent change from baseline (SEM)	-3.50 (3.54)	-13.01 (6.35)	-24.66 (3.54)	-10.99 (6.35)	-12.03 (3.54)	-29.82 (6.35)

Note: All means and standard errors are least-square means and standard errors based on the two-way ANOVA model extracting treatment and statin effects

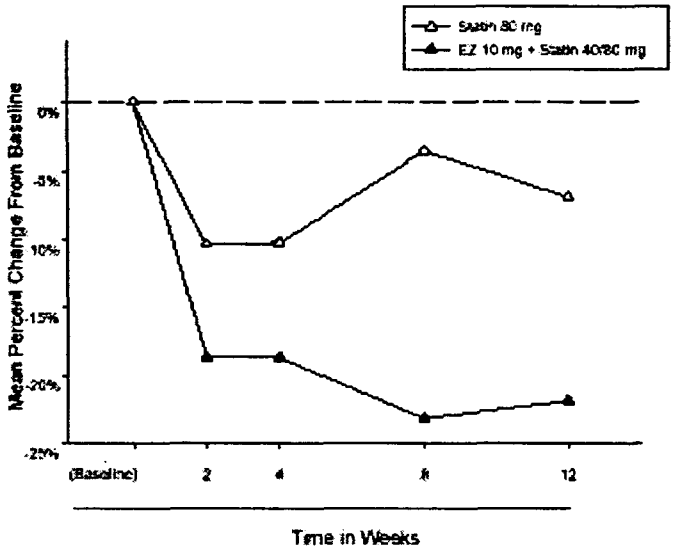
Source Data: **Section 14.2.2.1.1.2.**

Individual subject data appear in **Section 16.2.6.1.**

Results in none of the 6 treatment arms were in the opposite direction (i.e., worse than baseline), although there were appreciable numerical differences. Simvastatin 80 mg and Atorvastatin 80 mg results seem different. As a matter of fact (by reviewer's analyses), even with small number of patients, ezetimibe co-administartion with 80 mg statin was statistically superior to ezetimibe co-administartion with 40 mg statin (-27.28 vs –13.43).

Numerical results cast some doubt that ezetimibe 10mg + Simva 40 mg with a change from baseline in LDL-C of –12.03 is statistically superior to Simva 80 mg with a corresponding change of –10.99. With only 4 and 5 patients respectively, nothing can be concluded.

§ The LDL-C lowering effects of the ezetimibe coadministration were seen as early as Week 2 and were maintained for the duration of the study (12 weeks):



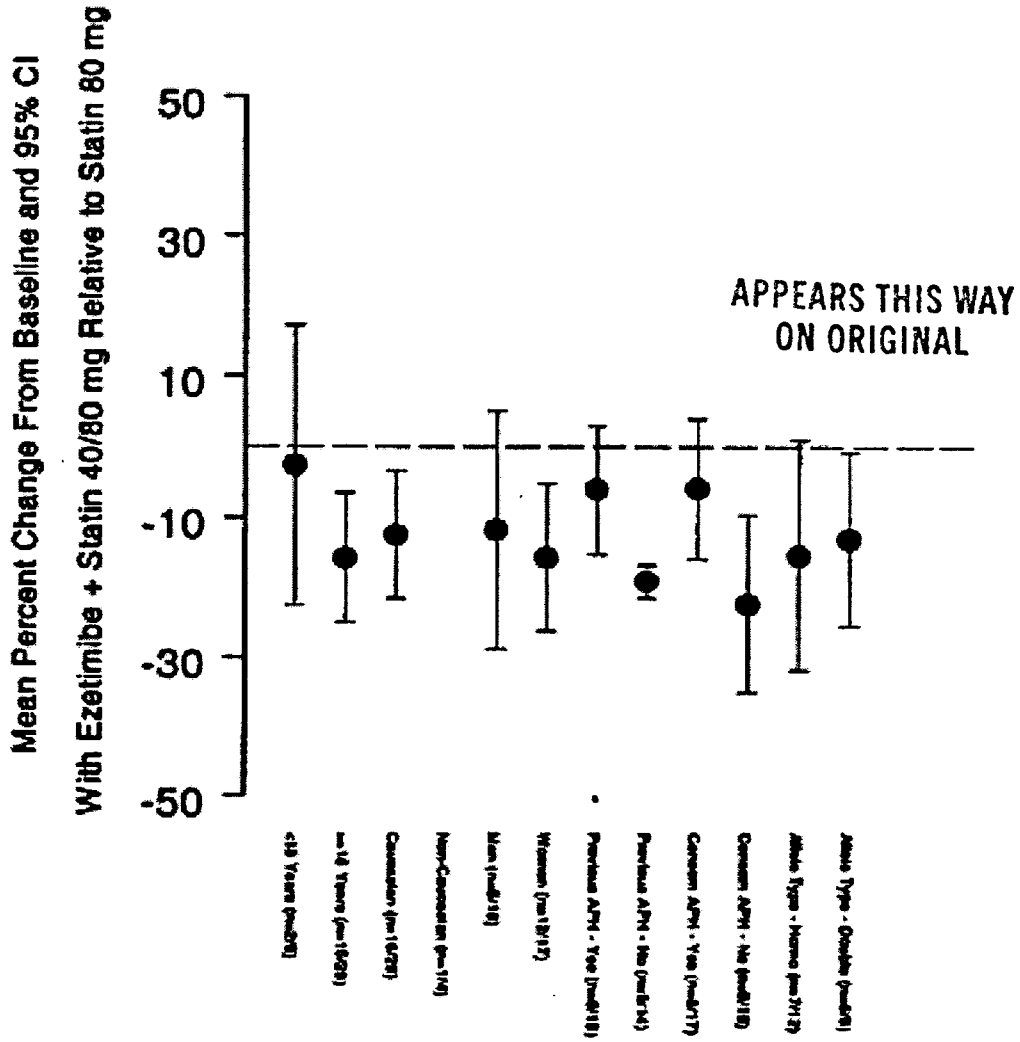
Coadministration of ezetimibe with both statins at both the 40- and 80-mg doses provided incremental reductions in plasma LDL-C concentrations over the 80-mg dose of statin monotherapy. A numerically greater reduction in plasma LDL-C levels was observed with ezetimibe coadministered with the statin 80 mg than was observed with ezetimibe coadministered with statin 40 mg.

§ Results for the primary efficacy variable (percent change from baseline in direct LDL-C) were examined, for the pooled primary treatment groups, in subgroups defined by subject baseline characteristics: sex, age, race, LDL-C, HDL-C, TG, hypertension, diabetes mellitus, BMI, known coronary heart disease, previous apheresis/plasmapheresis, concomitant apheresis/plasmapheresis, genotyping diagnosis, and estimated LDL-receptor residual activity. Although in some of the subgroups the number of subjects was small, the results of these analyses generally indicated that the overall increase in response resulting from the addition of ezetimibe 10 mg to statin monotherapy was consistent across most subgroups. The comparisons for baseline characteristics sex, age, and race are shown for the EZ 10 mg + Statin 40/80 mg and Statin 80 mg groups in Table 22 of the report for this study in the NDA.

§ Subjects with an estimated LDL-receptor residual activity of <5% had similar reductions in LDL-C concentrations resulting from the addition of ezetimibe 10 mg to statin monotherapy. For such subjects, both the EZ 10 mg + Statin 40/80 mg treatment group and the Statin 80 mg treatment group had a -3.8% mean percent change from baseline to endpoint. In contrast, subjects with an estimated LDL-receptor residual activity of ≥5% had an increase in response resulting from the addition of ezetimibe 10 mg to statin monotherapy. Such subjects treated with EZ 10 mg + Statin

40/80 mg had –32.4% mean percent change from baseline to endpoint compared with 11.6% for subjects treated with Statin 80 mg.

On a request for Figures for the subgroup results, the sponsor provided them on May 9, 2002 (corrections were made in the 7-22-02 submission). The confidence interval for Non-Caucasian could not be calculated because there was only one patient in the Statin 80 mg group.



The sponsor stated (May 9, 2002), "Conclusion: This exhaustive assessment of the relationship of baseline characteristics to the primary efficacy variable indicates that the conclusions about the

treatment group differences are not altered by consideration of these baseline characteristics."

However, the p-values for the treatment comparison provided in Table 4.3 of May 9, 2002 submission, after eliminating the effect of age, were 0.630 (age considered continuous) and 0.229 (age categorized, <18, >=18). The sponsor argues that the inclusion of age in the analysis model is not appropriate because neither the covariation nor the interaction for this factor was statistically significant. The sponsor also stated (7-22-02 submission):

> All the p-values for study P01030 quoted in Table 4.3 of the May 9th document are based on ANOVA models extracting effects for treatment, covariate, and treatment by covariate interaction. ... It may be noted that there is a huge imbalance in the sample sizes, with age-group <18 having only 7 subjects as opposed to age-group >=18 having 43 subjects. Consequently, an appropriate reduced ANOVA model extracting effects for treatment and age was implemented, dropping the interaction term. Specifically, one model with treatment and age as a categorical {<18, >=18} variable and another model with treatment and age as a continuous variable were used. Both these analyses rendered significant p-values for treatment [p<0.01]. Age was not significant [p>0.5] in these analyses. Thus, the effect of treatment after adjusting for the effect of age in study P01030 is statistically significant.

The following interaction p-values of baseline characteristics with treatment response were significant at the usual significance level of 0.1 for test of interaction:

Prior Apheresis (Yes, No) – 0.058
Concomitant Apheresis (Yes, No) – 0.091

No multiple comparison adjustments have been employed. However, since the power of the test of interaction is generally poor, we cannot neglect these either. Therefore, the superiority of the eze +Statin 40/80 mg over the Statin 80 mg group seemed to differ statistically significantly depending on these characteristics.

However, these interactions were quantitative and not qualitative; i.e. the ezetimibe co-administered group was superior to Statin 80 mg group irrespective of the Apheresis use (see Figures above for the amount of superiority).

Since the power of the test of interaction is generally poor and, most of all, since the studies were not powered for tests of interactions in subgroups, we cannot say whether the difference in superiority of the ezetimibe co-administered group over Statin 80 mg group in the above Figures with respect to other characteristics is real or not.

This reviewer performed analyses by 'Site'. There were only 5 patients in the 4 sites of U.S.A. The sites numbered 4, 15 (both in Canada) and 10 (Venezuela) with 8, 6, and 4 patients, respectively, produced the best relative (to Statin 80 mg) results for ezetimibe co-administration group. Exclusion of one or any two of these three sites does not lead to non-significance of the superiority of the co-administration. However, the exclusion of all three sites (18 patients or 36% patients) leads to the non-significance of the superiority of the co-administration (however, still, numerically

superior: LS means of -15.26 vs –11.38). This reviewer does not feel strongly that there should be statistical significance, even after the exclusion of 36% patients.

§ Results for calculated plasma concentrations of LDL-C (Friedewald equation) complemented the results obtained for direct LDL-C. The difference in mean percent change for calculated LDL-C from baseline to endpoint between the EZ 10 mg + Statin 40/80 mg and Statin 80 mg (-21.44% vs. -6.64%) was statistically significant ($p<.01$). Additionally, the difference in mean percent change for calculated LDL-C from baseline to endpoint between the two high dose comparison groups was statistically significant (means = EZ 10 mg + Statin 80 mg, -27.48; Statin 80 mg, -6.97; $p<.01$). In the individual treatment group comparisons, ezetimibe coadministration with statin 40 or 80 mg exhibited consistently greater mean percent changes in calculated LDL-C from baseline to endpoint compared with statin 80 mg treatment groups (-13.66% to -29.08% vs. -2.22% to -13.01%).

2.3.3.g. Reviewer's Comments and Conclusions on Study P01030

The sponsor's analyses as well as this reviewer's alternative analyses, performed with the data supplied by the sponsor electronically provided statistical evidence in favor of the superiority of overall co-administration of ezetimibe 10 mg plus Statin 40/80 mg over Statin 80 mg alone, with respect to the primary efficacy variable, Change From Baseline in Direct LDL-C.

Results in none of the 6 treatment arms were in the opposite direction (i.e., worse than baseline), although there were appreciable numerical differences. Numerical results cast some doubt that ezetimibe 10mg + Simva 40 mg with a mean percentage change from baseline in LDL-C of –12.03 is statistically superior to Simva 80 mg with a corresponding change of –10.99. With only 4 and 5 patients respectively, nothing can be concluded.

There was a statistically significant quantitative interaction (not qualitative) of "apheresis treatment" with the treatments in this study. The superiority of the (ezetimibe +Statin 40/80 mg) over the Statin 80 mg group was much larger in the group of patients with no apheresis treatment than that in the group with apheresis treatment. Ninety-five percent confidence intervals and other details are in the previous section.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Wilson

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CC:
Archival NDA 21-445/N_000

HFD-510/Dr. Parks
HFD-510/Dr. Temeck
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 09/30/02

This review consists of 20 pages of text and 3 pages of an appendix.

APPENDIX

Table 0.1.1

Description of Phase II/III Clinical Therapy Studies

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC) All	Ezetimibe	Treatment Groups Identity	No. Subjects
Phase II Ezetimibe Dose Response Studies								
C96-411/345	Effect of EZ on LDL-C and other lipids (dose ranging); safety; PK	R, DB, PC, PG	Primary hyper-cholesterolemic (PHC) subjects on a low-fat diet with LDL-C 160 to 220 mg/dL and TG ≤250 mg/dL	8 weeks; QD before AM meal	124 30 - 71 66/58 13/11	89 30 - 71 46/43 8 1/8	Placebo EZ 1 EZ 5 EZ 10 EZ 20 EZ 40 lovastatin (L) 40	17 17 20 18 16 18 18
C98-019	Effect of EZ on LDL-C and other lipids (dose response); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤300 mg/dL	12 weeks; QD before AM meal	243 28 - 75 139/104 223/20	191 28 - 75 108/83 176/15	Placebo EZ 0.25 EZ 1 EZ 5 EZ 10	52 47 49 49 46
C98-258	Effect of EZ on LDL-C and other lipids (dose regimen [AM vs PM dosing]); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤300 mg/dL	12 weeks; QD before AM meal or at bedtime (PM)	189 22 - 75 89/100 168/21	153 25 - 75 74/79 135/18	Placebo EZ 5 AM EZ 5 PM EZ 10 AM EZ 10 PM	35 36 40 39 38
Phase III Ezetimibe Monotherapy Studies - Primary Hypercholesterolemia								
P00474	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD in AM	827 20 - 86 397/430 746/81	622 20 - 86 302/320 565/57	Placebo EZ 10	205 622
P00475	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD in AM	892 18 - 85 434/458 809/83	666 18 - 85 332/334 688/58	Placebo EZ 10	226 666

(Table 0.1.1 Continued to next page)

Table 0.1.1 Continued

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC) All	Ezetimibe	Treatment Groups Identity	No. Subjects
Phase III Ezetimibe/Statin Coadministration – Factorial Coadministration Studies								
P00679	Effect of EZ when coadministered with lovastatin (L) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG <350 mg/dL	12 weeks; QD with PM meal	548 26 - 85 229/319 484/64	264 26 - 85 117/147 227/37	Placebo L 10 L 20 L 40 EZ 10 EZ 10+L 10 EZ 10+L 20 EZ 10+L 40	64 73 74 73 72 65 62 65
P00680	Effect of EZ when coadministered with simvastatin (S) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG <350 mg/dL	12 weeks; QD in PM	668 25 - 87 291/377 610/58	335 27 - 84 150/185 306/29	Placebo S 10 S 20 S 40 S 80 EZ 10 EZ 10+S 10 EZ 10+S 20 EZ 10+S 40 EZ 10+S 80	70 70 61 65 67 61 67 69 73 65
P00691	Effect of EZ when coadministered with pravastatin (P) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD at bedtime	538 20 - 86 238/300 462/76	268 20 - 86 106/162 236/32	Placebo P 10 P 20 P 40 EZ 10 EZ 10+P 10 EZ 10+P 20 EZ 10+P 40	65 66 69 70 64 71 66 67

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC) All	Ezetimibe	Treatment Groups Identity	No. Subjects
P00692	Effect of EZ when coadministered with atorvastatin (A) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks; QD in AM	628 18 - 86 250/358 533/95	320 25 - 86 136/184 279/41	Placebo A 10 A 20 A 40 A 80 EZ 10 EZ 10+A 10 EZ 10+A 20 EZ 10+A 40 EZ 10+A 80	60 60 60 66 62 65 65 62 65 63
Phase III Ezetimibe/Statin Coadministration– Add-On Study								
P02173	Effect of EZ when added to ongoing therapy with statins on LDL-C and other lipids; safety	R, DB, PC	Subjects with PHC, known CHD, or multiple CVD risk factors who are not at LDL-C targets with a stable regimen of statins and a low-fat diet	6 weeks; QD in AM or PM with statin as per statin label	759 22-85 443/326 693/76	379 25-85 222/157 337/42	Placebo (+ statin) EZ 10 (+ statin)	390 379
Phase III Ezetimibe Therapy in Special Dyslipidemic Populations								
P01030	Effect of EZ when coadministered with A or S on LDL-C and other lipids; safety	R, DB, PG	HoFH subjects with LDL-C ≥100 mg/dL on low-fat diet and taking OL A or S 40 mg/day for 6 weeks	12 weeks; QD in AM with A, QD in PM with S	50 11 - 74 21/29 45/5	33 11 - 74 16/17 29/4	A/S 80 EZ 10+A/S 40 EZ 10+A/S 80	17 16 17

(Table 0.1.1 Continued to next page)