

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200153Orig1s000**

**STATISTICAL REVIEW(S)**



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

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA #:** NDA 200153 / 0

**Supplement #:** Ezetimibe/Atorvastatin Fixed Dose Combination (10 mg ezetimibe + 10, 20, 40 or 80 mg atorvastatin)

**Drug Name:**

**Indication(s):** Reduces elevated total-C, LDL-C, Apo-B, TG and non-HDL-C and increases HDL-C in patients with hyperlipidemia

**Applicant:** MSP (Merck)

**Date(s):** Stamp Date: 11/5/12  
PDUFA goal date: 5/5/13

**Date of this review:** 3/27/13 (revised)

**Review Priority:** Standard  
Response to Complete Response (2/29/12)

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**Keywords:** NDA review, clinical studies

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## 1 EXECUTIVE SUMMARY

**Purpose:** This submission is in response to the Agency's complete response letter for ezetimibe/atorvastatin fixed dose combination (FDC) tablets in doses 10 mg/10 mg, 10/20, 10/40 and 10/80. In the complete response letter (2/29/12), the Agency communicated that bioequivalence at the 10/10 and 10/80 doses had been demonstrated, but not at the 10/20 and 10/40 doses. The Agency advised that positive results from two clinical equivalence studies would provide acceptable data relating to the 10/20 and 10/40 doses. This submission includes the study reports from Study P180, a clinical equivalence study of the 10/20 dose, and Study P190, a clinical equivalence study of the 10/40 dose.

**Design:** Both studies were multicenter, randomized, double blind, 2-period crossover studies consisting of a 5-week washout, a 2-week single blind placebo run-in period, and two 6-week treatment periods separated by a 6-week single blind placebo washout period. Eligible patients were at low, moderate or moderately high risk according to NCEP/ATP III guidelines. Each patient received both treatments, the FDC formulation and the co-administered tablets, in a randomized sequence. The primary endpoint was LDL-C, expressed as a percentage change from baseline after 6 weeks of treatment. The baseline was measured prior to starting treatment in Period 1.

**Results:** The clinical equivalence in the LDL-C endpoint for the FDC formulation compared to the co-administered tablets was supported by the results from Study P185 and Study P190. In both studies, the 95% confidence interval of the difference between the two treatments was within the clinical equivalence limits of  $\pm 4\%$  (see the table below).

Analysis of % change in LDL-C from baseline after 6 weeks of treatment	N	Baseline mean LDL-C (SD), mg/dl	Adjusted mean % change from baseline after 6 weeks (95% CI)	FDC – Co-admin: Difference in adjusted mean % change from baseline (95% CI)	Within clinical equiv. limits of $\pm 4\%$ ?
<b>Study P185</b>					
FDC: Ez/Ator 20 mg	353	162.5 (32.0)	-54.0% (-55.8, -52.2)	-0.2% (-1.7, 1.3)	Yes
Co-admin: Ez+Ator 20 mg	346	161.9 (32.4)	-53.8% (-55.7, -52.0)		
<b>Study P190</b>					
FDC: Ez/Ator 40 mg	280	162.4 (30.2)	-58.9% (-60.9, -56.9)	-0.2% (-1.9, 1.4)	Yes
Co-admin: Ez+Ator 40 mg	280	162.2 (30.2)	-58.7% (-60.7, -56.7)		
See Tables 8 and 9 in this review for more detailed information.					

The results from additional analyses, some using different versions of the analysis population and others using a different analysis model, supported these conclusions. The two treatments were also fairly similar in the average responses of the secondary lipid endpoints, including TC, HDL, non-HDL and TG. Clinical equivalence limits were not specified for the secondary lipid endpoints. Age and gender did not appear to have an impact on the conclusion of clinical equivalence in the LDL-C response. An assessment of the impact of race was limited because

most of the study participants were white (84% in Study P185 and 82% in Study P190). Both studies were conducted entirely within the U.S.

Statistical review comments: The study design was reasonable (although I believe that the treatment periods could have been longer), and the statistical methods were appropriate.

The statistical issues I encountered in my review of Study P185 and Study P190 came from the use of the 2-period crossover design. Although this is an appropriate design with which to evaluate clinical equivalence, a key assumption is that the six week treatment period was long enough to ensure that the LDL-C response was stabilized, with little to no carry-over effect from the end of Period 1 to the end of Period 2. Some of the study results challenged this assumption, especially with the 20 mg formulation in Study P185: A significant effect of “Period” appeared to be different for each treatment, and in both studies, approximately 10% of subjects had differences in LDL-C response between the two treatments that were greater than  $\pm 20$  percentage points. However, based on additional analyses that are summarized in this review, I don’t believe that this review concern affected the statistical support for clinical equivalence of either the 20 mg formulation or the 40 mg formulation.

Recommendations: I recommend that future studies of clinical equivalence that involve statin drugs be conducted with a longer treatment period, in order to provide more assurance that the response to therapy has stabilized for more subjects. Obtaining the baseline level as an average of several measurements will also reduce variability in the percentage change from baseline endpoint between the two periods. The pre-treatment washout and run-in periods may also need to be extended in order to stabilize the baseline level of LDL-C from which the percentage change from baseline is estimated.

Recommendations for the summaries of these studies in the label (Part 12.3 and Part 14.1) are included in Part 5.4 of this review.

## **2 INTRODUCTION**

This submission, dated 11/5/12, is in response to the Agency’s complete response (CR) letter, dated 2/29/12. The CR letter was based on the Agency’s review of NDA submission 200153/0, dated 4/29/11, for ezetimibe/atorvastatin fixed dose combination (FDC) tablets in doses 10 mg/10 mg, 10/20 mg, 10/40 mg and 10/80 mg. In the 2/29/12 CR letter, the Agency stated that bioequivalence at the 10/10 and 10/80 doses had been demonstrated, but not at the 10/20 and 10/40 doses. The Agency advised that positive results from two equivalence studies would provide acceptable and supportive pharmacodynamics data relating to the 10/20 and 10/40 FDC tablets. This submission includes the study reports from Study P185, a clinical equivalence study of the 10/20 FDC tablet and Study P190, a clinical equivalence study of the 10/40 FDC tablet. This review is the statistical review of these two clinical equivalence studies.

## 2.1 Overview

The ezetimibe/atorvastatin FDC tablets are proposed for approval as a more convenient single tablet when the combination of ezetimibe (Zetia™) and atorvastatin (Lipitor™) is prescribed for the treatment of hyperlipidemia. The original NDA submission included results from clinical studies of the co-administered components that are proposed for inclusion in the product label. The efficacy of the co-administered combination compared to its components has already been established as part of the approval of Zetia (2002).

The statistical review of the original NDA submission covered the results from five Phase clinical studies that were not reviewed as part of the clinical development program for either Zetia or Lipitor. The studies provided supportive information, but were not pivotal to the approval of the ezetimibe/atorvastatin FDC. In my statistical review (1/6/12), I concurred with the key results of each study. I made recommendations about the summary of each study in the Clinical Studies section of the product label.

The original NDA submission received a complete response because the Division concluded that the bioequivalence of the 10/20 and 10/40 FDC tablets with reference to their respective co-administered component tablets was not confirmed. The bioequivalence of the 10/10 and the 10/80 FDC was confirmed. Dr. S.W. Johnny Lau, the reviewing pharmacologist for the Office of Clinical Pharmacology, reviewed the evidence for bioequivalence.

Following the receipt of the CR letter, the applicant described two ongoing studies that were designed to evaluate the clinical equivalence of the 10/20 and 10/40 FDC tablets compared to their respective co-administered component tablets (one study for each dose). The Division concurred that “Pending a full review of the protocols and study results, we agree that Protocol 185 and 190 will provide clinical pharmacodynamic data to address the deficiencies (failed bioequivalence of the 10/20 mg FDC and 10/40 mg FDC to corresponding individual drugs) in the Complete Response (CR) letter dated February 29, 2012” (see the letter from the Division dated 5/17/12, response to issue #1).

This review is the statistical review of the two clinical equivalence studies, Study P185 and Study P190.

### 2.1.1 Class and Indication

The ezetimibe/atorvastatin FDC tablet is an immediate release (b) (4) tablet formulation containing a fixed dose of ezetimibe 10 mg combined with 10, 20, 40 or 80 mg of atorvastatin. The applicant proposes the ezetimibe/atorvastatin FDC tablet as therapy for patients with primary hyperlipidemia, including heterozygous familial and non-familial hyperlipidemia; mixed hyperlipidemia; or homozygous familial hypercholesterolemia. A similar product, Vytorin™, was approved in 2004. Vytorin is an FDC consisting of ezetimibe 10 mg combined with 10, 20, 40 or 80 mg of simvastatin.

### 2.1.2 Specific Studies Reviewed

I reviewed Study P185 and Study P190. A brief description of each study is shown below:

TABLE 1 Descriptive summary of the designs of Study P185 and P190

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Study P185	Phase 3; A randomized, double-blind, crossover, multi-center, international, active-controlled study, conducted entirely within the U.S.	Two treatment periods, each of 6 weeks' duration, separated by 6-week washout. See design diagram for additional detail.	There was no follow-up period	406 patients randomized; 203 to each of two treatment sequences: Ez/Ator FDC 10/20 → Ez+Ator 10+20 co-administered or Ez+Ator 10+10 co-administered → Ez/Ator FDC 10/20	Males and females aged 30 to 79 years, 18 years of age with primary hypercholesterolemia, at low, moderate or moderate high risk according to NCDP ATP III guidelines, naïve to lipid lowering agents or else eligible to be washed off their regular therapy and switched to study medication.
Study P190	As above	As above	As above	328 patients randomized; 164 to each of two treatment sequences: As above except with 40 mg atorvastatin	As above

### 2.1.3 Major Statistical Issues

The statistical issues I encountered in my review of Study P185 and Study P190 came from the use of the 2-period crossover design. Although this is an appropriate design with which to evaluate clinical equivalence, a key assumption is that the six week treatment period was long enough to ensure that the LDL-C response was stabilized, with little to no carry-over effect from the end of Period 1 to the end of Period 2. Some of the study results challenged this assumption, especially with the 20-mg formulation in Study P185: A significant effect of "Period" appeared to be different for each treatment group, and in both studies, approximately 10% of subjects had differences in LDL-C response between the two treatments that were greater than  $\pm 20$  percentage points. However, based on additional analyses that are summarized in this review, I don't believe that this review concern affected the statistical support for clinical equivalence of either the 20-mg formulation or the 40-mg formulation.

I recommend that future studies of clinical equivalence that involve statin drugs be conducted with a longer treatment period, in order to provide more assurance that the response to therapy has stabilized for more subjects. Obtaining the baseline level as an average of several measurements will also reduce variability in the percentage change from baseline endpoint between the two periods. The pre-treatment washout and run-in periods may also need to be extended in order to stabilize the baseline level of LDL-C from which the percentage change from baseline is estimated.

## 2.2 Data Sources

Submissions and data that I reviewed for this NDA are summarized in TABLE 2.

TABLE 2 Data sources for this submission

Number	Date	Description
0032	11/2/12	NDA 200153 response to Agency's complete response
\\cdesub1\evsprod\NDA200153		

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

I do not have review concerns about data and analysis quality in the parts of the submission that I reviewed.

### 3.2 Evaluation of Efficacy

Study P185 and P190 had a similar design and study population. The main difference between the two studies was the dose of atorvastatin (TABLE 1). For this reason, I review them together.

#### 3.2.1 Study Design and Endpoints

Design: Study P185 and P190 were multicenter, randomized, double blind, 2-period, crossover studies consisting of a 5-week washout, a 2-week single blind placebo run-in period, and two 6-week treatment periods separated by a 6-week single blind placebo washout period. Eligible patients were at low, moderate or moderately high risk (according to NCEP/Adult Treatment Panel [ATP] III guidelines) who were naïve to lipid-lowering agents or currently taking allowable statin or ezetimibe-statin combination therapy, but who were otherwise eligible to be washed off their regular therapy and switched to study medication. High risk patients (CHD or CHD risk equivalent) were not eligible. Eligible patients were enrolled in a 7-week washout run-in period. During this time they received lifestyle and diet counseling, treatment compliance recommendations, and placebo treatment during the run-in from week -2 to day -1. Eligibility for randomization was determined at the end of the run-in phase.

Patient were randomized in a 1:1 ratio to one of two blinded treatment sequences, each of which consisted of two 6-week treatment periods separated by a 6-week washout period (FIGURE 1). Patients received their first allocated treatment once daily for six weeks (Period 1), then underwent a washout period for six weeks while taking placebo. Following the washout period, patients were crossed over to receive their second allocated treatment once daily for an additional six weeks (Period 2). Study endpoints were assessed at the ends of Period 1 and Period 2.

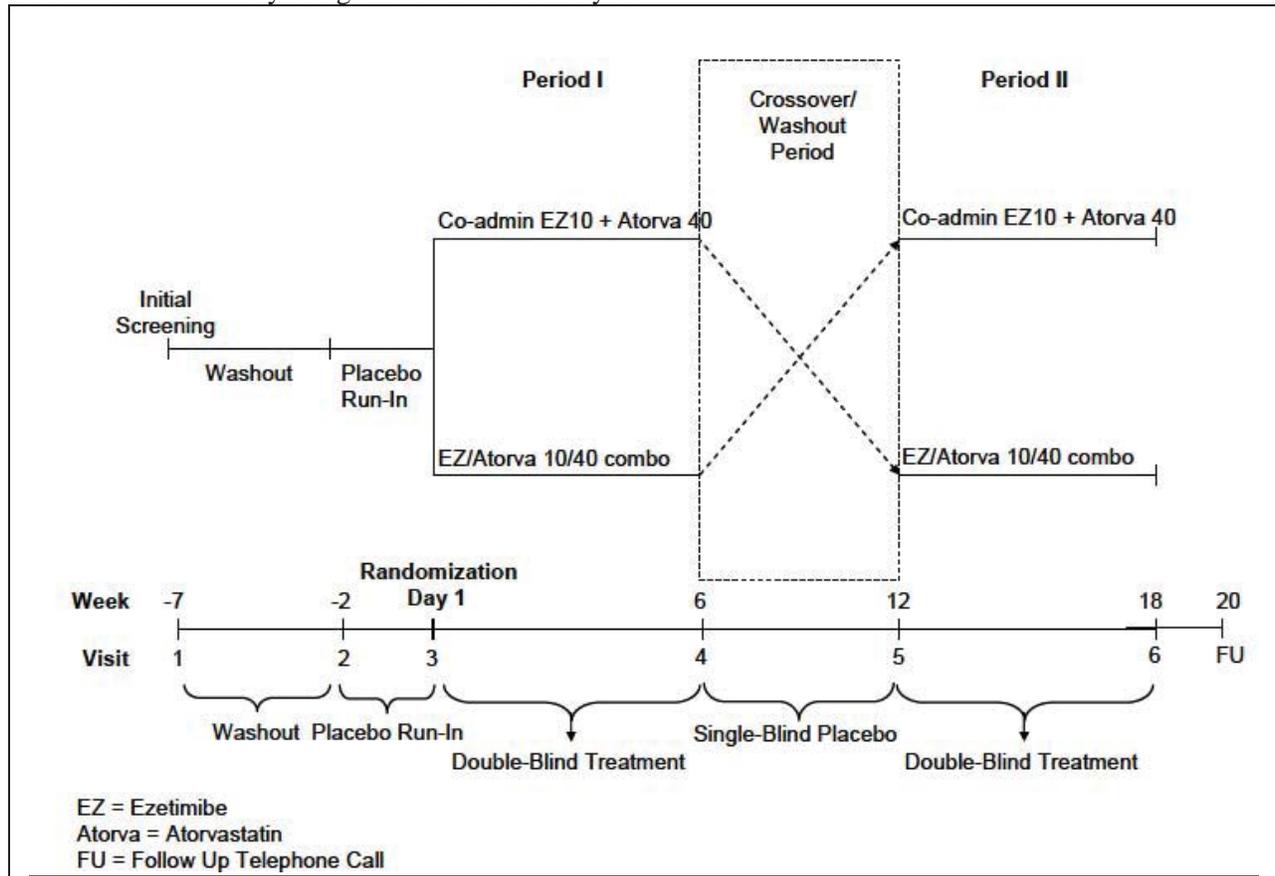
The DB2 biometrics team did not review the protocols for Studies P185 and P190. A review concern is whether or not the six week treatment period was long enough to ensure that the lipid response to each therapy was stabilized, with little to no carry-over effect from the end of Period 1 to the end of Period 2. This assumption is critically important to the analysis of the study endpoints. As S. Senn notes: “No help regarding this problem [*i.e.*, *assessing the presence of carry-over effects*] is to be expected from the data. The solution lies entirely in design. The trialist must only use cross-over trials in appropriate indications and he [*sic*] must allow for adequate wash-out.”<sup>1</sup> Dr. Iffat Chowdhury, the clinical reviewer of this submission, has commented that the six week treatment period should be sufficient to stabilize the LDL-C response.

Study sites: Study P185 randomized patients at 57 centers and Study P190 randomized patients at 46 centers, all entirely within the United States (TABLE 3). There was no overlap between the two studies in the study investigators. In Study P185, the first subject was enrolled on October 24, 2011 and the final visit of the last subject was on April 19, 2012. In Study P190, the first subject was enrolled on October 21, 2011 and the final visit of the last subject was on May 30, 2012.

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<sup>1</sup> Senn, S. 1993, *Cross-over Trials in Clinical Research*, NY: John Wiley & Sons, Chapter 3 “The AB/BA Design with Normal Data,” p. 69.

FIGURE 1 Study design schematic for Study P190



Note: Study P185 had the same design, using atorvastatin 20 mg (see Study P185 protocol Figure 1-1)

Source: Study P190 clinical report, Figure 9-1

TABLE 3 Study sites for P185 and P190; number and percentage of patients enrolled

Region of the U.S.	Study P185			Study P190		
	Number of sites	Number randomized	Percentage	Number of sites	Number randomized	Percentage
Northeast	10	53	13.1%	6	61	18.6%
Southeast	17	99	24.4%	6	33	10.1%
Midwest	16	127	31.3%	8	41	12.5%
Northwest	3	34	8.4%	3	26	7.9%
Southwest	11	93	22.9%	23	167	50.9%
	57	406		46	328	

Source: Analysis by this reviewer

Statistical power and the size of each study: The number of subjects to be randomized in each study was based on the following assumptions and specifications:

- Clinical equivalence limits of  $\pm 4\%$ , referring to the difference between the two treatments in mean LDL-C, expressed as the percentage change from baseline after six weeks of treatment
- The assumption that the true difference between the two treatments is within  $\pm 1.4\%$  for the 20-mg strength in Study P185 and within  $\pm 1.1\%$  for the 40-mg strength in Study 190, referring to LDL-C as expressed above
- The assumption that the standard deviation of this difference is 12.8%
- An assessment of clinical equivalence through the use of two one-sided tests each at an  $\alpha$  of 0.025
- Approximately 90% power
- An estimate that 85% of enrolled, randomized subjects would be “evaluable.”

The applicant noted that the equivalence limits of  $\pm 4\%$  relates to two-thirds of the effect of doubling a statin dose. They obtained the estimate of the standard deviation of the within-subject treatment difference from data from 6 prior studies with treatment arms including ezetimibe and simvastatin or ezetimibe and atorvastatin and a similar patient population to P185 and P190. The true treatment differences were based on a model that relates percentage change in LDL-C to dose-response parameters<sup>2</sup>, and to pharmacokinetic / pharmacodynamic data available to the applicant. The sample size calculation was based on the two one-sided tests procedure of Schuirmann<sup>3</sup> as implemented in the East™ package. The criterion to support a conclusion of clinical equivalence is that the 95% CI for the mean difference between the FDC tablets and co-administered tablets in percentage change from baseline in LDL-C needed to be contained within  $\pm 4\%$ .

For Study P185, these assumptions led to the estimate that 376 patients would need to be enrolled, which would result in 160 evaluable patients per sequence. This would result in 95% power for the evaluation of clinical equivalence. For Study P190, these assumptions led to enrolling 300 patients, 150 for each sequence, which would result in 127 evaluable patients per sequence, for 95% power for the evaluation of clinical equivalence. Although the term

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<sup>2</sup> Mandema JW, Hermann D, Wang D, Sheiner T, Milad M, Bakker-Arkema R, Hartman D. Model-based development of gemcabene, a new lipid-altering agent. (2005) The AAPS Journal 7:E513-522.

<sup>3</sup> Schuirmann, DJ (1987) A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of the average bioavailability. J. Pharmacokin. Biopharm. 15: 657-680.

“evaluable” is not defined in the protocols, I believe it refers to the inclusion of subjects in the PP analysis set, which is the primary analysis set.

The DB2 biometrics team did not review the protocols for Studies P185 and P190. However, in a review of a similar protocol<sup>4</sup>, [REDACTED] (b) (4) the Division concurred that clinical equivalence limits of  $\pm 4\%$  were reasonable for the LDL-C endpoint. I confirmed the statistical power calculations reported by the applicant. I used the statistical package nQuery Advisor™ 7.0 for t-tests of equivalence in means for a crossover design. The difference in size between the two studies is due to the assumption that the difference in mean response between the FDC tablets and the co-administered tablets is within  $\pm 1.4\%$  for the 10/20 mg dose in Study P185 and within  $\pm 1.1\%$  for the 10/40 mg dose in Study 190, referring to the primary endpoint, LDL-C as expressed as a change from baseline after six weeks of treatment.

Efficacy endpoints: The primary endpoint was LDL-C, expressed as the percent change from baseline in LDL-C after 6 weeks of treatment. The protocol describes the baseline level as the last available measurement in the baseline period, which is up to and including Day 1, where Day 1 is defined as the first day a nonzero dose of double-blind study therapy is taken. The secondary lipid endpoints were in TC, TG, HDL-C, non-HDL-C and Apo B after 6 weeks of treatment, all expressed as the percent change from baseline.

### 3.2.2 Statistical Methodologies

Analysis sets: The applicant used the per protocol (PP) analysis set as the primary analysis set for the analysis of efficacy data. The protocol described deviations from the protocol that could exclude data from a patient in one or both treatment periods, as follows:

- The patient received less than 4 weeks of study medication within the 6-week treatment period
- Compliance with study medication was less than 75% in the 6-week treatment period
- The patient received the same treatment in both Period 1 and Period 2
- The patient failed to take the assigned drug therapy for 3 or more consecutive days, and was back on the assigned therapy for < 14 consecutive days prior to observation
- The patient did not have a baseline observation
- The patient did not have a post-baseline observation for the analysis endpoint that was within 3 days of the last study medication in the treatment period.

The final determination on protocol violations was made prior to the final unblinding of the database.

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<sup>4</sup> [REDACTED]

(b) (4)

The applicant conducted a supportive analysis on the primary endpoint using the Full Analysis Set (FAS). The FAS consisted of all randomized patients who: (1) received at least one dose of study treatment; (2) had a baseline observation; and (3) had at least one post-baseline observation for the analysis endpoint subsequent to at least one dose of study treatment. In both the PP analysis set and the FAS, patients were included in the treatment sequence to which they were randomized, following the Intention-to-Treat principle. There was no imputation for missing data.

I note that in the statistical review of a similar protocol [REDACTED] (b) (4) [REDACTED] the DB2 review team recommended that the primary analysis be conducted with the completers set, the subjects who completed both Period 1 and Period 2. For this reason, I will also evaluate the completers set for the LDL-C endpoint.

Statistical analysis methods for the primary efficacy endpoint: The primary analysis was an analysis of covariance (ANCOVA) repeated measures model with fixed effects for treatment, period, and sequence, and with baseline LDL-C as a covariate. I also conducted a robust regression analysis of the LDL-C endpoint, in which outliers were downweighted using the method of M estimation. This exploratory approach was based on my assessment of outliers in the LDL-C data.

The clinical equivalence of the FDC formulation compared to the co-administered tablets was assessed from the 95% confidence interval (CI) of the treatment comparison. A 95% CI that was entirely within the equivalence limits of  $\pm 4\%$  for the LDL-C endpoint (% change from baseline after 6 weeks of treatment) supported the conclusion of clinical equivalence. The applicant used a version of the 95% CI which allows for the expansion of the interval to include 0 under certain circumstances: For the upper bound, the 97.5% limit is calculated, and if this limit is  $< 0$ , then the limit is expanded to 0. For the lower bound, the 97.5% limit is calculated, and if this limit is  $> 0$ , then the limit is expanded to 0. This method is conservative in the assessment of clinical equivalence because the CI may be widened to an upper bound of 0 in the event that the CI is entirely less than 0, or widened to a lower bound of 0 in the event that the CI is entirely greater than 0. This approach is explained in more detail in the reference by Bofinger, 1985.<sup>5</sup>

The secondary lipid endpoints were analyzed using the same ANCOVA repeated measures model as was described for the LDL-C endpoint, except that each model included a baseline covariate corresponding to the parameter being analyzed. The exception to this approach was with the triglyceride endpoint (TG). A log transform was applied to TG data, and the analysis model was applied to the log-transformed data. I believe that the log transform is a reasonable approach to dealing with TG. On the original scale of measurement, TG tends to present a skewed distribution, outliers, and a mean/variance relationship, all of which are departures from the analysis of variance assumptions of error terms that are normally distributed with a constant variance. The log transform can improve the stability of the error variance and reduce the influence of outliers. In addition, the applicant used a longitudinal analysis method that is

<sup>5</sup> Bofinger, E., 1985. Expanded confidence intervals. *Comm. Statist.-Theor. Meth.* 14:1849-1864.

described Liang and Zeger<sup>6</sup>. This method incorporates both the baseline and the post-baseline measures of TG as longitudinal levels of time. Other model terms were treatment, period and sequence, with a restriction of the same baseline mean across sequence groups. The covariance matrix was specified as unstructured. Linear contrasts were used to construct the comparisons of interest. The back-transformed least squares means were used to calculate the geometric mean percent changes from baseline. Senn (1993) describes this modeling approach for cross-over studies with one baseline determination (prior to the start of Period 1)<sup>7</sup>. The potential advantage of the model with three time periods is that the standard error for treatment comparisons might be smaller than estimates from a model with two time periods. This may have been the reason that the applicant selected the longitudinal approach to modeling TG data. In this review, I did not assess the sensitivity of the TG results to the assumptions of the longitudinal model, or look at alternate models for TG. My reason for not evaluating the TG results further is that TG is one of several secondary lipid endpoints, none of which have pre-specified clinical equivalence limits.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Disposition: In Study P185, 365 of the 406 patient randomized completed the study (89.7%; TABLE 4). In Study P190, 284 of the 304 randomized patients completed the study (85.6%). In both studies, most of the discontinuations occurred in Period 1, and the most common reason for discontinuation was due to adverse events (TABLE 5). In both studies, most of the patients in the Per Protocol analysis set were classified as ‘PP’ in both periods (TABLE 6). Most of the patients who were classified as having completed the study also had complete data for the primary LDL endpoint (TABLE 6).

Demographic and baseline characteristics: The two studies were fairly similar to each other with respect to key demographic categories and baseline clinical characteristics (TABLE 7).

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<sup>6</sup> Liang, K-Y. and S.L. Zeger, 2000. Longitudinal data analysis of continuous and discrete responses for pre-post designs. *Sankya: The Indian Journal of Statistics*. 62 (Ser B Pt 1): 134-148.

<sup>7</sup> See Chapter 3, “The AB/BA design with normal data” in *Cross-over Trials in Clinical Research*, S. Senn, 1993; John Wiley & Sons.

TABLE 4 The process of disposition in Study P185 and in Study P190 by sequence and period

	Study P185			Study P190		
	Sequence 1	Sequence 2	Total	Sequence 1	Sequence 2	Total
	Co-admin Ez+Ator20	FDC Ez/Ator20		Co-admin Ez+Ator40	FDC Ez/Ator40	
<b>Period 1</b>	203	203	406	164	164	328
Discontinued	-16	-11	-27	-14	-10	-24
Completed	187	192	379	150	154	304
<b>Crossover Washout</b>	↓	↓		↓	↓	
Discontinued	-6	-6	-12	-9	-4	-13
Completed	181	186	367	141	150	291
	↓	↓		↓	↓	
	FDC Ez/Ator20	Co-admin Ez+Ator20		FDC Ez/Ator40	Co-admin Ez+Ator40	
<b>Period 2</b>						
Discontinued	-1	-2	-3	-3	-4	-7
Completed	180	184	364	138	146	284
<b>Total</b>						
Discontinued	23	19	42	26	18	44
Completed	180	184	364	138	146	284

*Source:* P185 clinical report, Table 10-2  
P190 clinical report, Table 10-2

TABLE 5 Reasons for discontinuation in Study P185 and Study P190

	Study P185	Study P190
Randomized	406	328
Completed	364 (89.7%)	284 (85.6%)
Discontinued	42 (10.3%)	44 (13.4%)
Adverse event	18	16
Lost to follow-up	6	5
Protocol violation	4	5
Non-compliance with study drug	1	2
Withdrawal by patient	12	16
Sponsor decision	1	0

*Source:* P185 clinical report, Table 10.2; P190 clinical report, Table 10.2

TABLE 6 Number of cases in the analysis datasets (FAS, PP, completers) for each study

	Study P185	Study P190
Randomized	406	328
Full Analysis Set	380	312
Per Protocol:		
PP in one or both periods	370	298
Period 1 only	16	16
Period 2 only	14	6
Both Period 1 and Period 2	340	276
Completed the study	364	284
With complete LDL-C endpoint data for Period 1 and Period 2	352	276
<i>Source: Analysis by this reviewer</i>		

TABLE 7 Demographic and baseline characteristics in Study P185 and Study P190

	Study P185	Study P190
	406	328
Sex; n (%)		
Male	158 (38.0%)	142 (43.3%)
Female	248 (61.1%)	186 (56.7%)
Age (yr) <sup>1</sup>		
Mean (SD)	56.1 (9.5)	55.4 (9.3)
≥ 65 yrs	69 (17.0%)	55 (16.8%)
Race; n (%)		
White	341 (84.0%)	268 (81.7%)
Black	54 (13.3%)	53 (16.2%)
Other	11 (2.7%)	7 (2.1%)
Ethnicity; n(%)		
Hispanic or Latino	65 (16.0%)	30 (9.1%)
Weight (kg)		
Mean (SD)	84.5 (19.1)	84.8 (17.1)
BMI (kg/m <sup>2</sup> )		
Mean (SD)	30.1 (5.7)	30.0 (5.2)
< 30	220 (54.2%)	175 (53.4%)
≥ 30	186 (45.8%)	153 (46.6%)
Duration of hypercholesterolemia (yrs)		
Mean (SD)	7.6 (6.8)	8.5 (7.7)
Median	5	6
Range	1 to 42	1 to 39
Baseline lipid values (mg/dL); Mean (SD)		

	Study P185	Study P190
LDL-C	162.1 (31.8)	162.1 (30.4)
Total Cholesterol	246.5 (36.3)	248.3 (35.9)
HDL-C	53.3 (14.3)	54.2 (13.8)
non-HDL-C	193.1 (35.0)	194.1 (34.6)
Triglycerides	154.9 (73.0)	157.3 (78.4)
<i>Sources:</i> P185 study report, Tables 10-5, 10-6 and 10-7 P190 study report, Tables 10-5, 10-6 and 10-7		

### 3.2.4 Results and Conclusions

Primary endpoint (LDL-C % change from baseline): The conclusion of clinical equivalence in LDL-C for the FDC formulation compared to the co-administered tablets was supported by the results from Study P185 (the 20 mg dose of atorvastatin) and Study P190 (the 40 mg dose). In both studies, the 95% confidence interval (CI) of the difference between the FDC formulation and the co-administrated tablets for the mean % change in LDL-C from baseline stayed within the clinical equivalence limits of  $\pm 4\%$  (TABLE 8 and TABLE 9). I confirmed the results from the primary analysis with the PP analysis set, and also with the FAS and the LDL-C completers analysis set. In the reports for Studies P185 and P190, a 95% CI that is used to evaluate clinical equivalence is referred to as a “97.5% expanded CI,” because of the protocol-specified approach to include 0 as a bound in the event that a 95% CI was entirely  $< 0$  or entirely  $> 0$ . For most of the results in the study reports, the 95% CIs did include 0, and so the expansion to 0 as a confidence limit did not take place. For this reason, I report and discuss the 95% CI in the summary of results without further reference to the 97.5% expanded CI.

*The effect of Period*: Because the effect of “Period” was statistically significant in Study P185 (TABLE 8), I explored this effect in more detail. The Period effect was not significant in Study P190 (TABLE 9). The statistical significance of Period in Study P185 is driven by a somewhat greater LDL-C lowering effect in Period 1 compared to Period 2 in Study P185, when averaged across the two treatments (FIGURE 2). However, the two treatments differ in the effect of Period: the FDC formulation has a greater LDL-C lowering effect in Period 1 than in Period 2, and the co-administered tablets have a greater LDL-C lowering effect in Period 2 than in Period 1 (FIGURE 2). The limitations of this crossover design make it challenging to interpret these differences further. The design is based on an assumption that the carry-over effect is negligible. With the main effects of treatment, sequence and period in the model, the additional effect of the treatment by period interaction, which is aliased with the carry-over effect, is not estimable.

To gain additional insight, I conducted a separate ANCOVA on the Period 1 data from Study P185. The comparison of “FDC formulation – Co-administered tablets” in Period 1 has an adjusted mean of -2.7 with 95% CI of (-6.1, 0.7). The upper bound remains within the clinical equivalence limit of 4, and the lower bound falls outside the limit of -4, in the direction of greater LDL lowering for the FDC (20 mg) formulation. I believe that the results from the Period 1 data

support the overall conclusion of clinical equivalence from the primary analysis model, even with the observed differences between Period 1 and Period 2 in the effect of the FDC formulation.

*The effect of “outliers”:* I observed the occurrence of outliers initially from pairwise plots of subject-level data from Period 2 vs. Period 1 (FIGURE 3). These plots depict the plots overlaid by a shaded ellipse. The ellipse is intended to represent the area where 90% of the data would be expected to occur if the paired observations came from a bivariate normal probability density. The points outside the ellipse are widely scattered and represent large differences in the LDL-C response of some subjects between the two periods. I examined these outlying differences further from the percentiles of the within-subject difference between the FDC and co-administered treatments. The most extreme differences in either direction, shown by the 95<sup>th</sup> and 5<sup>th</sup> percentiles, are greater than approximately  $\pm 15$  percentage points (FIGURE 4). I also developed a histogram of these differences (FIGURE 4). I selected the histogram bins to represent cutpoints of potential clinical interest: (a) within the clinical equivalence limits of  $\pm 4\%$  that were defined for the target population mean; (b) within the broader limits of  $\pm 15\%$  that may represent a clinically important difference; and (c) outside the limits of  $\pm 30\%$  that apply to the more extreme outlying paired LDL-C results. This exploration led me to define “outliers” heuristically for these studies as differences greater than  $\pm 20$  percentage points, which encompasses approximately the most extreme 10% of the differences, i.e., 5% in either direction.

I believe that several factors may contribute to the occurrence of a large difference in the LDL-C levels for about 10% of subjects between the FDC and co-administered treatment in each study. Of concern from a design perspective is the possibility that the LDL-C levels had not stabilized, at least for a percentage of the subjects, after a 6-week treatment period. This lack of stabilization, if it exists, may lead to two situations: (1) the within-subject variability of response may be greater than it would be if the LDL-C response were more stabilized for more subjects; and (2) a subject’s LDL-C endpoint in Period 2 is more likely to be influenced by the LDL-C endpoint in Period 1. The design consequence of situation #2 is the occurrence of a carry-over effect, which is problematic in this study design. A substantial carry-over effect is essentially not separable from the treatment effect in this study design. However, the six-week washout period in Studies P185 and P190 may provide additional assurance that a carry-over effect is minimal in the LDL-C response at the end of Period 2.

Another design concern is the possibility that the baseline level of LDL-C was not stable. The baseline was obtained from one measurement taken after a 5-week washout period and 2-week single blind placebo run-in period. A high level of within-subject variability in LDL-C at this point would drive variability in the percentage change from baseline measures in both periods. For a future study, it may be reasonable to estimate the baseline from an average of several measurements. The washout and run-in periods may also need to be extended.

In addition, a patient’s lack of compliance with different aspects of the study protocol could contribute to a large difference in LDL-C endpoint between the two periods, as could error in some aspect of determining the LDL-C level or in entering or transcribing the data.

However, I believe that the occurrence of large differences in response in about 10% of subjects does not affect the statistical conclusions about clinical equivalence in LDL-C. The occurrence of outliers will tend to inflate the estimated within-subject variance of the estimated LDL-C response. A longer treatment period, for example, 12 weeks instead of 6, might have resulted in a smaller percentage of subjects with paired responses that are outside  $\pm 20$  percentage points. However, the inflation of within-subject variance, if it exists, will tend to widen the confidence interval for the clinical equivalence evaluation. Because the 95% CI for the “FDC – Co-administered” difference in LDL-C is within the clinical equivalence limits in each study, the possibility that these CI’s may have been somewhat widened by the occurrence of outliers does not affect the statistical support to the conclusion of clinical equivalence.

Even though the occurrence of outliers in the LDL-C response would not affect the statistical conclusion, I conducted an exploratory analysis that applied a robust method to estimate the difference between the two formulations. I used a robust linear regression model with M estimation, which down weights the influence of outliers on the estimated error variance<sup>8</sup>. The dependent variable was the subject-level difference between Period 1 and Period 2, and the predictor variable was “sequence” (FDC  $\rightarrow$  Co-administered or Co-administered  $\rightarrow$  FDC). I compared the results from the robust linear regression with the same model fit by ordinary least squares (OLS). The robust version produced a narrower confidence interval for the comparison between the FDC formulation and the co-administered tablets than did the OLS version (TABLE 8 and TABLE 9). Both versions produced CIs that were within the clinical equivalence limits. The CIs from the robust and the OLS models were both wider than the CIs from the ANCOVA models. I attribute this finding to the capacity of the ANCOVA models to partition variance due to period and to the baseline covariate away from the error variance, which I was not able to do with the two regression models.

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<sup>8</sup> See “Robust Regression” (D.F. Andrews) in the Encyclopedia of Biostatistics, Online<sup>(C)</sup> 2005, John Wiley & Sons, Ltd.

TABLE 8 Study P185; Analysis of primary efficacy endpoint: LDL-C after 6 weeks of treatment, % change from baseline

	N	Baseline mean LDL-C (SD), mg/dl	Adjusted mean % change from baseline after 6 weeks (95% CI) <sup>2</sup>	FDC – Co-admin: Difference in adjusted mean % change from baseline (95% CI)	Within clinical equivalence limits of ± 4%?
<b>Primary analysis</b>					
1. PP, primary analysis of covariance model <sup>1</sup>					
FDC: Ez/Ator 20 mg	353	162.5 (32.0)	-54.0% (-55.8, -52.2)	-0.2% (-1.7, 1.3)	Yes
Co-admin: Ez+Ator 20 mg	346	161.9 (32.4)	-53.8% (-55.7, -52.0)		
<b>Supportive analysis</b>					
2. FAS, primary analysis of covariance model					
FDC: Ez/Ator 20 mg	368	162.1 (32.0)	-53.8% (-55.6, -52.0)	-0.1% (-1.6, 1.4)	Yes
Co-admin: Ez+Ator 20 mg	364	161.7 (31.9)	-53.7% (-55.5, -51.9)		
3. LDL-C Completers <sup>3</sup> , primary analysis of covariance model					
FDC: Ez/Ator 20 mg	352	161.9 (32.2)	-53.9% (-55.7, -52.0)	0.0% (-1.4, 1.5)	Yes
Co-admin: Ez+Ator 20 mg	352	161.9 (32.2)	-53.9% (-55.7, -52.1)		
<b>Exploratory analysis</b>					
4. LDL-C Completers, regression analysis (ordinary least squares) <sup>4, 5</sup>					
FDC – Co-Administered	352	161.9 (32.2)	---	0.0% (-3.0, 3.0)	Yes
5. LDL-C Completers, robust regression analysis (M estimation) <sup>4, 5</sup>					
FDC – Co-Administered	352	161.9 (32.2)	---	-0.5% (-2.2, 1.3)	Yes
<b>Model Term</b>	1. Primary analysis with PP analysis set		2. Supportive analysis with FAS		3. Supportive analysis with LDL-C completers
	p-value		p-value		p-value
Treatment	0.825		0.880		0.970
Baseline LDL-C	< 0.001		< 0.001		< 0.001
Period	0.011		0.010		0.013
Sequence	0.133		0.090		0.102
<i>Source:</i>	P185 study report, Tables 11-1 and 14.2.1.1.1		P185 study report, Table 14.2.1.1.2		Analysis by this reviewer

*Notes:*

1. The primary analysis model was an analysis of covariance, repeated measures model with terms for treatment, baseline LDL-C, period and sequence
2. In the reports for Studies P185 and P190, a 95% CI that is used to evaluate clinical equivalence is referred to as a “97.5% expanded CI,” because of the protocol-specified approach to include 0 as a bound in the event that a 95% CI was entirely < 0 or entirely > 0. For most of the results in the study report, the 95% CIs did include 0, and so the expansion to 0 as a confidence limit did not take place. For this reason, I report and discuss the 95% CI in the summary of results without further reference to the 97.5% expanded CI.
3. The “LDL-C Completers” population refers to patients who had LDL-C endpoint data for both periods.
4. Analysis by this reviewer. The form of the dependent variable in the linear regression model was the within-subject difference, Period 2 – Period 1, in LDL-C response, expressed as a percentage change from baseline for each period. The regression model had no intercept and one predictor, which was “Sequence” (FDC → Co-administered and Co-administered → FDC), coded as 1, -1 respectively. The estimated effect and 95% CI of FDC vs. Co-administered was calculated as  $-2x$  the regression coefficient for “Sequence.”
5. The linear regression was fit by ordinary least squares and by a robust procedure, using M-estimation and the bisquare weight function, obtained in the software package ROBUSTREG in SAS® Version 9.1

TABLE 9 Study P190; Analysis of primary efficacy endpoint: LDL-C after 6 weeks of treatment, % change from baseline

	N	Baseline mean LDL-C (SD), mg/dl	Adjusted mean % change from baseline after 6 weeks (95% CI) <sup>2</sup>	FDC – Co-admin: Difference in adjusted mean % change from baseline (95% CI)	Within clinical equivalence limits of ± 4%?
<b>Primary analysis</b>					
1. PP, primary analysis of covariance model <sup>1</sup>					
FDC: Ez/Ator 40 mg	280	162.4 (30.2)	-58.9% (-60.9, -56.9)	-0.2% (-1.9, 1.4)	Yes
Co-admin: Ez+Ator 40 mg	280	162.2 (30.2)	-58.7% (-60.7, -56.7)		
<b>Supportive analysis</b>					
2. FAS, primary analysis of covariance model					
FDC: Ez/Ator 40 mg	293	162.3 (30.0)	-58.8% (-60.8, -56.9)	0.1% (-1.6, 1.7)	Yes
Coadministered EZ 10 mg and Atorva 20 mg	295	162.6 (30.8)	-58.9% (-60.8 -57.0)		
3. LDL-C Completers <sup>3</sup> , primary analysis of covariance model					
FDC: Ez/Ator 40 mg	276	162.4 (30.3)	-59.6% (-61.5, -57.8)	0.0% (-1.6, 1.6)	Yes
Co-admin: Ez+Ator 40 mg	276	162.4 (30.3)	-59.6% (-61.5, -57.8)		
<b>Exploratory analysis</b>					
4. LDL-C Completers, regression analysis (ordinary least squares) <sup>4,5</sup>					
FDC – Co-Administered	276	162.4 (30.3)	---	-0.4% (-3.5, 2.8)	Yes
5. LDL-C Completers, robust regression analysis (M estimation) <sup>4,5</sup>					
FDC – Co-Administered	276	162.4 (30.3)	---	-1.0% (-2.8, 0.8)	Yes
Model Term	1. Primary analysis with PP analysis set		2. Supportive analysis with FAS		3. Supportive analysis with LDL-C completers
	p-value		p-value		p-value
Treatment	0.805		0.951		0.989
Baseline LDL-C	< 0.001		< 0.001		< 0.001
Period	0.443		0.508		0.310
Sequence	0.508		0.596		0.537
Source:	P190 study report, Tables 11-1 and 14.2.1.1.1		P185 study report, Table 14.2.1.1.2		Analysis by this reviewer

*Notes:*

1. The primary analysis model was an analysis of covariance, repeated measures model with terms for treatment, baseline LDL-C, period and sequence
2. In the reports for Studies P185 and P190, a 95% CI that is used to evaluate clinical equivalence is referred to as a “97.5% expanded CI,” because of the protocol-specified approach to include 0 as a bound in the event that a 95% CI was entirely < 0 or entirely > 0. For most of the results in the study report, the 95% CIs did include 0, and so the expansion to 0 as a confidence limit did not take place. For this reason, I report and discuss the 95% CI in the summary of results without further reference to the 97.5% expanded CI.
3. The “LDL-C Completers” population refers to patients who had LDL-C endpoint data for both periods.
4. Analysis by this reviewer. The form of the dependent variable in the linear regression model was the within-subject difference, Period 2 – Period 1, in LDL-C response, expressed as a percentage change from baseline for each period. The regression model had no intercept and one predictor, which was “Sequence” (FDC → Co-administered and Co-administered → FDC), coded as 1, -1 respectively. The estimated effect and 95% CI of FDC vs. Co-administered was calculated as  $-2x$  the regression coefficient for “Sequence.”
5. The linear regression was fit by ordinary least squares and by a robust procedure, using M-estimation and the bisquare weight function, obtained in the software package ROBUSTREG in SAS® Version 9.1

FIGURE 2 Results for treatment group by period; Study P185 and P190, LDL-C completers

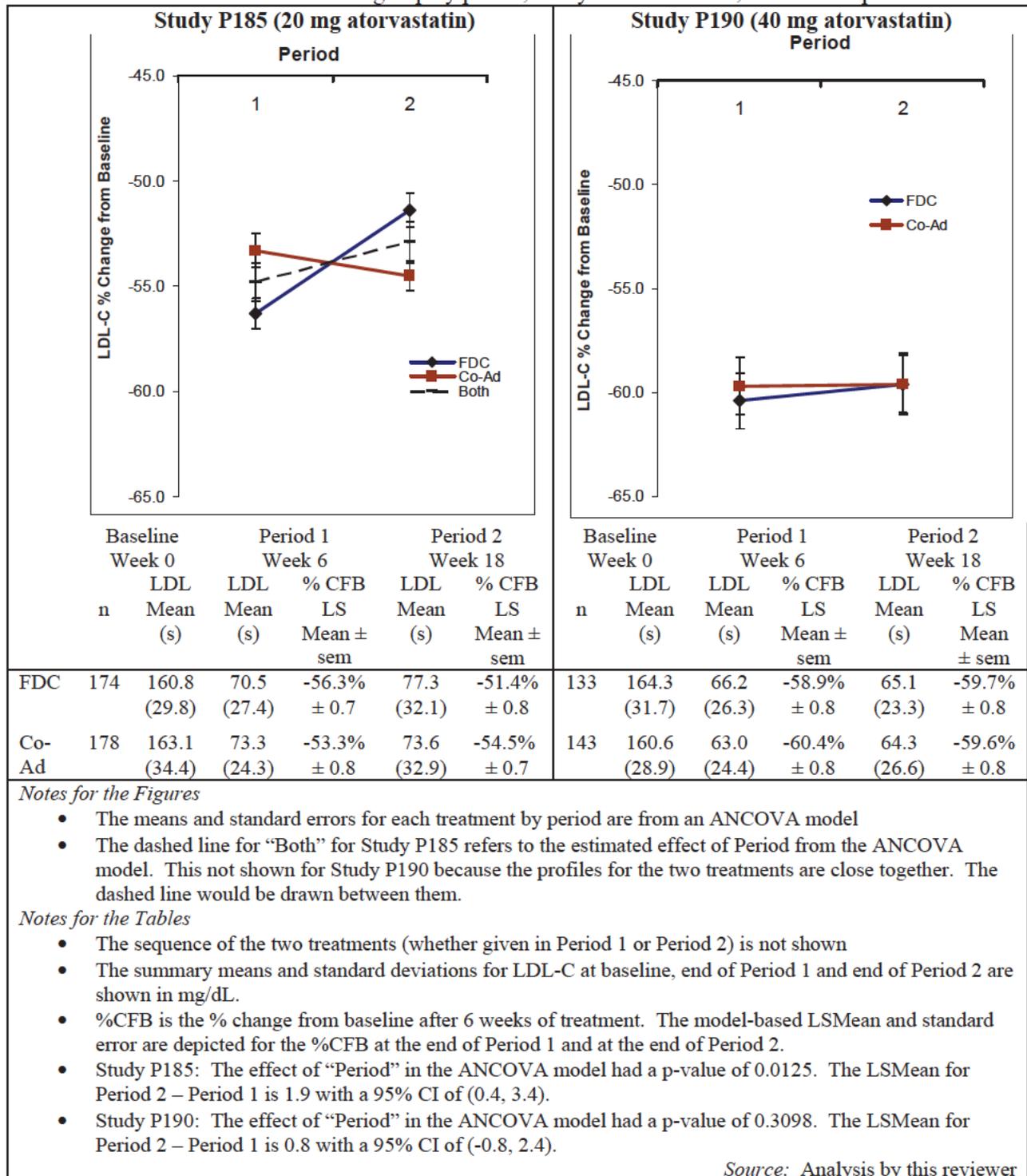
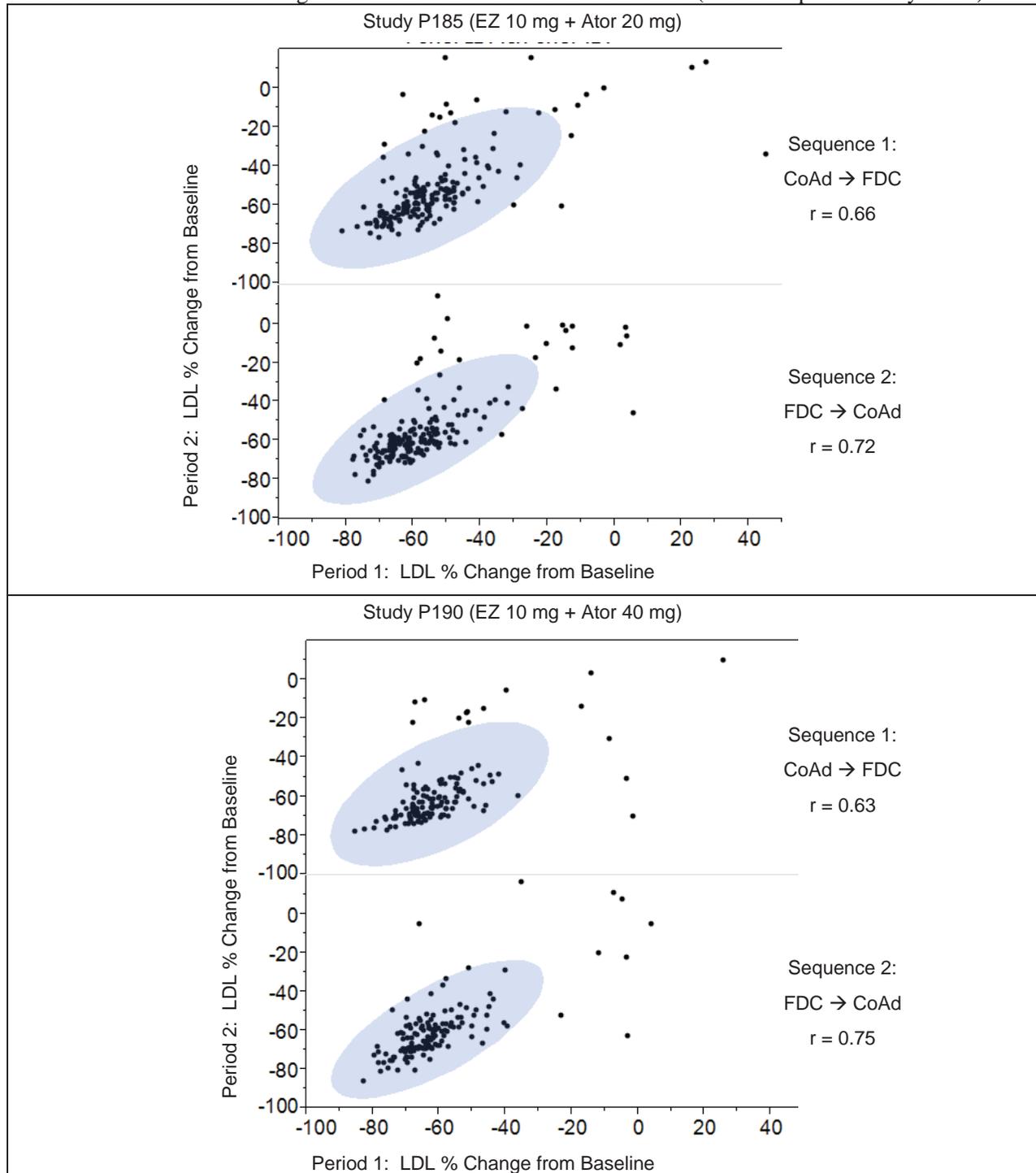


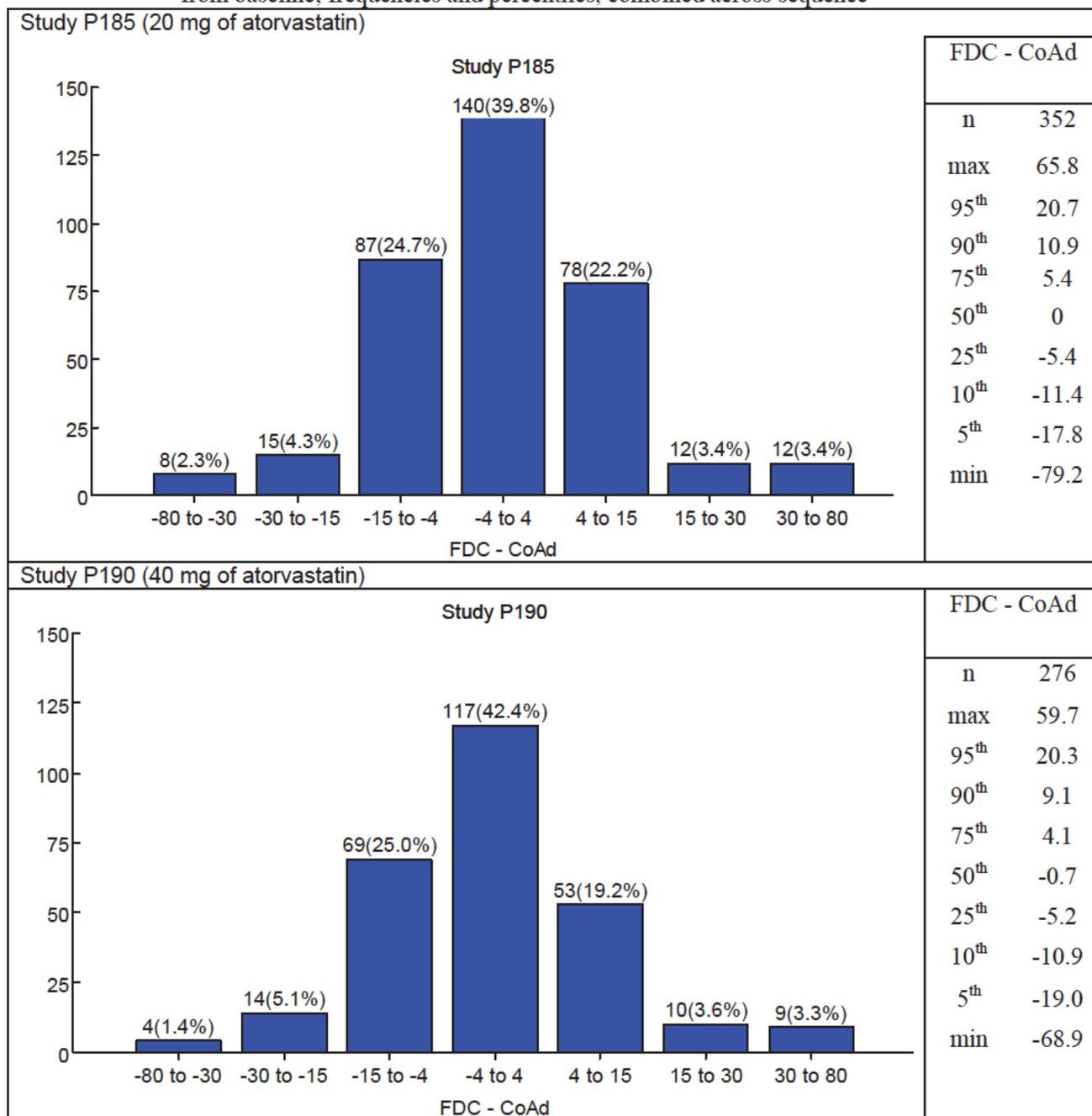
FIGURE 3 LDL % change from baseline in Period 1 and Period 2 (LDL-completers analysis set)



Note: The shaded ellipse identifies the region of 90% confidence for a bivariate normal density, based on the observed data

Source: Analysis by this reviewer

FIGURE 4 Within-subject differences for FDC – Co-Administered treatments in LDL-C % change from baseline; frequencies and percentiles, combined across sequence



Source: Analysis by this reviewer

**Secondary lipid endpoints:** Results from the analysis of the secondary lipid endpoints were supportive of conclusion of clinical equivalence in LDL-C. Although there were no pre-specified clinical equivalence limits for the secondary lipid endpoints, the mean results for the FDC formulation appeared to be fairly similar to the mean results for the co-administered tablets, using the clinical equivalence limits of  $\pm 4\%$ , established for LDL-C, as a reference value (TABLE 10, TABLE 11).

TABLE 10 Study P185, Results for secondary lipid endpoints, PP analysis set

Study P185, PP population	N	Baseline mean LDL-C (SD), mg/dl	Adjusted mean % change from baseline after 6 weeks (95% CI) <sup>2</sup>	FDC – Co-admin: Difference in adjusted mean % change from baseline (95% CI) <sup>2</sup>
<b>Total Cholesterol<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	353	247.3 (36.5)	-38.1% (-39.5, -36.8)	0.3% (-0.8, 1.4)
Co-admin: Ez+Ator 40 mg	346	247.1 (36.7)	-38.5% (-39.8, -37.1)	
<b>HDL-C<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	353	53.6 (14.7)	5.4% (4.0, 6.7)	0.8% (-0.6, 2.2)
Coadministered EZ 10 mg and Atorva 20 mg	346	53.5 (14.4)	4.6% (3.2, 5.9)	
<b>Non-HDL-C<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	353	95.1 (32.4)	-50.1% (-51.8, -48.5)	0.0% (-1.3, 1.4)
Co-admin: Ez+Ator 40 mg	346	95.3 (17.1)	-50.2% (-51.8, -48.5)	
<b>TG<sup>3</sup></b>				
FDC: Ez/Ator 40 mg	353	139.8 (65.0)	-28.3 (-32.4, -24.0)	1.6% (-3.2, 6.3)
Co-admin: Ez+Ator 40 mg	346	141.4 (66.5)	-29.9 (-32.4, -27.3)	

Notes:

- 1 LS Means and 95% CI were obtained from the primary ANCOVA, using the PP analysis set. The primary ANCOVA was a repeated measures model with terms for treatment, baseline level of the dependent variable, period and sequence.
2. In the reports for Studies P185 and P190, a 95% CI that is used to evaluate clinical equivalence is referred to as a “97.5% expanded CI,” because of the protocol-specified approach to include 0 as a bound in the event that a 95% CI was entirely  $< 0$  or entirely  $> 0$ . For most of the results in the study report, the 95% CIs did include 0, and so the expansion to 0 as a confidence limit did not take place. For this reason, I report and discuss the 95% CI in the summary of results without further reference to the 97.5% expanded CI.
- 3 LSMeans and 95% CI were obtained from a longitudinal model which included the log-transformed baseline and post-baseline measurements in the response vector, with fixed effects for treatment, period and sequence. An unstructured covariance matrix was used. The baseline geometric mean and the back-transformed SD are presented. The back-transformed SD was derived as the geometric mean x the SD on the log scale, using a Taylors series expansion.

Source: Study P185, Tables 11-2, 11-3, 11-4, 11-5 and 11-7

TABLE 11 Study P190, Results for secondary lipid endpoints, PP analysis set

Study P190, PP population	N	Baseline mean LDL-C (SD), mg/dl	Adjusted mean % change from baseline after 6 weeks (95% CI) <sup>2</sup>	FDC – Co-admin: Difference in adjusted mean % change from baseline (95% CI) <sup>2</sup>
<b>Total Cholesterol<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	280	248.5 (35.2)	-43.0% (-44.0, -41.5)	-0.1% (-1.48, 1.2)
Co-admin: Ez+Ator 40 mg	280	249.1 (35.8)	-42.9% (-44.4, -41.4)	
<b>HDL-C<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	280	54.4 (13.6)	2.3% (0.8, 3.8)	-0.3% (-1.8, 1.2)
Coadministered EZ 10 mg and Atorva 20 mg	280	54.3 (13.6)	2.6% (1.2, 4.1)	
<b>Non-HDL-C<sup>1</sup></b>				
FDC: Ez/Ator 40 mg	280	194.1 (33.8)	-55.4% (-57.2, -53.5)	-0.2% (-1.7, 1.4)
Co-admin: Ez+Ator 40 mg	280	194.8 (34.5)	-55.2% (-57.0, -53.4)	
<b>TG<sup>3</sup></b>				
FDC: Ez/Ator 40 mg	280	157.4 (78.4)	-36.2 (-40.4, -31.6)	0.0% (-4.9, 4.9)
Co-admin: Ez+Ator 40 mg	280	160.7 (80.1)	-36.2 (-38.8, -33.5)	
Notes:				
1 LS Means and 95% CI were obtained from the primary ANCOVA, using the PP analysis set. The primary ANCOVA was a repeated measures model with terms for treatment, baseline level of the dependent variable, period and sequence.				
2. In the reports for Studies P185 and P190, a 95% CI that is used to evaluate clinical equivalence is referred to as a “97.5% expanded CI,” because of the protocol-specified approach to include 0 as a bound in the event that a 95% CI was entirely < 0 or entirely > 0. For most of the results in the study report, the 95% CIs did include 0, and so the expansion to 0 as a confidence limit did not take place. For this reason, I report and discuss the 95% CI in the summary of results without further reference to the 97.5% expanded CI.				
3 LSMeans and 95% CI were obtained from a longitudinal model which included the log-transformed baseline and post-baseline measurements in the response vector, with fixed effects for treatment, period and sequence. An unstructured covariance matrix was used. The baseline geometric mean and the back-transformed SD are presented. The back-transformed SD was derived as the geometric mean x the SD on the log scale, using a Taylors series expansion.				
<i>Source:</i> Study P190, Tables 11-2, 11-3, 11-4, 11-5 and 11-7				

### **3.3 Evaluation of Safety**

For an evaluation of the safety endpoints from Study P185 and P190, see the clinical review by Dr. Chowdhury.

## **4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

### **4.1 Gender, Race, Age, and Geographic Region**

The applicant provided the results from several separate analyses of the LDL-C endpoint, subdivided by gender, age, and race (TABLE 12, TABLE 13). None of these analyses showed substantial differences in the assessment of clinical equivalence. The interpretation of results from the analyses subdivided by race is limited by the large majority of white subjects in both studies (84% in Study P185 and 82% in Study P190). I believe that the applicant's descriptive approach is appropriate to the crossover study design, and I did not use a statistical approach to evaluate the subgroup by treatment group interaction within the ANCOVA model.

The studies were conducted entirely within the United States, and for this reason neither I nor the applicant evaluated the effect of geographic region on the assessment of clinical equivalence further.

TABLE 12 Study P185; separate analysis by sex, age and race; FDC vs. co-administered tablets in the LDL-C endpoint (PP analysis set)

Subgroup	FDC (Ez / Atorva 20 mg)				Co-admin (Ez + Atorva 20 mg)				FDC – Co-admin:		Within clinical equivalence limits of ± 4%?
	n	Mean (SD)	LSMean	95% CI	n	Mean (SD)	LSMean	95% CI	Difference in % change from baseline <sup>1</sup>	95% CI	
<b>Sex</b>											
Male	136	157.1 (28.6)	-52.4	(-55.5, -49.3)	136	156.9 (28.9)	-51.5	(-54.6, -48.4)	-0.9	(-3.5, 1.8)	Yes
Female	217	165.8 (33.5)	-55.1	(-57.3, -52.9)	210	165.1 (34.1)	-55.3	(-57.6, -53.1)	0.2	(-1.6, 2.0)	Yes
<b>Age (yrs)</b>											
< 65	294	163.6 (31.3)	-52.9	(-55.0, -50.9)	286	163.0 (31.9)	-52.9	(-55.0, -50.8)	0.0	(-1.8, 1.7)	Yes
≥ 65	59	156.8 (34.7)	-59.5	(-62.2, -56.8)	60	156.8 (34.4)	-58.5	(-61.2, -55.9)	-0.9	(-3.6, 1.8)	Yes
<b>Race</b>											
White	300	162.6 (32.1)	-55.3	(-57.1, -53.4)	292	162.6 (32.6)	-55.1	(-57.0, -53.3)	-0.1	(-1.7, 1.5)	Yes
Black	44	158.5 (30.0)	-46.4	(-52.4, -40.3)	44	155.6 (29.2)	-46.2	(-52.3, -40.1)	-0.1	(-4.6, 4.3)	No
Asian <sup>2</sup>	5	181.4 (43.2)	-47.3 (35.9)		6	170.8 (46.5)	-48.9 (22.9)				
Other <sup>2</sup>	4	169.5 (27.7)	-64.2 (8.2)		4	169.5 (27.7)	-56.3 (9.4)				
<b>Notes:</b>											
1. The primary analysis of covariance model was applied separately to each subgroup. The 95% CIs are nominal.											
2. Because the “Asian” and “Other” racial subgroups are so small, only descriptive summaries are shown.											
										<i>Source:</i>	
										Study report, Table 14.2.1.2.1	

TABLE 13 Study P190; separate analysis by sex, age and race; FDC vs. co-administered tablets in the LDL-C endpoint (PP analysis set)

Subgroup	FDC (Ez / Atorva 40 mg)				Co-admin (Ez + Atorva 40 mg)				FDC – Co-admin:		Within clinical equivalence limits of ± 4%?	
	n	Mean (SD)	LSMean	95% CI	n	Mean (SD)	LSMean	95% CI	Difference in % change from baseline <sup>1</sup>	LSMean Difference		95% CI
<b>Sex</b>												
Male	125	160.0 (30.8)	-60.0	(-62.5, -57.5)	125	159.6 (31.1)	-61.0	(-63.5, -58.5)		1.0	(-1.2, 3.2)	Yes
Female	155	164.4 (29.7)	-58.1	(-61.1, 55.2)	155	164.3 (29.3)	-57.0	(-59.9, -54.0)		-1.2	(-3.6, 1.2)	Yes
<b>Age (yrs)</b>												
< 65	233	163.4 (31.3)	-58.1	(-60.3, -55.9)	233	163.6 (31.4)	-58.5	(-60.7, -56.3)		0.4	(-1.4, 2.3)	Yes
≥ 65	47	157.8 (23.6)	-63.4	(-67.7, -59.0)	47	155.1 (22.2)	-60.2	(-64.4, -56.1)		-3.1	(-6.8, 0.5)	No
<b>Race</b>												
White	232	162.4 (30.7)	-60.3	(-62.3, -58.4)	233	161.6 (30.6)	-60.4	(-62.3, -58.4)		0.1	(-1.6, 1.7)	Yes
Black	42	164.0 (29.1)	-51.3	(-58.7, -44.0)	42	166.0 (28.9)	-49.4	(-56.6, -42.1)		-2.0	(-8.7, 4.7)	No
Asian <sup>2</sup>	2	164.5 (36.1)	-68.8 (1.7)		2	164.5 (36.1)	-72.1 (2.2)					
Other <sup>2</sup>	4	147.8 (13.7)	-59.8 (4.2)		3	154.0 (7.0)	-58.2 (8.8)					

**Notes:**

- The primary analysis of covariance model was applied separately to each subgroup. The 95% CIs are nominal.
- Because the “Asian” and “Other” racial subgroups are so small, only descriptive summaries are shown.

**Source:**

Study report, Table 14.2.1.2.1

## 4.2 Other Special/Subgroup Populations

I did not evaluate other special or subgroup populations in this review.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

The statistical issues I encountered in my review of Study P185 and Study P190 came from the use of the 2-period crossover design. The statistical comparisons between the FDC formulation and the co-administered tablets are based on the assumption that the six week treatment period was long enough to ensure that the LDL-C response to each therapy was stabilized, with little to no carry-over effect from the end of Period 1 to the end of Period 2. Some of the study results challenged this assumption, especially with the 20-mg formulation in Study P185: A significant effect of “Period” appeared to be different for each treatment group, and in both studies, approximately 10% of subjects had differences in LDL-C response between the two treatments that were greater than  $\pm 20$  percentage points. However, based on additional analyses that are summarized in this review, I don’t believe that this review concern affected the statistical support for clinical equivalence of either the 20-mg formulation or the 40-mg formulation.

I recommend that future studies of clinical equivalence that involve statin drugs be conducted with a longer treatment period, in order to provide more assurance that the response to therapy has stabilized for more subjects. Obtaining the baseline level as an average of several measurements will also reduce variability in the percentage change from baseline endpoint between the two periods. The pre-treatment washout and run-in periods may also need to be extended in order to stabilize the baseline level of LDL-C from which the percentage change from baseline is estimated.

### 5.2 Collective Evidence

The collective evidence from Study P185 and P190 supported the conclusion of clinical equivalence of ezetimibe / atorvastatin FDC to co-administered ezetimibe + atorvastatin with respect to LDL-C response after 6 weeks of treatment, for both the 20 mg and 40 mg formulations. The study design was reasonable (although I believe that the treatment periods could have been longer), and the statistical methods were appropriate.

### 5.3 Conclusions and Recommendations

The conclusion of clinical equivalence in LDL-C for the FDC formulation compared to the co-administered tablets was supported by the results from Study P185 (the 20 mg dose of atorvastatin) and Study P190 (the 40 mg dose). In both studies, the 95% confidence interval (CI) of the difference between the FDC formulation and the co-administrated tablets for the mean % change in LDL-C from baseline stayed within the clinical equivalence limits of  $\pm 4\%$ . My

additional analyses supported these conclusions. The results from the secondary lipid endpoints, including TC, HDL, non-HDL and TG, also supported the conclusion of clinical equivalence. Age and gender did not appear to have an impact on the conclusion of clinical equivalence. An assessment of the impact of race was limited because the large majority (84% in Study P185 and 82% in Study P190) of the study participants was white. Both studies were conducted entirely within the U.S.

#### **5.4 Labeling Recommendations**

The summary of results from Study P185 and P190 in the draft label (from 11/12/2012), along with my proposed edits, is shown in TABLE 14 on the next page.

TABLE 14 Summary of Study P185 and P190 in the draft label, and recommendations

Proposed summary of Study P185 and P190 in the draft label [highlights show text with proposed edits]	Proposed edits from statistical review perspective
<p><b>12.3 Pharmacokinetics</b></p> <p>(b) (4)</p>	<p><i>Edit:</i> ... have been shown to be clinically equivalent in LDL-C response after six weeks of treatment, to their corresponding coadministered components.</p>
<p><b>14 CLINICAL STUDIES</b></p> <p><b>14.1 Primary Hyperlipidemia</b></p> <p><i>ATOZET 10/20 and 10/40 - Clinical Equivalence to Coadministered Components</i></p> <p>ATOZET has been shown to be bioequivalent to coadministration of corresponding doses of its ezetimibe and atorvastatin components with the exception of slightly lower atorvastatin Cmax for the 10/20 and 10/40 mg doses [see <i>Clinical Pharmacology (12.3)</i>], (b) (4)</p> <p>(b) (4)</p> <p>In these two multicenter, double-blind, controlled, crossover studies, patients with primary hypercholesterolemia and low, moderate, or moderately high cardiovascular risk received ATOZET 10/20-mg (Study 1) or 10/40 -mg (Study 2) tablets or the corresponding coadministered components once daily for 6 weeks. (b) (4) to the coadministered components or ATOZET at corresponding doses for an additional 6 weeks. From untreated baseline, mean changes in LDL-C for ATOZET vs. the coadministered components, respectively, were -54.0% vs. -53.8% for 10/20-mg (Study 1), and -58.9% vs. -58.7% for 10/40-mg (Study 2). (b) (4)</p>	<p><i>Edit:</i> ... which, in two separate studies, have been shown to be clinically equivalent in LDL-C response after six weeks of treatment, to their corresponding coadministered components.</p> <p><i>Edit:</i> They then crossed over, after a 6-week washout, ...</p> <p><i>Replace final sentence with:</i> Mean changes for total-C, Apo B, TG, non-HDL-C and HDL-C were also fairly similar between the two treatment groups and supported the conclusion of clinical equivalence.</p>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE A DERR

03/29/2013

This revised review corrects typos in the review signed 3/21/13 which has been deleted in Darrts.

JON T SAHLROOT

04/03/2013

concur



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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA:** 200153/0  
**Drug Name:** Atozet Fixed Dose Combination (10 mg ezetimibe + 10, 20, 40 or 80 mg atorvastatin)  
**Indication(s):** Reduces elevated total-C, LDL-C, Apo-B, TG and non-HDL-C and increases HDL-C in patients with hyperlipidemia  
**Applicant:** MSP (Merck)  
**Date(s):** Stamp date: 4/29/11; PDUFA Goal Date: 2/29/12  
**Date of this Review:** January 6, 2012  
**Review Priority:** Standard  
**Biometrics Division:** DB2  
**Statistical Reviewer:** Janice Derr, Ph.D.  
**Concurring Reviewers:** J. Todd Sahlroot, Ph.D., Team Leader and Deputy Division Director  
**Medical Division:** Division of Metabolism and Endocrinology Products  
**Clinical Team:** Iffat Chowdhury, M.D.  
Eric Colman, M.D., Deputy Division Director  
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Keywords: NDA review, clinical studies

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## 1 EXECUTIVE SUMMARY

Atozet™ is a fixed dose combination (FDC) tablet that contains ezetimibe 10 mg and atorvastatin (10, 20, 40 or 80 mg). Atozet is proposed for approval as a more convenient single tablet when the combination of ezetimibe (Zetia™) and atorvastatin (Lipitor™) is prescribed for the treatment of hyperlipidemia. The NDA submission includes results from clinical studies of the co-administered components that are proposed for inclusion in the Atozet label. The efficacy of the co-administered combination compared to its components has already been established as part of the approval of Zetia. The bioequivalence of the FDC product compared to the co-administered components is under review by the Dr. Lau, the reviewing pharmacologist for the Office of Clinical Pharmacology. This statistical review is an evaluation of the proposed summary of results from five Phase 3 clinical studies that were not reviewed as part of the clinical development program for either Zetia or Lipitor. These studies provide supportive information, but are not pivotal to the approval of Atozet.

I reviewed two studies that were long-term extensions of studies that are currently described in the Zetia label. I concluded that the proposed summaries were supported by the results from these extension studies.

The remaining three studies that I reviewed were designed to evaluate the effect of adding ezetimibe 10 mg to ongoing atorvastatin therapy, compared to doubling the dose of atorvastatin:

- Study P693 evaluated ezetimibe 10 mg + atorvastatin 10 mg vs. atorvastatin 20 mg
- Study P079 evaluated ezetimibe 10 mg + atorvastatin 20 mg vs. atorvastatin 40 mg
- Study P090 evaluated ezetimibe 10 mg + atorvastatin 40 mg vs. atorvastatin 80 mg

The patient populations for each study were different with respect to their baseline level of risk for cardiovascular disease, with lower risk subjects enrolled in P693 and higher risk subjects enrolled in P090. Each study had a run-in phase prior to randomization, during which subjects received atorvastatin at the lower dose of the co-administration arm. At the start of the double-blind treatment period, ezetimibe 10 mg was added to one arm and the atorvastatin dose was doubled in the other arm. Each study demonstrated that the addition of ezetimibe 10 mg to ongoing atorvastatin therapy reduced LDL-C to a greater extent than doubling the dose of atorvastatin. The summary statistics of the lipid results are reported accurately in the proposed label for Atozet. The nominal p-values were < 0.001 for LDL-C and secondary endpoints Total-C, TG, Apo-B and non-HDL-C. The p-values of these comparisons may be low enough to overcome review concerns about the lack of a pre-specified plan to control Type I error. The proposed label summary, including the use of a nominal  $p < 0.001$ , is similar to the description of a similar study in the Vytorin™ (ezetimibe / simvastatin) label.

## 2 INTRODUCTION

Atozet™ is a combination tablet that contains ezetimibe and atorvastatin. Ezetimibe is a cholesterol absorption inhibitor developed for the treatment of primary hyperlipidemia and the rare conditions homozygous familial hypercholesterolemia (HoFH) and phytosterolemia. Ezetimibe reduces intestinal cholesterol absorption leading to a reduction in hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe was first approved in the USA in 2002 (Zetia™) under NDA 021445. Atorvastatin is a HMG-CoA reductase inhibitor (“statin”) that was developed for the treatment of primary hyperlipidemia, hypertriglyceridemia, and primary dysbetalipoproteinemia. Atorvastatin was first approved in the USA in 1996 (Lipitor™) under NDA 020702. Atorvastatin inhibits cholesterol biosynthesis, which leads to induction of the LDL-C receptor, increasing removal of LDL-C from the blood and lowering circulating LDL-C levels<sup>1</sup>.

The current label for Zetia includes information in support of the combined use of Zetia with atorvastatin or other statins. This combined use is supported by results from four clinical studies that were designed to evaluate the combination of Zetia with statins in comparison with Zetia monotherapy and the statin monotherapy. Each study evaluated a different statin in combination with Zetia. Study P0692 evaluated the combination of Zetia with atorvastatin. The applicant intends the ezetimibe/atorvastatin FDC tablet, which is described in this NDA, to provide a more convenient single tablet when the combination of these two drugs is prescribed.

### 2.1 Overview

The purpose of this statistical review is to evaluate information in the proposed label for Atozet from five Phase 3 clinical studies that were not reviewed as part of the clinical development program for either Zetia or Lipitor. These five studies all make use of co-administered ezetimibe and atorvastatin tablets rather than the FDC tablet. Dr. Lau, the reviewing pharmacologist for the Office of Clinical Pharmacology, is evaluating the bioequivalence of the FDC tablet to the co-administered components. The establishment of bioequivalence is a key link to the already existing information about safety and efficacy from clinical studies of the co-administered components.

#### 2.1.1 Class and Indication

Atozet has been developed as an immediate release (b) (4) tablet formulation containing a fixed dose of ezetimibe 10 mg combined with 10, 20, 40 or 80 mg of atorvastatin. The applicant proposes the ezetimibe/atorvastatin combination tablet as therapy for patients with primary hyperlipidemia, including heterozygous familial and non-familial hyperlipidemia; mixed hyperlipidemia; or homozygous familial hypercholesterolemia. A similar product, Vytorin™,

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<sup>1</sup> The source of Part 2.0 is the Introduction to the NDA, submitted 4/27/11, and paraphrased by this reviewer.

was approved in 2004. Vytorin is a combination tablet consisting of ezetimibe 10 mg combined with 10, 20, 40 or 80 mg with simvastatin.

### 2.1.2 Specific Studies Reviewed

This review is organized in three parts, as shown below:

A. Study P2154 is a 48-week extension of Study P0692. Study P0692 was the factorial combination study that supported the separate contributions of ezetimibe and atorvastatin to the efficacy of the combination. The proposed label for Atozet includes the previously approved summary for Study P0692 (a 12-week treatment period). In addition, the applicant proposes the following statement, which is based on the results from Study P2154: “The change in lipid endpoints after an additional 48 weeks of treatment with Atozet (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.”

B. Studies P693, P079 and P090 were designed to evaluate the co-administered ezetimibe + atorvastatin in comparison with atorvastatin monotherapy. In each study, the dose of atorvastatin in the monotherapy arm was twice as much as the dose of atorvastatin in the combination:

- Study P693 evaluated ezetimibe 10 mg + atorvastatin 10 mg vs. atorvastatin 20 mg
- Study P079 evaluated ezetimibe 10 mg + atorvastatin 20 mg vs. atorvastatin 40 mg
- Study P090 evaluated ezetimibe 10 mg + atorvastatin 40 mg vs. atorvastatin 80 mg

For each study, the proposed label provides a summary table of results and the summary statement “Atozet 10/10 [10/20, 10/40] is significantly more effective than doubling the dose of atorvastatin to 20 [40, 80] mg in further reducing total-C, LDL-C, TG, and non-HDL-C.”

C. Study P1417 is a 24-month extension of Study P1030. This study and its extension were conducted in support of the efficacy of ezetimibe in combination with either atorvastatin or simvastatin in patients with Homozygous Familial Hypercholesterolemia (HoFH). The results of Study P1030 (a 12-week treatment period) are summarized in the Zetia label. The proposed Atozet label includes a summary of the portion of Study P1030 that involved atorvastatin. In addition, the applicant proposes the following statement, which is based on the results from Study P1417: “At the end of the 24 months, ATOZET ... produced a reduction of LDL-C that was consistent with that seen in the 12-week study.”

### 2.1.3 Major Statistical Issues

A. Study P2154: No major statistical issues.

B. Studies P693, P079 and P090: These studies have a similar design and are summarized in a similar way to a clinical study that is summarized in the Vytorin label (ezetimibe / simvastatin

FDC tablets). Studies P079 and P090 had a similar statistical analysis plan which was well aligned with the proposed label summaries in terms of the primary and secondary efficacy endpoints. Study P693 was conducted earlier, and had several differences in the design and analysis of efficacy endpoints. None of the studies had a pre-specified plan for controlling Type I error across the secondary efficacy endpoints that are clinically important in hyperlipidemia. However, the low nominal p-values from the comparison of the ezetimibe + atorvastatin arm and the atorvastatin comparator arm in each study ( $p < 0.001$ ) may alleviate concerns about multiplicity.

C. Study P1417: No major statistical issues.

## 2.2 Data Sources

The submissions to NDA 200153 shown in TABLE 1 served as the basis of my review.

TABLE 1 Data sources for this submission to NDA 200153

Number	Date	Description
0008	4/27/11	NDA submission in response to complete response letter from Division
0009	4/29/11	Annotated package insert
\\cdesub1\evsprod\NDA 200153\		

### A. Long-term extension to a factorial combination study: Study P2154, long-term extension of Study P0692.

The primary objective of the long-term extension Study P2154 was to evaluate the long-term safety and tolerability of daily co-administered ezetimibe 10 mg with atorvastatin 10-80 mg/day for up to 12 months in subjects with primary hypercholesterolemia who had successfully completed the P0692 clinical study. The secondary objective was to further evaluate the effect of ezetimibe plus atorvastatin on LDL-C, HDL-C and triglyceride levels.

## 3A Statistical Evaluation

### 3.1A Data and Analysis Quality

I did not evaluate data and analysis quality in the Study P2154.

### 3.2A Evaluation of Efficacy

#### 3.2.1A Study Design and Endpoints

Study P2154 was a 12-month, multicenter study that was an extension of Study P0692. Eligible subjects had completed the 12-week randomized, double-blind study in which they received

either placebo, ezetimibe 10 mg, atorvastatin monotherapy (10-80 mg), or ezetimibe 10 mg co-administered with atorvastatin 10 mg once daily. Assignment to double-blind medication (ezetimibe or placebo) was based on the blinded treatment to which a subject was randomized in Protocol P0692, as follows:

- Subjects randomized to placebo in Study P0692 were assigned to receive placebo in the extension study, in addition to open-label atorvastatin 10 mg/day.
- Subjects randomized to receive ezetimibe (alone or in combination with atorvastatin) in Study P0692 were assigned to receive ezetimibe in the extension study, in addition to open-label atorvastatin 10 mg/day.
- Subjects randomized to receive atorvastatin alone in the parent study were randomized to receive ezetimibe or placebo in a 3:1 ratio in the extension study, in addition to open-label atorvastatin 10 mg/day.

In the extension study P2154, subjects were initially dosed with either double-blind ezetimibe 10 mg or matching placebo co-administered with open-label atorvastatin 10 mg once daily. After at least 6 weeks, the atorvastatin dose could be titrated up by doubling the dose to a maximum of 80 mg once daily to achieve the subject's National Cholesterol Education Program (NCEP) Adult Treatment Panel II target LDL-C level. Subjects were to continue to follow a NCEP Step 1 or stricter diet during the extension study. Study visits were scheduled at 1.5, 3, 6, 9 and 12 months following entry into P2154.

Study P2154 enrolled 246 subjects, 145 women and 101 men, 26 to 86 years of age: 45 were assigned to placebo + atorvastatin and 201 to ezetimibe 10 mg + atorvastatin. The study was conducted in the U.S. (25 sites, 114 subjects) and in 15 countries outside the U.S. (28 sites, 132 subjects; TABLE 3). The study period was 10/1/01 to 8/8/02.

TABLE 2 Randomization in Study P2154 based on assignment in Study P0692

Assignment in Study P0692 (12-week treatment period)			Assignment in P2154 (12-month treatment period)		
Treatment arms	n Started	n Finished	Both arms had open-label atorvastatin 10 mg/day, titratable after 6 weeks by doubling the dose, up to a maximum of 80 mg/day, based on NCEP guidelines		
			A. Plac.	B. Eze.	Randomization
Placebo	60	55	→ 20		A. Placebo
Ezetimibe 10 mg	65	60	→	30	B. Ezetimibe 10 mg
Atorvastatin 10 mg	60	55	→ 6	14	Randomized to B or A in a 3:1 ratio
Ezetimibe 10 mg + Atorvastatin 10 mg	65	64	→	28	B. Ezetimibe 10 mg
Atorvastatin 20 mg	60	56	→ 3	18	Randomized to B or A in a 3:1 ratio
Ezetimibe 10 mg + Atorvastatin 20 mg	62	58	→	26	B. Ezetimibe 10 mg
Atorvastatin 40 mg	66	59	→ 10	24	Randomized to B or A in a 3:1 ratio
Ezetimibe 10 mg + Atorvastatin 40 mg	65	57	→ 1 <sup>a</sup>	20	B. Ezetimibe 10 mg
Atorvastatin 80 mg	62	59	→ 5	20	Randomized to B or A in a 3:1 ratio
Ezetimibe 10 mg + Atorvastatin 80 mg	63	53	→	21	B. Ezetimibe 10 mg
Summary:					
Placebo	60	55	→ 20		A. Placebo
Ezetimibe 10 mg monotherapy	65	60	→	30	B. Ezetimibe 10 mg
Atorvastatin monotherapy (all doses)	248	229	→ 24	76	Randomized to B or A in a 3:1 ratio
Ezetimibe 10 mg + Atorvastatin (all doses)	255	232	→ 1 <sup>a</sup>	95	B. Ezetimibe 10 mg
Totals	628	576	45	201	246
<i>Notes:</i>					
<sup>a</sup> Shaded boxes indicate a treatment that was not assigned. However, one subject was incorrectly randomized.					
<i>Source:</i> Study P2154 clinical report, Table 6; Study P0692 clinical report, Table 7; and additional analysis by this reviewer					

TABLE 3 Study P2154 sites, countries and subjects

Country	Number of sites	Number of subjects enrolled
U.S.	25	114
Germany	5	37
Canada	5	16
Brazil	1	15
Argentina	2	12
France	4	9
Belgium	1	8
Mexico	2	7
Venezuela	1	7
Greece	1	6
Australia	1	5
Spain	1	3
Chile	1	3
Portugal	1	2
Italy	1	1
UK	1	1
	53	246

### 3.2.2A Subject Disposition, Demographic and Baseline Characteristics

The majority of subjects completed at least 12 months of treatment in Study P2154, and did not require an up-titrated dose of atorvastatin (TABLE 4, TABLE 5). The baseline characteristics of subjects who enrolled in Study P2154 are summarized in (TABLE 6).

TABLE 4 Study P2154; Number of months in the study by subjects in each treatment arm

Treatment	Duration (months) in the study					Miss- ing	Median duration Min - Max
	< 3	3 to < 6	6 to < 9	9 to < 12	≥ 12		
Atorvastatin (n=45)	5 (11%)	1 (2%)	0	9 (20%)	30 (67%)	0	12.1 0.3 - 13.8
Ezetimibe 10 mg + Atorvastatin (n=201)	14 (7%)	7 (3%)	10 (5%)	44 (22%)	126 (63%)	0	10.9 0.0 - 13.7

Source: Study P2154 clinical report, Table 15

TABLE 5 Study P2154; Number of subjects with up-titration of atorvastatin dose

Treatment	Study P0692		LTE Study P2154					
	Started	Finished	Started	Up-titration of Atorvastatin?		Titrated dose of atorvastatin		
				no	yes	20 mg	40 mg	80 mg
Atorvastatin (n=45)			45	35 (78%)	10 (22%)	3	4	3
Ezetimibe 10 mg + Atorvastatin (n=201)			201	182 (91%)	19 (9%)	9	7	3
	628	576	245					

Source: Study P2154 clinical report, Part 14.1.1.1, and Table 2 of this review

TABLE 6 Study P2154; Demographic and baseline characteristics

	Atorvastatin (n=45)	EZ 10 mg + Atorvastatin (n=201)
Age (years)		
Mean (SD)	58.5 (9.5)	57.6 (11.2)
Min, Max	34 – 76	26 – 86
n (%) < 65 years	30 (67%)	146 (73%)
Sex		
Female	22 (49%)	123 (61%)
Male	23 (51%)	78 (39%)
Race		
Caucasian	39 (87%)	174 (87%)
Black	2 (4%)	12 (6%)
American Indian	0	6 (3%)
Asian	0	1 (<1%)
Hispanic	4 (9%)	8 (4%)
Baseline Values for Lipids, calculated at the start of Study P0692:		
LDL-C (mg/dL; calculated); Mean (SD)	185.6 (24.3)	181.1 (21.4)
Total Cholesterol (mg/dL); Mean (SD)	269.8 (25.8)	267.7 (26.1)
Triglycerides (mg/dL); Mean (SD)	163.7 (60.9)	172.3 (67.1)
HDL-C (mg/dL); Mean (SD)	51.5 (10.5)	52.4 (14.2)

Source: Study P2154 clinical report, Table 9

### 3.2.3A Statistical Methodologies

The baseline used in Study P2154 is the original untreated baseline at the start of the treatment period of Study P0692. Changes from baseline of lipid parameters by visit and at study endpoint were summarized using descriptive statistics.

**3.2.4A Results and Conclusions**

The applicant proposes to include the following statement regarding the lipid results from Study P0692 in the Atozet label: “The changes in lipid endpoints after an additional 48 weeks of treatment with Atozet (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.” The 12-week data refers to the results from Study P0692, which are summarized in TABLE 7. (b) (4)

However, I proposed modifications to the label text to more clearly indicate that the 48-week extension data came from subjects who completed Study P0692 and who volunteered to participate in the extension (245/576, or 43% of subjects who completed Study P0692).

TABLE 7 Study P0692; Lipid results expressed as mean % change from untreated baseline after 12 weeks

	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C
Pooled data (All ezetimibe + atorvastatin doses)	255	-41	-56	-45	-33	+7	-52
Pooled data (all atorvastatin doses)	248	-32	-44	-36	-24	+4	-41
Ezetimibe 10 mg	65	-14	-20	-15	-5	+4	-18
Placebo	60	+4	+4	+3	-5	+4	+4

Notes: This table is a part of Table 7 proposed for the Atozet label

Source: Zetia label (2011), Table 8

(b) (4)

**3.3A Evaluation of Safety**

For an evaluation of safety issues of clinical studies of the co-administered ezetimibe + atorvastatin combination, see the clinical review by Dr. Chowdhury.

#### **4A Findings In Special/Subgroup Populations**

I did not evaluate the findings from Study P2154 further by subgroup.

#### **B. Comparisons of Ezetimibe + atorvastatin to Atorvastatin at double the dose: Studies P693, P079 and P090**

##### **3B Statistical Evaluation**

##### **3.1B Data and Analysis Quality**

I did not evaluate data and analysis quality in the Studies P693, P079 and P090.

##### **3.2B Evaluation of Efficacy**

##### **3.2.1B Study Design and Endpoints**

Studies P693, P079 and P090 had a similar design. In each study, ezetimibe 10 mg co-administered with atorvastatin was compared with atorvastatin monotherapy in a two-arm design. The dose of atorvastatin differed among studies, but in each study, the atorvastatin dose in the monotherapy arm was double the atorvastatin dose in the co-administration arm:

- Study P693 evaluated ezetimibe 10 mg + atorvastatin 10 mg vs. atorvastatin 20 mg
- Study P079 evaluated ezetimibe 10 mg + atorvastatin 20 mg vs. atorvastatin 40 mg
- Study P090 evaluated ezetimibe 10 mg + atorvastatin 40 mg vs. atorvastatin 80 mg

The primary objective of these studies was to show that the addition of ezetimibe 10 mg to ongoing atorvastatin therapy would reduce LDL-C to a greater extent than doubling the dose of atorvastatin.

The patient populations for each study were different with respect to their baseline level of risk for cardiovascular disease, with lower risk subjects enrolled in P693 and higher risk subjects enrolled in P090 (TABLE 9). Each study had a run-in phase prior to randomization, during which subjects received atorvastatin at the lower dose of the co-administration arm. This served as a washout / run-in period for subjects who had enrolled in the study on other lipid lowering therapies. At the end of this run-in phase, the eligibility of subjects was re-assessed with respect to qualifying levels of LDL-C and TG, which differed among the studies (TABLE 9). At the start of the double-blind treatment period, ezetimibe 10 mg was added to one arm and the atorvastatin dose was doubled in the other arm. The double-blind treatment period was 14 weeks in Study P693 and 6 weeks in the other two studies. The primary endpoint in Study P693 was the subject's status at week 14 with respect to the LDL-C target of  $\leq 100$  mg/dl. The primary endpoint in Studies P079 and P090 was the subject's LDL-C at week 6, expressed as a percentage change from baseline (TABLE 9). Schematics for each design are available in

FIGURE 1, FIGURE 2 and FIGURE 3.

A study with a similar design is described in the Vytorin (ezetimibe / simvastatin) label. Study 021 was a randomized, double-blind, multi-center, 24-week trial comparing co-administration of ezetimibe 10 mg + simvastatin 20 mg to simvastatin 40 mg in patients with Type 2 diabetes. This study had a similar role in the review of Vytorin as Studies P693, P079 and P090 have in the review of Atozet. Study 021 received a statistical review by Dr. Sahlroot, who assessed the accuracy of the point estimates to be summarized in the Vytorin label.

TABLE 9 Design of Study P693, P079 and P090

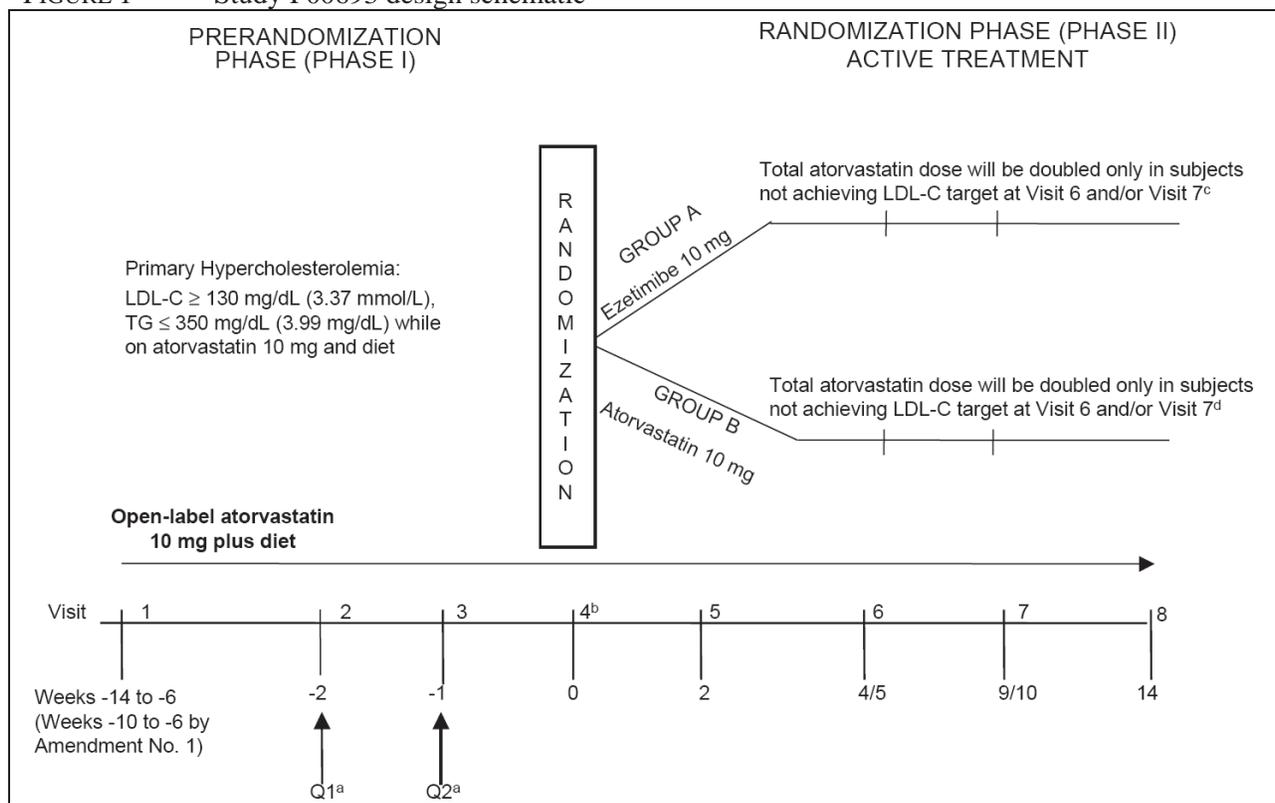
	Study P693		Study P079		Study P090	
<b>Randomized:</b>	Eze10mg+ Ator 10mg 305	Ator 20mg 316	Eze10mg+ Ator 20mg 98	Ator 40mg 98	Eze10mg+ Ator 40mg 288	Ator 80mg 291
	Total: 621		Total: 196		Total: 579	
<b>Statistical power:</b>	<ul style="list-style-type: none"> <li>•480 subjects randomized 1:1</li> <li>•90% power</li> <li>•endpoint is the proportion of subjects achieving target LDL-C</li> <li>•effect size of 0.15, between-group difference of proportions</li> <li>• two-tailed <math>\alpha</math> of 0.05</li> </ul>		<ul style="list-style-type: none"> <li>•160 subjects randomized 1:1</li> <li>•95% power</li> <li>•endpoint is the percent change from baseline in LDL-C</li> <li>•effect size is 10 percentage points, difference between group means</li> <li>•within group standard deviation is 17%</li> <li>•two-tailed <math>\alpha</math> of 0.05</li> </ul>		<ul style="list-style-type: none"> <li>•554 subjects randomized 1:1</li> <li>•92% power</li> <li>•endpoint is the percent change from baseline in LDL-C</li> <li>•effect size is 5 percentage points, difference between group means</li> <li>•within group standard deviation is 17%</li> <li>•two-tailed <math>\alpha</math> of 0.05</li> </ul>	
<b>Inclusion criteria:</b>						
1. Risk factors	Primary hyperlipidemia and either: (1) HeFH or (2) CHD or $\geq 2$ risk factors for CHD		Primary hyperlipidemia and: ATP III level of risk (without CHD or CHD risk equivalent), with $\geq 2$ cardiovascular risk factors that confer a 10-year risk for CHD of 10 to 20% by Framingham risk scoring		Primary hyperlipidemia and: ATP III high risk patient: with CHD or other forms of atherosclerosis, or with $\geq 2$ cardiovascular risk factors that confer a 10-year risk for CHD $> 20\%$ by Framingham risk scoring	
2. LDL-C and other lipids while on pre-trial lipid lowering therapy	LDL-C $\geq 130$ mg/dL TG $\leq 350$ mg/dL		LDL-C between 100 mg/dL and 160 mg/dL TG $\leq 350$ mg/dL		LDL-C between 70 and 160 mg/dL TG $\leq 350$ mg/dL	

	<b>Study P693</b>	<b>Study P079</b>	<b>Study P090</b>
3. Pre-trial lipid lowering therapy	atorvastatin 10 mg/day for at least 4 weeks; other lipid lowering therapies were washed out for 6-12 weeks prior to Q1 (first qualifying lipid sample)	atorvastatin 20 mg/day or other approved lipid lowering therapy for at least 6 weeks, or naïve to statin and/or ezetimibe	atorvastatin 40 mg/day or other approved lipid lowering therapy for at least 6 weeks, or naïve to statin and/or ezetimibe
<b>Prerandomization / Atorvastatin Run-In Phase</b>			
	6-10 weeks of open-label atorvastatin 10 mg run-in	4-5 weeks single blind screening/stabilization period with atorvastatin 20 mg	4-5 weeks single blind screening/stabilization period with atorvastatin 40 mg
<b>Criteria for randomization:</b>			
	Mean of Q1 (Week -2) and Q2 (Week -1): LDL-C $\geq$ 130 mg/dL with no single value < 125 mg/dL.	Week -1 (qualifying visit): LDL-C between 100 mg/dL and 160 mg/dL TG $\leq$ 350 mg/dL	Week -1 (qualifying visit): LDL-C between 70 and 160 mg/dL TG $\leq$ 350 mg/dL
<b>Stratification:</b>			
	No stratification factors	LDL-C levels: 100 to < 130 mg/dL 130 to $\leq$ 160 mg/dL	LDL-C levels: 70 to < 100 mg/dL 100 to < 130 mg/dL 130 to $\leq$ 160 mg/dL
<b>Double-blind treatment phase:</b>			
1. Duration of treatment	14 weeks of treatment with double-blind investigational treatment and open-label atorvastatin 10 mg	6-week treatment period double-blind treatment	6-week treatment period double-blind treatment
2. Lipid determinations	Weeks 2, 4, 9 and 14	Week 6	Week 6
3. Adjustments	If LDL-C target ( $\leq$ 100 mg/dL) was not achieved at week 4 and/or week 9, total dose of atorvastatin was doubled at week 5 or week 10 (double-blind)	None	None
<b>Primary endpoint:</b>			

	<b>Study P693</b>		<b>Study P079</b>		<b>Study P090</b>	
	Proportion of subjects achieving the target LDL-C levels ( $\leq$ 100 mg/dL) at week 14.		Percent change from baseline to week 6 in LDL-C		Percent change from baseline to week 6 in LDL-C	
<b>Key secondary endpoint:</b>	LDL-C endpoints at week 4		Proportion of subjects reaching LDL-C goal of $<$ 100 mg/dL at week 6		Percentage of subjects that reached LDL-C goal of $<$ 70 mg/dL at week 6	
<b>Other secondary endpoints:</b>	Lipid metabolism endpoints at weeks 4, 9, and 14. Health Related Quality of Life assessment (SF-36) PRO endpoints measuring muscle ache(s) and pain(s)		Lipid metabolism endpoints at week 6.		Lipid metabolism endpoints at week 6.	
<b>Number of subjects in study sites by country</b>	106 subjects from 37 sites in U.S. (17.1% of randomized subjects)		120 subjects from 43 sites in U.S. (61.2% of randomized subjects)		533 subjects from 74 sites in U.S. (92.1% of randomized subjects)	
Country	# of sites	# of subjs.	# of sites	# of subjs.	# of sites	# of subjs.
U.S.	37	106	43	120	74	533
Canada	7	42	2	8	4	46
Austria	3	22	2	42		
Costa Rica	---	---	1	26		
Netherlands	17	80				
Spain	17	147				
Germany	6	33				
France	5	34				
Italy	3	20				
South Africa	3	23				
Greece	2	16				
Peru	2	13				
Sweden	2	2				
Belgium	1	3				
Denmark	1	32				
Ecuador	1	4				
Finland	1	11				
Guatemala	1	4				
Mexico	1	10				

	Study P693		Study P079		Study P090	
Norway	1	8				
Taiwan	1	9				
UK	1	2				
Totals:	113	621	48	196	78	579
<b>Study period:</b>	April 8, 2000 to November 19, 2001		April 5, 2006 to January 16, 2008		February 13, 2006 to February 28, 2008	
<i>Note:</i> This summary includes key points that are important to the statistical review. More detail is available in the protocol and report of each study.						

FIGURE 1 Study P00693 design schematic

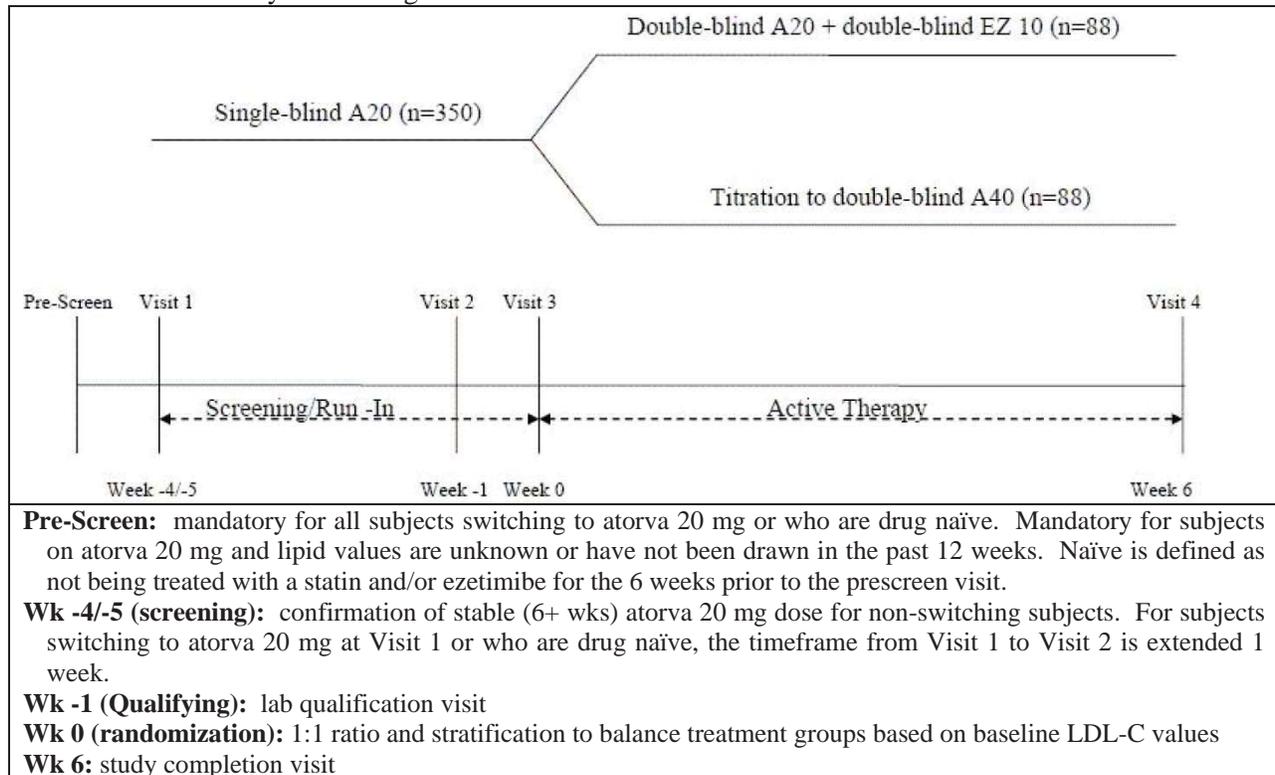


Notes:

- a: Q1 and Q2 = The first and second qualifying LDL-C, respectively, using the Friedewald calculation; Q1 and Q2 must be drawn at least 1 week apart.
- b: Randomization to double-blind treatment occurs at Visit 4.
- c: Subjects randomized to receive ezetimibe (Group A) not achieving LDL-C target (100 mg/dL or less) after 4 weeks (Visit 6) and/or 9 weeks (Visit 7) of therapy will have their total atorvastatin dose doubled at Week 5 (Visit 6) and/or Week 10 (Visit 7). Therefore, the maximum possible total daily dose of atorvastatin received in this group will be 40 mg (10 mg open label plus 30 mg blinded).
- d: Subjects randomized to receive blinded atorvastatin 10 mg (Group B) not achieving LDL-C target after 4 weeks (Visit 6) and/or 9 weeks (Visit 7) of therapy will have their total atorvastatin dose doubled at Week 5 (Visit 6) and/or Week 10 (Visit 7). Therefore, the maximum possible total daily dose of atorvastatin received in this group will be 80 mg (10 mg open label plus 70 mg blinded).

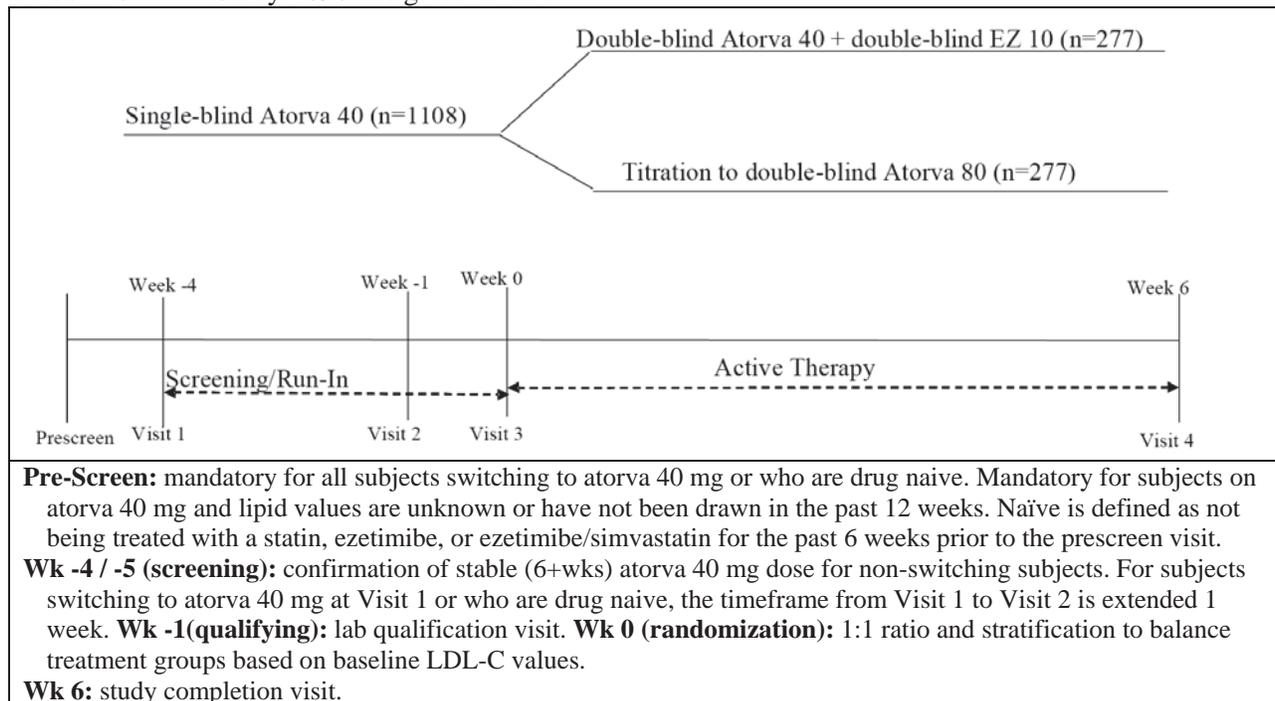
Source: Study P00693 study report, Figure 1

FIGURE 2 Study P079 design schematic



Source: Study P079 clinical report, Figure 9-1

FIGURE 3 Study P090 design schematic



Source: Study 090 clinical report, Figure 9-1

**3.2.2B Subject Disposition, Demographic and Baseline Characteristics**

The large majority of subjects, over 90% in each study, completed the treatment period (14 weeks in Study P693 and 6 weeks in Studies P079 and P090 (TABLE 10 - TABLE 12). The baseline characteristics of subjects in each study are summarized in (TABLE 13 - TABLE 15).

TABLE 10 Study P693; Overall disposition of subjects with respect to the 14-week treatment period

	Ezetimibe 10 mg + Atorvastatin 10 mg		Atorvastatin 20 mg		Total	
Discontinued before randomization					1226	
Randomized	305		316		621	
Completed	278	91.1%	290	91.8%	568	91.5%
Discontinued	27	8.9%	26	8.2%	53	8.5%
Adverse event	13	4.3%	14	4.4%	27	4.3%
Noncompliance with protocol	9	3.0%	5	1.6%	14	2.3%
Lost to follow-up	3	0.1%	1	<0.1%	4	0.1%
Did not wish to continue	2	0.1%	6	1.9%	8	1.3%

Source: Study P693 clinical report, Tables 6 and 7

TABLE 11 Study P079; Overall disposition of subjects with respect to the 6-week treatment period

	Ezetimibe 10 mg + Atorvastatin 20 mg		Atorvastatin 40 mg		Total	
Screen failures					1151	
Randomized	98		98		196	
Completed	92	93.9%	91	92.9%	183	93.4%
Discontinued	6	6.1%	7	7.1%	13	6.6%
Adverse event	0	0.0%	2	2.0%	2	1.0%
Deviation from protocol	4	4.1%	3	3.1%	7	3.6%
Lost to follow-up	2	2.0%	2	2.0%	4	2.0%

Source: Study P079 clinical report, Table 10-2

TABLE 12 Study P090; Overall disposition of subjects with respect to the 6-week treatment period

	Ezetimibe 10 mg + Atorvastatin 40 mg		Atorvastatin 80 mg		Total	
Screen failures					1541	
Randomized	288		291		579	
Completed	279	96.9%	278	95.5%	557	96.2%
Discontinued	9	3.1%	13	4.5%	22	3.8%
Adverse event	4	1.4%	7	2.4%	11	1.9%
Deviation from protocol	0	0.0%	1	0.3%	1	0.2%
Lost to follow-up	1	0.3%	1	0.3%	2	0.3%
Other	0	0.0%	1	0.3%	1	0.2%
Withdrew consent	4	1.4%	3	1.0%	7	1.2%

*Source:* Study P090 clinical report, Table 10-2

TABLE 13 Study P693; Demographic and baseline characteristics

	Ezetimibe 10 mg + Atorvastatin 10 mg n=305	Atorvastatin 20 mg n=316
Gender		
Male	159 (52%)	171 (54%)
Female	146 (48%)	145 (46%)
Age (years)		
Mean (SD)	53 (12.6)	52 (13.2)
min, max	18, 82	18, 80
< 65	240 (79%)	266 (84%)
≥ 65	65 (21%)	50 (16%)
Race		
White	279 (91%)	289 (91%)
Black	6 (2%)	4 (1%)
Asian	4 (1%)	6 (2%)
Hispanic	15 (5%)	17 (5%)
Other	1 (<1%)	0 (0%)
Body Mass Index (kg/m <sup>2</sup> )		
Mean (SD)	27.1 (4.0)	27.1 (4.3)
min, max	18, 42	19, 45

*Source:* Study P693 clinical report, Table 9

TABLE 14 Study P079; Demographic and baseline characteristics

	Ezetimibe 10 mg + Atorvastatin 20 mg n=98	Atorvastatin 40 mg n=98	Total n=196
Gender			
Male	58 (59.2%)	49 (50.0%)	107 (54.6%)
Female	40 (40.8%)	49 (50.0%)	89 (45.4%)
Age (years)			
Mean (SD)	56.4 (10.3)	58.0 (9.7)	57.2 (10.0)
min, max	24, 78	34, 76	24, 78
< 65	77 (78.6%)	69 (70.4%)	146 (74.5%)
≥ 65	21 (21.4%)	29 (29.6%)	50 (25.5%)
Race			
White	58 (59.2%)	60 (61.2%)	118 (60.2%)
Black	3 (29.6%)	9 (9.2%)	12 (6.1%)
Asian	7 (7.1%)	8 (8.2%)	15 (7.7%)
American Indian or Alaska Native	1 (1.0%)	0 (0.0%)	1 (0.5%)
Multi-Racial	29 (29.6%)	21 (21.4%)	50 (25.5%)
Body Mass Index (kg/m <sup>2</sup> )			
< 30	68 (69.4%)	63 (64.3%)	131 (66.8%)
≥ 30	29 (29.6%)	35 (35.7%)	64 (32.7%)
Missing	1 (1.0%)	0 (0.0%)	1 (0.5%)
Visit 2 LDL-C strata:			
≥ 100 and < 130 mg/dL	76 (77.6%)	76 (77.6%)	152 (77.6%)
≥ 130 and ≤ 160 mg/dL	22 (22.4%)	22 (22.4%)	44 (22.4%)

Source: Study P079 clinical report, Tables 10-7 and 10-9

TABLE 15 Study P090: Demographic and baseline characteristics

	Ezetimibe 10 mg + Atorvastatin 40 mg n=288	Atorvastatin 80 mg n=291	Total n=579
<b>Gender</b>			
Male	173 (60.1%)	178 (61.2%)	351 (60.6%)
Female	115 (39.9%)	113 (38.8%)	228 (39.4%)
<b>Age (years)</b>			
Mean (SD)	60.6 (9.9)	62.0 (9.3)	61.3 (9.6)
min, max	31, 80	34, 79	31, 80
< 65	183 (63.5%)	163 (56.0%)	346 (59.8%)
≥ 65	105 (36.5%)	128 (44.0%)	233 (40.2%)
<b>Race</b>			
White	237 (82.3%)	232 (79.7%)	469 (81.0%)
Black	32 (11.1%)	29 (10.0%)	61 (10.5%)
Asian	4 (1.4%)	8 (2.7%)	12 (2.1%)
Multi-Racial	15 (5.2%)	22 (7.6%)	37 (6.4%)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
< 30	138 (47.9%)	135 (46.4%)	273 (47.2%)
≥ 30	150 (52.1%)	154 (52.9%)	304 (52.5%)
Missing	0 (0.0%)	2 (0.7%)	2 (0.3%)
<b>Visit 2 LDL-C strata:</b>			
≥ 70 and < 100 mg/dL	224 (77.8%)	225 (77.3%)	449 (77.5%)
≥ 100 and < 130 mg/dL	59 (20.5%)	60 (20.6%)	119 (20.6%)
≥ 130 and ≤ 160 mg/dL	5 (1.7%)	6 (2.1%)	11 (1.9%)

Source: Study P090 clinical report, Tables 10-7 and 10-9

### 3.2.3B Statistical Methodologies

Studies P079 and P090 were both conducted in 2006-2008 and they shared the same or very similar statistical analysis plan. Study P693 was conducted in 2000-2001, with an analysis plan that is different from the other two studies in some substantial ways. (b) (4)

(b) (4) For this reason, I chose to describe and critique the statistical methods for all three studies together, topic by topic. Because the primary endpoint for Study P693 is a categorical version of the LDL-C endpoint, while the primary endpoint for Studies P079 and P090 is the continuous version, I have organized the descriptions by type of endpoint rather than by whether the endpoint is primary or secondary. I address the issue of primary and secondary endpoints in the discussion of the protection of Type I error (b) (4)

Analysis populations:

*Study P693:* The primary analysis included all randomized subjects with at least one post-baseline lipid determination. This was termed the “intent-to-treat” (ITT) population. For the primary responder endpoint at week 14, subjects who dropped out earlier than the 14-week endpoint were classified as non-responders. The LDL-C-responder status was also assessed at intermediate time points (weeks 2, 4 and 9), and the same non-responder rule was applied to these intermediate time points. For the secondary continuous LDL-C endpoint at week 4, subjects who dropped out prior to week 4 would only be in the ITT analysis set if they had a LDL-C value for week 2. If so, the LDL-C value at week 2 was applied to the week 4 endpoint.

The analysis plan also described an “evaluable subject subset” defined as randomized subjects who met key eligibility and evaluability criteria determined before database closure. This subset excluded subjects and/or data points with clinically important deviations from protocol specified criteria. The purpose of this subset was to provide confirmatory efficacy analyses.

*Studies P079 and P090:* The primary analysis of efficacy was based on the Full Analysis Set (FAS), which included all randomized subjects who took at least one dose of study medication, had a baseline value and at least one post baseline value. Because there were no intermediate measurements of LDL-C (or other lipids), the FAS set did not include subjects who dropped out prior to the week 6 endpoint. This means that an imputation rule for missing data would not be needed.

The analysis plan also defined a per protocol (PP) population that excluded all subjects who met any of the criteria for protocol violations.

Analysis of the “responder” (categorical) version of LDL-C endpoint:

*Study P693:* “Responders” were subjects who achieved the target LDL-C goal of  $\leq 100$  mg/dL after 14 weeks of treatment. The primary analysis was a chi-square test between the two treatment arms. A 95% confidence interval was calculated from the difference of proportions between the two treatment arms. Subjects who dropped out before the 14-week endpoint were classified as non-responders.

*Studies P079 and P090:* “Responders” in Study P079 achieved the target goal of  $< 100$  mg/dL after 6 weeks of treatment. In Study P090, the target goal was  $< 100$  mg/dL after 6 weeks of treatment. The primary analysis was a logistic regression model including terms for treatment and baseline LDL-C. The treatment comparison was expressed as an odds ratio along with a 95% confidence interval for the odds ratio. No imputation rule was needed for dropouts because the FAS analysis set included completers only.

Analysis of the continuous version of the LDL-C endpoint:

*Study P693:* The percentage change in LDL-C from baseline at week 4 was analyzed by an analysis of variance model with “treatment” as a factor. Subjects who discontinued prior to week 4 were included in the ITT analysis set only if they had an LDL-C endpoint at week 2. If so, the value of LDL-C at week 2 was used to represent the week 4 level.

*Studies P079 and P090:* The percentage change in LDL-C from baseline at week 6 was analyzed by an analysis of covariance model with terms for treatment and baseline LDL-C. Subjects who discontinued prior to week 4 were not included in the FAS analysis set because there were no intermediate post-baseline determinations of lipids in these studies.

#### Definition of baseline for LDL-C:

*Study P693:* The baseline was defined as the average of the last three values prior and including the week 0 visit. This includes week -2, -1 and 0. If a value of a lipid parameter at one or two of the three visits was missing, the baseline value was the average of the non-missing values for those visits.

*Studies P079 and P090:* The baseline was defined as the average of week -1 and day 1 (predose). If either observation was missing, the available measurement was used.

#### Analysis of other secondary lipid endpoints:

*Study P693:* The analysis of variance model for the continuous LDL-C endpoint was applied to other continuous endpoints. The analysis approach to the categorical LDL-C endpoint was also applied to other categorical endpoints.

*Studies P079 and P090:* The analysis of covariance mode for the continuous LDL-C endpoint was also applied to other continuous endpoints, with the exception of TG and hs-CRP. The analysis plan described a nonparametric approach to the analysis of TG, and a specific longitudinal data analysis method for hs-CRP. More details of each of these approaches are available in the statistical analysis plan. The logistic regression analysis of the categorical LDL-C endpoint was also applied to other categorical endpoints.

#### Protection of Type I error: Primary LDL-C endpoint

*Study P693:* The primary endpoint was the percent of subjects achieving target LDL-C after 14 weeks of treatment.

*Studies P079 and P090:* The primary endpoint was the percent change from baseline in LDL-C after 6 weeks of treatment.

For all three studies, the applicant noted that the primary study hypothesis consisted of a single treatment comparison of one variable at one time point. For this reason, no alpha adjustment was used for the primary study hypothesis in each study.

### Protection of Type I error: Secondary lipid endpoints

Secondary lipid endpoints are clinically important in the evaluation of drugs for hyperlipidemia. For this reason, these endpoints are typically included in the indication. (b) (4)

Because of their clinical importance, I believe that the statistical evaluation of these endpoints should be controlled for Type I error. This is not the case in Studies P693, P079 and P090. However, these clinical studies are not pivotal to the approval or to the indication for Atozet. The support for the Atozet indication is derived from the original indications for Zetia™ and Lipitor™. For this reason, the review of secondary lipid endpoints in Studies P693, P079 and P090 is focused on the summaries of these studies in the Atozet label.

*Study P693:* The analysis plan identified two key secondary endpoints: (1) the mean percent change from baseline in direct LDL-C at week 4; and (2) the proportion of subjects achieving target LDL-C target after 4 weeks of treatment. However, the applicant stated that all other analyses were viewed as supportive of the primary analysis. The analysis plan did not include a method for the protection of Type I error in other endpoints and analyses.

*Studies P079 and P090:* The analysis plan defined three families of lipoproteins: 1) LDL-C lipoproteins (8 variables); 2) HDL-C lipoproteins (10 variables), and 3) Other lipoproteins (15 variables). Within each family, the applicant applied a false discovery rate (FDR) procedure. This procedure controls the expected proportion of false positives within the family of comparisons (Benjamini and Hochberg, 1995).<sup>2</sup> Results were reported with both the nominal p-values and the FDR-adjusted p-values. However, this approach does not control Type I error across the set of key endpoints and comparisons that are described in the Atozet label. For this reason, I believe that the use of the FDR procedure in Studies P079 and P090 has limited relevance to the evaluation of key lipid endpoints.

### **3.2.4B Results and Conclusions**

The summary statistics of the lipid results for studies P693, P079 and P090 are reported accurately in tables of the proposed label for Atozet (TABLE 16 - TABLE 18). The comparisons between the ezetimibe + atorvastatin combination arm and the atorvastatin arm in each study were significantly different in the direction of superiority of the combination arm for LDL-C, Total-C, TG and non-HDL-C in all three studies, and in Apo-B in Studies P079 and P090 (Apo-B was not evaluated in Study P693). The nominal p-values for these comparisons were < 0.001. The p-values of these comparisons may be low enough to overcome review concerns about the lack of a pre-specified plan to control Type I error in the statistical evaluation of clinically

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<sup>2</sup> Benjamini Y and Hochberg Y, 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B*; 57: 289-300.

important endpoints. The treatment comparisons for HDL-C had p-values  $> 0.05$  in each study (TABLE 16 - TABLE 18).

The “responder” version of the LDL-C endpoint was also significantly different between the treatment arms in the direction of superiority in each study (TABLE 19). These results are described in the text of the proposed label for Atozet (and are not summarized in a table). This endpoint at week 14 was the primary endpoint, and the pre-specified analysis showed a significant difference between treatment arms. However, the proposed label describes this endpoint at week 4, probably because this time frame is more comparable to the results at week 6 from Studies P079 and P090.

An excerpt of the proposed label text used to describe the conclusions of Study 693 is as follows: “Atozet 10/10 was significantly more effective than doubling the dose of atorvastatin to 20 mg in further reducing total-C, LDL-C, TG and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different. (See Table 8). In addition, at Week 4 significantly more patient receiving Atozet 10/10 attained LDL-C  $< 100$  mg/dL ( $< 2.6$  mmol/L) compared to those receiving atorvastatin 20 mg, 12% vs. 2%.” The conclusions of Study P079 and Study P090 are described in a similar way. The use of the term “significantly,” representing findings with nominal p-values of  $p < 0.001$ ” may be acceptable.

The results from a similarly designed study from the Vytorin label were described as follows: “Vytorin 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg.” The study results were not summarized in a table, but were reported in the label text, as follows: “The median percent changes from baseline for Vytorin vs. simvastatin were: LCL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.” The medians were reported instead of the means on the basis of a recommendation by Dr. Sahlroot (the statistical reviewer for the Vytorin submission), because he found that the % change data were not normally distributed. Dr. Sahlroot also noted that the mean and median treatment differences were similar and highly significant, with (nominal) p-values  $< 0.001$ . In this review, I did not evaluate the error distribution of the % change data from Studies P693, P079 and P090. For this reason, I do not know how the median compares with the mean as a summary statistic in these studies. However, I note that the use of a nominal p-value of  $p < 0.001$  to support for the label text use of the term “significantly” in the Atozet label is similar to its use in the Vytorin label.

TABLE 16 Study P693; Lipid results at Week 4 (proposed for inclusion in the Atozet label)<sup>1</sup>

		Total-C	LDL-C <sup>2</sup>	HDL-C	TG <sup>3</sup>	non-HDL-C
Eze 10 mg + Ator 10 mg N=305	Baseline mean (SD)	262.0 (47.3)	185.9 (47.3)	50.0 (12.3)	median 117.3 mean 130.6	212.1 (47.3)
	% change from baseline at week 4	-17.3	-23.8	+2.1	median -9.3 mean -6.1	-22.0
	<b>Proposed label summary:</b>	<b>-17</b>	<b>-24</b>	<b>+2</b>	<b>-9</b>	<b>-22</b>
Ator 20 mg N=316	Baseline mean (SD)	264.2 (48.0)	186.8 (46.3)	49.9 (12.5)	median 118.8 mean 137.3	214.3 (49.8)
	% change from baseline at week 4	-6.1	-9.0	+1.3	median -3.9 mean +1.78	-7.8
	<b>Proposed label summary:</b>	<b>-6</b>	<b>-9</b>	<b>+1</b>	<b>-4</b>	<b>-8</b>
Difference between Eze 10 mg + Ator 10 mg and Ator 20 mg	Difference in % change from baseline 95% CI <sup>3</sup>	-11.3 (-12.8, -9.7)	-14.9 (-16.9, -12.8)	+0.9 (-0.7, +2.5)	mean -7.9 (-12.1, -3.7)	-14.2 (-16.2, -12.3)
	pooled standard deviation	9.5	12.5	9.9	26.1	11.7
	p-value <sup>4</sup>	<0.001	<0.001	0.28	<0.001	<0.001
<i>Notes:</i>						
<sup>1</sup> All units are mg/dL						
<sup>2</sup> Summary statistics are from the calculated LDL-C						
<sup>3</sup> The percentage change in the endpoint from baseline at week 4 was analyzed by an analysis of variance model with “treatment” as a factor.						
<sup>4</sup> The applicant reported low p-values as p<0.01. I calculated these out to the 3rd decimal place based on the pooled standard deviation in the data listings.						
<i>Sources (from Study P693 clinical report):</i>						
	Table 21 and Section 14.2.2.3.1.1	Table 19 and Section 14.2.2.1.3.1.1	Table 25 and Section 14.2.2.2.1.1.1	Table 23 and Section 14.2.2.4.1.1	Table 27 and Section 14.2.2.6.1	

TABLE 17 Study P079; Lipid results at the Week 6 endpoint (proposed for inclusion in the Atozet label)<sup>1</sup>

		Total-C	LDL-C	Apo-B	HDL-C	TG <sup>3</sup>	non-HDL-C
Eze 10 mg + Ator 20 mg N = 92	Baseline mean (SD)	203.4 (25.2)	120.3 (19.7)	123.4 (22.5)	50.9 (12.2)	154.8 (71.9)	152.4 (24.3)
	% change from baseline at week 6	-19.7	-30.8	-21.4	+3.2	-17.8	-26.7
	<b>Proposed label summary:</b>	<b>-20</b>	<b>-31</b>	<b>-21</b>	<b>+3</b>	<b>-18</b>	<b>-27</b>
Ator 40 mg N = 92	Baseline mean (SD)	200.5 (22.0)	118.1 (17.2)	120.0 (21.2)	52.1 (11.7)	147.5 (77.4)	148.5 (21.6)
	% change from baseline at week 6	-7.4	-10.9	-7.7	+0.8	-5.5	-10.2
	<b>Proposed label summary:</b>	<b>-7</b>	<b>-11</b>	<b>-8</b>	<b>+1</b>	<b>-6</b>	<b>-10</b>
Difference between Eze 10 mg + Ator 20 mg and Ator 40 mg	Difference in % change from baseline 95% CI <sup>2</sup> p-value	-12.2 (-15.8, -8.6) p<0.001	-19.9 (-25.2, -14.5) p<0.001	-13.7 (-17.8, -9.6) p<0.001	+2.4 (-1.9, +6.6) p=0.270	-8.9 (-17.7, -0.4) p<0.001	-16.4 (-21.2, -11.7) p<0.001
<i>Notes:</i>							
<sup>1</sup> All units are mg/dL							
<sup>2</sup> The percentage change from baseline at week 6 was analyzed by an analysis of covariance model with terms for treatment and baseline.							
<sup>3</sup> For TG, the median and robust SD are reported. The 95% CI and p-value are from a non-parametric analysis of variance							
<i>Sources (from Study P079 clinical report):</i> Table 11-5      Table 11-1      Table 11-7      Table 11-3      Table 11-6      Table 11-4							

TABLE 18 Study P090; Lipid results at the Week 6 endpoint (proposed for inclusion in the Atozet label)<sup>1</sup>

		Total-C	LDL-C	Apo-B	HDL-C	TG <sup>2</sup>	non-HDL-C
Eze 10 mg + Ator 40 mg N = 277	Baseline mean (SD)	165.0 (21.5)	88.6 (16.3)	101.1 (18.8)	47.7 (10.6)	131.0 (72.1)	117.4 (20.8)
	% change from baseline at week 6	-16.9	-27.4	-17.8	-0.5	-12.3	-23.3
	<b>Proposed label summary:</b>	<b>-17</b>	<b>-27</b>	<b>-18</b>	<b>0</b>	<b>-12</b>	<b>-23</b>
Ator 80 mg N = 279	Baseline mean (SD)	164.9 (23.0)	89.7 (16.0)	102.0 (18.5)	46.9 (10.4)	135.5 (71/6)	118.0 (22.0)
	% change from baseline at week 6	-6.9	-11.0	-7.7	-1.0	-5.9	-9.0
	<b>Proposed label summary:</b>	<b>-7</b>	<b>-11</b>	<b>-8</b>	<b>-1</b>	<b>-6</b>	<b>-9</b>
Difference between Eze 10 mg + Ator 40 mg and Ator 80 mg	Difference in % change from baseline	-10.0 (-12.0, -7.9)	-16.3 (-19.4, -13.2)	-10.1 (-12.7, -7.6)	+0.5 (-1.1, +2.1)	-7.3 (-11.5, -3.1)	-14.3 (-17.1, -11.6)
	95% CI						
	p-value	p<0.001	p<0.001	p<0.001	p=0.551	p<0.001	p<0.001
<i>Notes:</i>							
<sup>1</sup> All units are mg/dL							
<sup>2</sup> For TG, the median and robust SD are reported. The 95% CI and p-value are from a non-parametric analysis of variance							
<i>Sources (from Study P079 clinical report):</i> Table 11-5      Table 11-1      Table 11-6      Table 11-3      Table 11-6      Table 11-4							

TABLE 19 Studies P693, P079 and P090; Percentage of subjects who attained the target LDL-C goal of the study

	N	Target LDL-C goal, analysis population	Number (%) of subjects who attained target LDL-C goal, <b>% reported in the text of the proposed Atozet label</b>	Statistical comparison between Atorva + EZ and Atorva arms.		
				Difference between percentages	95% CI of difference between percentages	p-value <sup>1</sup>
Study P693		≤ 100 mg/dL at week 14				
Ezetimibe 10 mg + Atorvastatin 10 mg	305	ITT population	67 (22.0%)	14.7%	(9.2%, 20.1%)	<0.01
Atorvastatin 20 mg	316		23 (7.3%)			
		≤ 100 mg/dL at week 4 <sup>2</sup>	37 (12.1%), <b>12%</b> 5 (1.6%), <b>2%</b>	10.6%	(6.7%, 14.9%)	<0.001
Study P079		< 100 mg/dL at week 6		Adjusted odds ratio from logistic model <sup>3</sup>	95% CI for odds ratio	p-value
Ezetimibe 10 mg + Atorvastatin 20 mg	92	FAS population	78 (83.7%), <b>84%</b>			
Atorvastatin 40 mg	92		45 (48.9%), <b>49%</b>	8.6	(3.8, 19.5)	< 0.001
Study P090		< 70 mg/dL at week 6				
Ezetimibe 10 mg + Atorvastatin 40 mg	277	FAS population	204 (73.6%), <b>74%</b>			
Atorvastatin 80 mg	479		88 (31.5%), <b>32%</b>	8.4	(5.5, 12.8)	<0.001
<i>Notes:</i>						
<sup>1</sup> Study P693: The p-value is based on a chi-square test, and the 95% CI is from the difference of two binomial proportions (asymptotic method)						
<sup>2</sup> Study P693: Analysis by this reviewer following the methods pre-specified for the primary (week 14) endpoint						
<sup>3</sup> Studies P090 and P079: The summary statistics and p-values are based on the logistic model with terms for treatment and baseline LDL-C						
<i>Sources:</i> Study P693: Table 12 and Section 14.2.2.1.2 Studies P090, P079: Table 11-2						

### **3.3B Evaluation of Safety**

For an evaluation of safety issues of clinical studies of the co-administered ezetimibe + atorvastatin combination, see the clinical review by Dr. Chowdhury.

## **4B Findings In Special/Subgroup Populations**

### **4.1B Gender, Race, Age and Region**

Results for the “responder” version of the LDL-C endpoint, evaluated at week 14 in Study P693, support the interpretation that the comparison between ezetimibe 10 mg + atorvastatin 10 mg and atorvastatin 20 mg was generally consistent among subgroups defined by gender, age and race (TABLE 20).

Results from the continuous version of the LDL-C endpoint, evaluated at week 6 in Study P079 and P090, were generally consistent among subgroups defined by age, gender, race and region (FIGURE 4 and FIGURE 6; the region effect defined by “US / non-US” was evaluated in Study P079 only).

### **4.2B Other Special/Subgroup Populations**

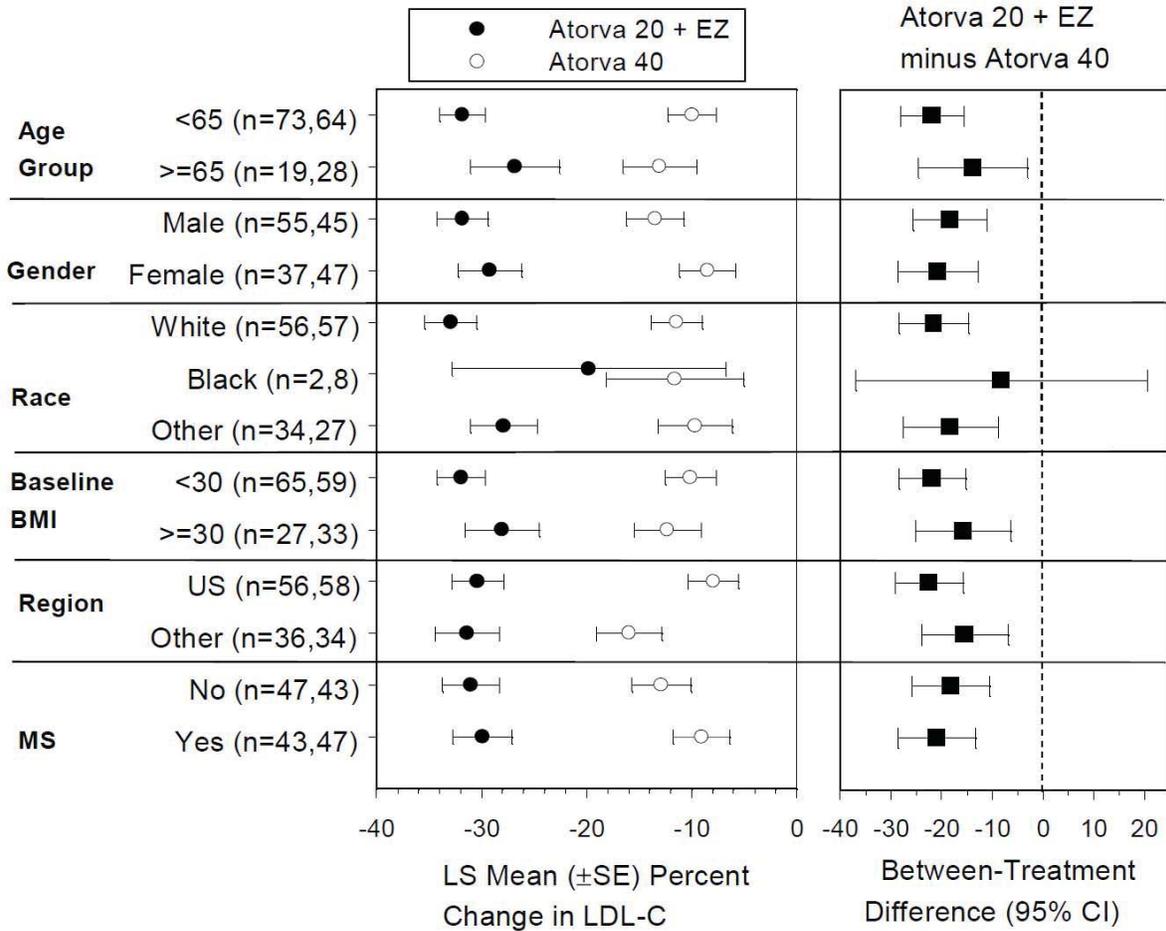
The consistency of the effect of ezetimibe + atorvastatin combinations compared with the doubled dose of atorvastatin was demonstrated in the following subgroups:

- Baseline body mass; Study P693 TABLE 20; Study P693 FIGURE 4; and P090 FIGURE 6
- Baseline LDL-C (the levels used for stratification); Study P079 FIGURE 5; Study P090 FIGURE 7
- Baseline HDL-C; Study P079 FIGURE 5; Study P090 FIGURE 7
- Baseline TG ; Study P079 FIGURE 5; Study P090 FIGURE 7
- The occurrence of metabolic syndrome at baseline (Study P079 FIGURE 4; Study P090 FIGURE 7)
- The occurrence of diabetes at baseline; Study P090 FIGURE 7
- The co-occurrence of metabolic syndrome and diabetes at baseline; Study P090 FIGURE 7

TABLE 20 Study P693; Subgroup analysis of the number of subjects reaching target LDL-C goal at week 14 (ITT population)

	Ezetimibe 10 mg + Atorvastatin 10 mg	Atorvastatin 20 mg	Ezetimibe 10 mg + Atorvastatin 10 mg vs. Atorvastatin 20 mg Point estimate (95% CI)
<b>Gender</b>			
Male	40/159 (25%)	10/171 (6%)	19 (12, 27)
Female	27/146 (18%)	13/145 (9%)	10 (2, 17)
<b>Age</b>			
< 65	47/240 (20%)	17/266 (6%)	13 (7, 19)
≥ 65	20/65 (31%)	6/50 (12%)	19 (4, 33)
<b>Race</b>			
Caucasian	60/279 (22%)	20/289 (7%)	15 (9, 20)
Non-Caucasian	7/26 (27%)	3/27 (11%)	16 (-5, 37)
<b>Body Mass Index</b>			
< 30 kg/m <sup>2</sup>	57/243 (23%)	20/242 (8%)	15 (9, 22)
≥ 30 kg/m <sup>2</sup>	9/60 (15%)	3/74 (4%)	11 (1, 21)
<i>Source:</i> Study P693 clinical report, Section 14.2.2.1.2.1			

FIGURE 4 Study P079; Percent change from baseline in LDL-C (mg/dL) at week 6 by subgroup age, gender, race, BMI, region and metabolic syndrome (FAS population)



Source: Study P079 clinical report, Figure 11-1

FIGURE 5 Study P079; Percent change from baseline in LDL-C (mg/dL) at week 6 by subgroup baseline LDL-C, HDL-C and TG

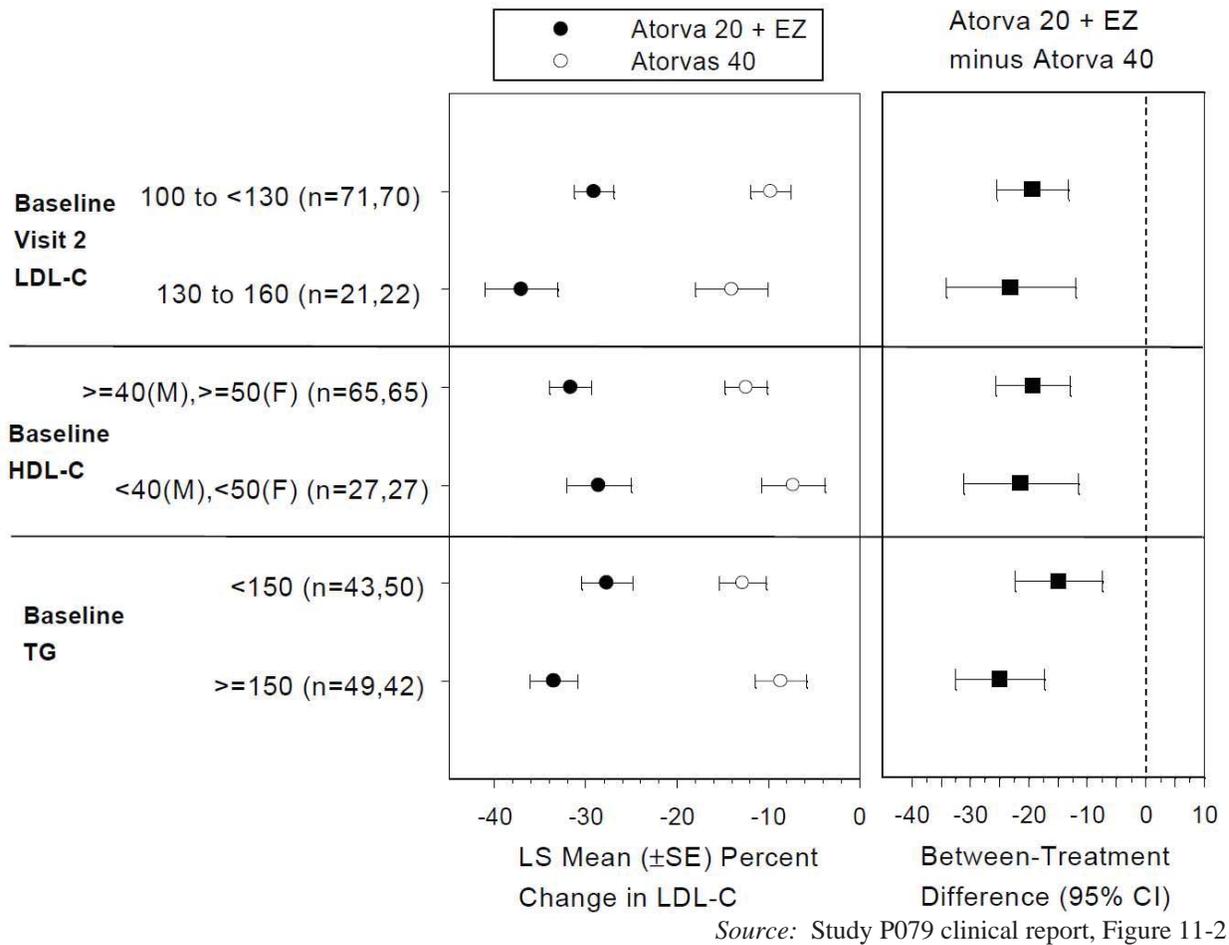
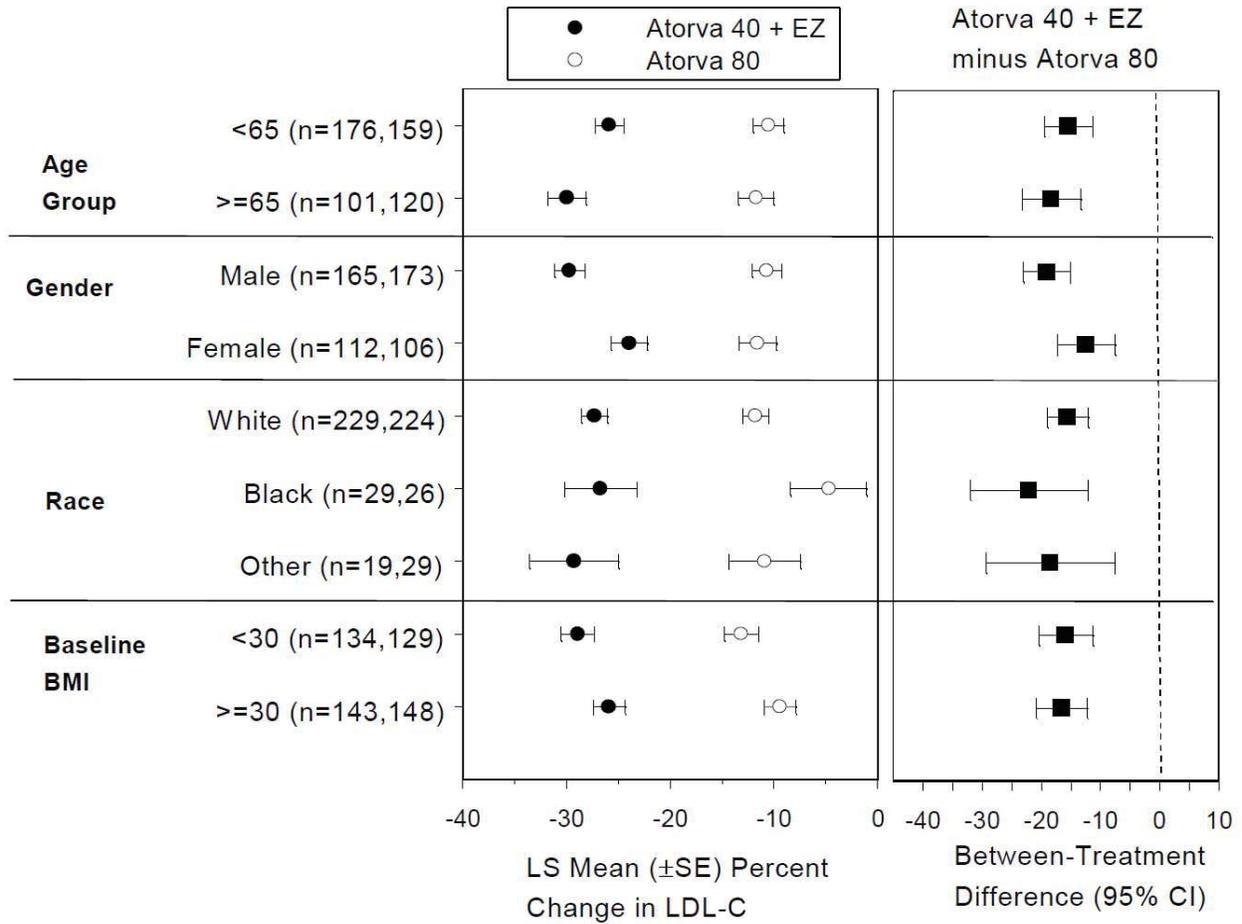
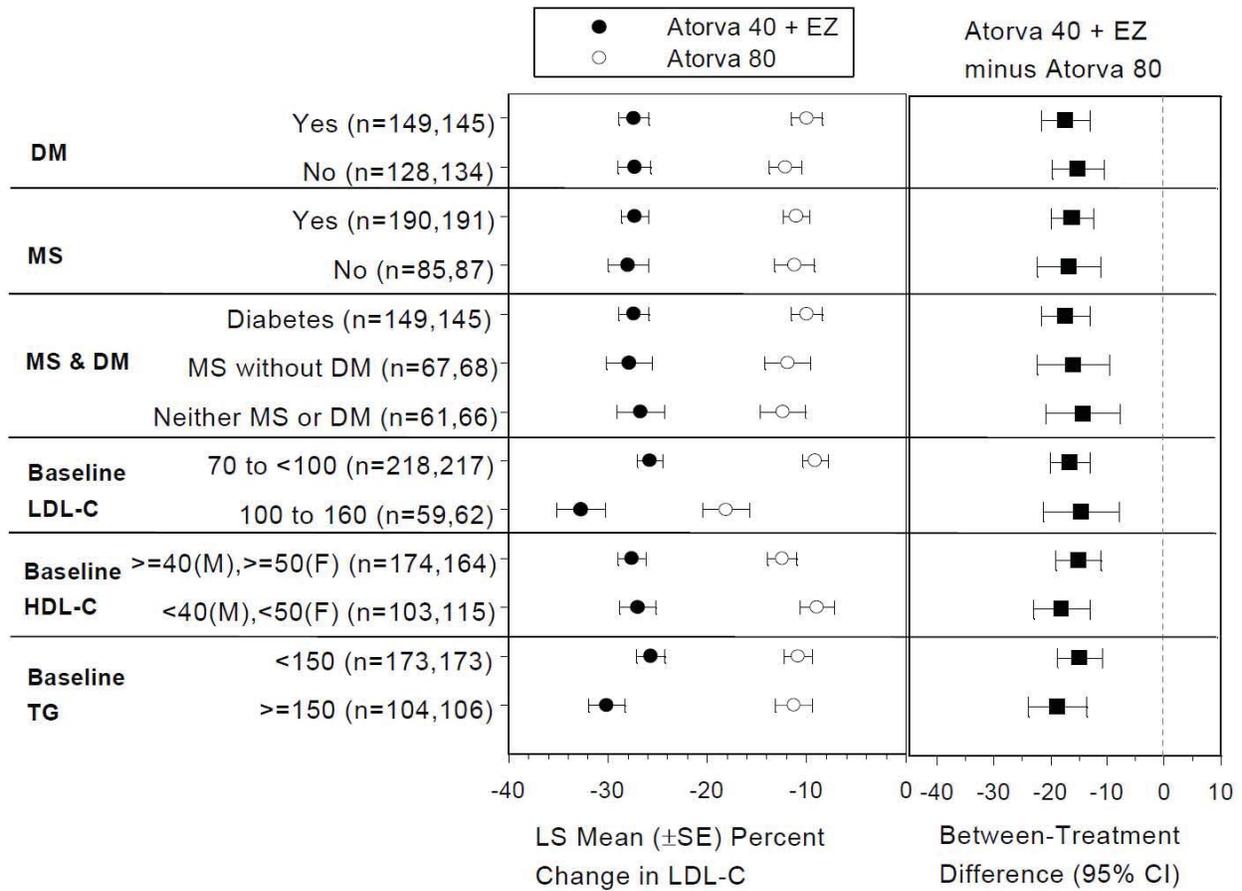


FIGURE 6 Study P090; Percent change from baseline in LDL-C (mg/dL) at week 6 by subgroup age, gender, race and BMI (FAS population)



Source: Study P090 clinical report, Figure 11-1

FIGURE 7 Study P090; Percent change from baseline in LDL-C (mg/dL) at week 6 by subgroup diabetes, metabolic syndrome, and baseline LDL-C, HDL-C and TG (Full analysis set population)



Source: Study P090 clinical report, Figure 11-2

### **C. Long-term extension in patients with Homozygous Familial Hypercholesterolemia: Study P1417, LTE of Study P1030.**

The primary objective of the long-term extension Study P1417 was to evaluate the long-term safety and tolerability of ezetimibe 10 mg dosed daily co-administered with either atorvastatin or simvastatin 40-80 mg dosed daily for up to 24 consecutive months in subjects with Homozygous Familial Hypercholesterolemia.

#### **3C Statistical Evaluation**

##### **3.1C Data and Analysis Quality**

I did not evaluate data and analysis quality in the Study P1417.

##### **3.2C Evaluation of Efficacy**

###### **3.2.1C Study Design and Endpoints**

Study P1417 was a 24-month, multicenter study that was an extension of Study P1030. Study P1030 enrolled 50 subjects, of whom 48 completed the 12-week randomized, double-blind study in which they received ezetimibe 10 mg co-administered with either atorvastatin or simvastatin (TABLE 21). Forty-four subjects continued to the extension study, 35 of whom received open-label ezetimibe 10 mg co-administered with atorvastatin 40 mg and 7 received ezetimibe 10 mg co-administered with simvastatin 40 mg for up to 24 months. Subjects continued with the same statin as had been assigned in Study P1030 (TABLE 21). The atorvastatin or simvastatin dose was doubled if an LDL-C target concentration of 100 mg/dL was not achieved after at least 1 month of treatment. Study visits were scheduled at months 1, 3, 6, 9, 12, 18, and 24. Additional visits were scheduled 4 and 12 weeks after upward dose titration of atorvastatin or simvastatin. A schematic of the design for Study P2154 as an extension of Study P0692 is shown in FIGURE 8.

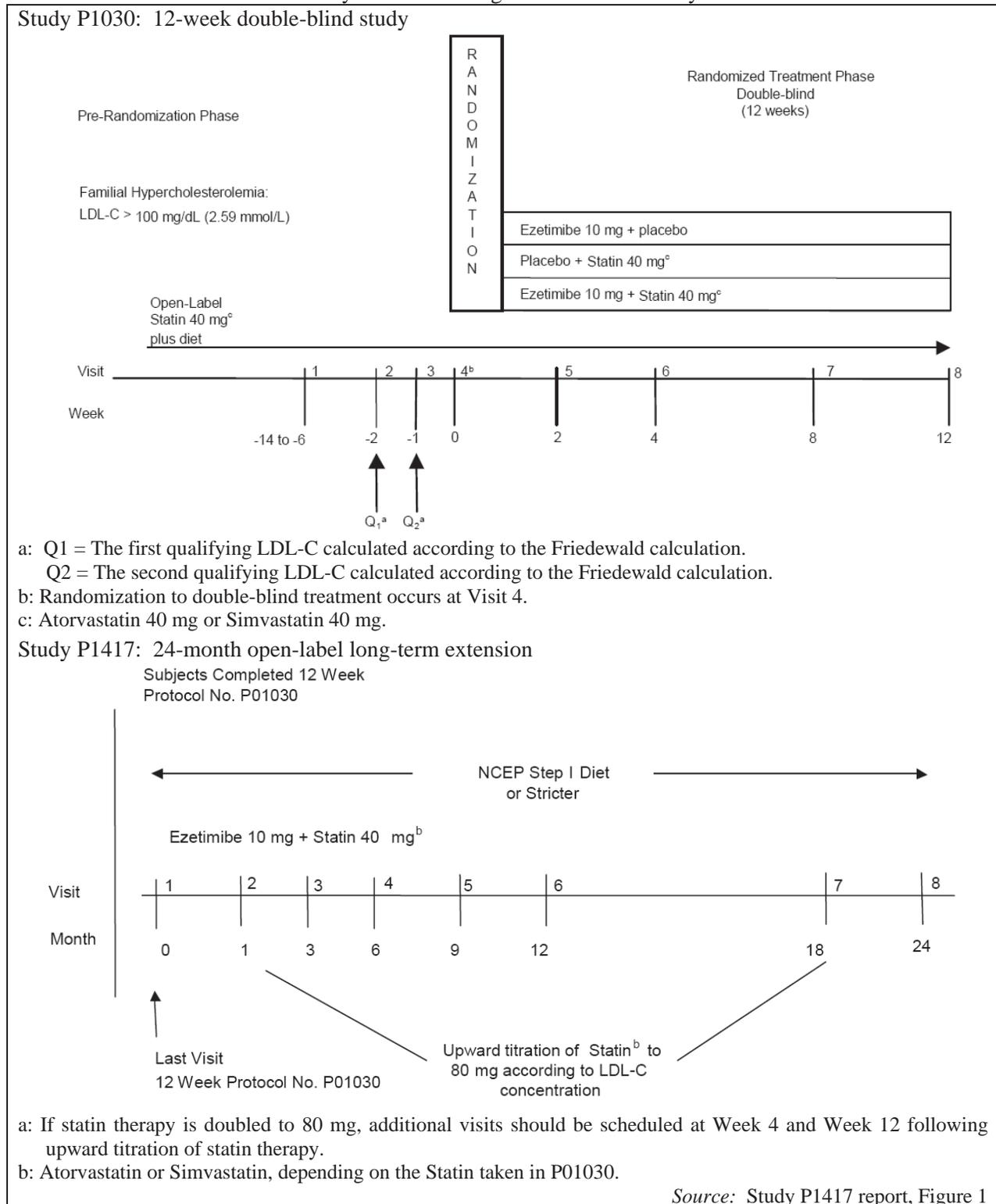
Study P1417 was conducted at 5 sites (11 subjects) in the U.S. and 6 countries outside the U.S.: Canada (1 site, 8 subjects); South Africa (2 sites, 7 subjects); Italy (2 sites, 7 subjects); France (1 site, 5 subjects); and Germany (1 site, 2 subjects). The study period was 5/3/2000 through 8/1/2003.

TABLE 21 Randomization in Study P1417 based on assignment in Study P1030

Assignment in Study P1030 (12-week double-blind treatment period)					Assignment in P1417: (open-label for up to 24 months)	
Treatment arms	n Started	n Finished		n Started	Treatment arms	
Atorvastatin 80 mg	12	12	→	12	Ezetimibe 10 mg + Atorvastatin 40 mg	
EZ 10 mg + Ator 40 mg	12	11	→	11		
EZ 10 mg + Ator 80 mg	12	12	→	12		
	<u>36</u>	<u>35</u>		<u>35</u>		
Simvastatin 80 mg	5	5	→	3	Ezetimibe 10 mg + Simvastatin 40 mg	
EZ 10 mg + Sim 40 mg	4	4	→	2		
EZ 10 mg + Sim 80 mg	5	4	→	4		
	<u>14</u>	<u>14</u>		<u>9</u>		
	<u>50</u>	<u>48</u>		<u>44</u>	Overall total	

Source: Study P1030 clinical report, Table 9; Study P1417 clinical report, Display A-27

FIGURE 8 Schematic for Study P1030 and long-term extension study P1417



### 3.2.2C Subject Disposition, Demographic and Baseline Characteristics

Of the 44 subjects enrolled in Study P1417, 11 subjects discontinued treatment early, 5 because of an adverse event, 3 because of non-compliance with the protocol, and 3 because they did not wish to continue. Demographic and baseline characteristics are summarized in TABLE 22.

TABLE 22 Study P1417; Demographic and baseline characteristics

	P1030/1417 All treated subjects n=44
Age (years)	
Mean (SD)	31.4 (13.8)
Min, Max	11, 74
Sex	
Female	26 (59%)
Male	18 (41%)
Race	
Caucasian	39 (89%)
Black	1 (2%)
Hispanic	4 (9%)
Baseline Values for Lipids, calculated at the start of Study P1030:	
LDL-C (mg/dL; calculated); Mean (SD)	337.2 (120.8)
Total Cholesterol (mg/dL); Mean (SD)	398.5 (123.7)
Triglycerides (mg/dL); Mean (SD)	105.9 (54.7)
HDL-C (mg/dL); Mean (SD)	40.1 (10.1)

Source: Study P1417 clinical report, Display A-2.5

### 3.2.3C Statistical Methodologies

The baseline used in Study P1417 is the original baseline at the start of the treatment period of Study P1030. Changes from baseline of lipid parameters by visit and at study endpoint were summarized using descriptive statistics.

### 3.2.4C Results and Conclusions

I believe that the summary results from the 24-month treatment period in Study P1417 are reasonably consistent with the results from the 12-week treatment period in Study P1030 (TABLE 23). For this reason, I believe that the following proposed label statement, describing Study P1030 and the extension Study P1417, is reasonable from a statistical perspective:

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline. Increasing the dose of atorvastatin from 40 to 80 mg (n=12) produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/40 and 10/80 pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg. In those patients co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/80, n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg was produced.

After completing the 12-week study, eligible patients (n=35), who were receiving atorvastatin 40 mg at baseline, were assigned to co-administered ezetimibe and atorvastatin equivalent to ATOZET 10/40 for up to an additional 24 months. Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg. At the end of the 24 months, ATOZET (10/40 and 10/80 pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week study.

TABLE 23 Study P1030 and extension Study P1417; Lipid results expressed as mean % change from baseline at the study endpoint (12 weeks for Study P1030; 24 months for Study P1417)

	N	Total-C	LDL-C	TG	HDL-C
Study P1030 (the Atorvastatin arms)					
Atorvastatin 80 mg	12	-2	-2	-4	+5
Ezetimibe 10 mg + Atorvastatin 40 mg	12	-13	-14	-4	-6
Ezetimibe 10 mg + Atorvastatin 80 mg	12	-22	-25	-14	-4
Study P1417					
Ezetimibe 10 mg + Atorvastatin 40 mg or 80 mg	44	-12	-15	-15	+9

*Source:* Study P1417 clinical report, Table 15; Study P1030 clinical report, Part 14.2.2.1.3.2 (calculated LDL-C), Part 14.2.2.2.1.2 (HDL-C), Part 14.2.2.3.2 (Total-C), Part 14.2.2.4.2 (TG)

### 3.3C Evaluation of Safety

For an evaluation of safety issues of clinical studies of the co-administered ezetimibe + atorvastatin combination, see the clinical review by Dr. Chowdhury.

### 4C Findings In Special/Subgroup Populations

I did not evaluate the findings from Study P1417 further by subgroup.

## 5. Summary And Conclusions

### 5.1 Statistical Issues and Collective Evidence

The five studies that I covered in this review provide supportive information to the Atozet label. They are not pivotal to the approval of Atozet.

Studies P693, P079 and P090 had a similar design and are reported in a similar way to a clinical study that is reported in the Vytorin label (simvastatin + ezetimibe FDC tablets). Studies P079 and P090 had a similar statistical analysis plan which was well aligned with the proposed label summaries in terms of the primary and secondary efficacy endpoints. Study P693 was conducted earlier, and had several differences in the design and analysis of efficacy endpoints. None of the studies included a plan for the control of Type I error across the secondary efficacy endpoints that are clinically important drugs that treat hyperlipidemia. However, the low nominal p-values from the comparison of the ezetimibe + atorvastatin arm and the atorvastatin comparator arm in each study ( $p < 0.001$ ) may alleviate concerns about multiplicity.

### 5.2 Conclusions

Study P0692: The applicant proposes to include the following statement regarding the lipid results from Study P0692 in the Atozet label: “The changes in lipid endpoints after an additional 48 weeks of treatment with ATOZET (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.” I believe that the lipid results from Study P0692 support the inclusion of this proposed statement.

Study P693, P079, and P090: The summary statistics of the lipid results for studies P693, P079 and P090 are reported accurately in tables of the proposed label for Atozet. The comparisons between the ezetimibe + atorvastatin combination arm and the atorvastatin arm in each study were significantly different in the direction of superiority of the combination arm for LDL-C, Total-C, TG and non-HDL-C in all three studies, and in Apo-B in Studies P079 and P090 (Apo-B was not evaluated in Study P693). The p-values of these comparisons may be low enough to overcome review concerns about the lack of a pre-specified plan to control Type I error in the statistical evaluation of clinically important endpoints.

Study P1417: The applicant proposes to include the following statement regarding the lipid results from Study P1417 in the Atozet label: “At the end of the 24 months, ATOZET (10/40 and 10/80 pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week study.” I believe that the lipid results from Study P1417 support the inclusion of this proposed statement.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

**CHECK LIST**

The check list describes the three randomized studies P693, P079 and P090. The two long-term extension studies (P2154 and P1417) are not included in the checklist.

Protocol Number (s):	P693	P079	P090
Phase:	3	3	3
Control:	Atorvastatin 20 mg	Atorvastatin 40 mg	Atorvastatin 80 mg
Blinding:	Yes	Yes	Yes
Number of Centers:	37	43	74
Region(s) (Country):	US and 20 other countries	US and 3 other countries	US and Canada
Duration:	14 weeks (double blind treatment phase)	6 weeks (double blind treatment phase)	6 weeks (double blind treatment phase)
Treatment Arms:	2	2	2
Treatment Schedule:	6-10 week run-in followed by double blind treatment phase	4-5 weeks run-in followed by double blind treatment phase	4-5 weeks run-in followed by double blind treatment phase
Randomization:	Yes	Yes	Yes
Ratio:	1:1	1:1	1:1
Method of Randomization:	IVRS	IVRS, blocks of 4 within strata	IVRS, blocks of 4 within strata
If stratified, then the Stratification Factors:	No stratification factors	Baseline LDL-C levels (2 categories)	Baseline LDL-C levels (3 categories)
Primary Endpoint:	Proportion of subjects achieving the target LDL-C levels ( $\leq 100$ mg/dL) at week 14.	Percent change from baseline to week 6 in LDL-C	Percent change from baseline to week 6 in LDL-C
Primary Analysis Population:	Intention-to-Treat	Full Analysis Set	Full Analysis Set
Statistical Design:	Superiority	Superiority	Superiority
Primary Statistical Methodology:	p-value from chi-square test; 95% CI from difference of	Analysis of covariance	Analysis of covariance

Protocol Number (s):	P693	P079	P090
Interim Analysis?	None	None	None
DSMB?	No	No	No
Sample Size:			
Sample size determination:	Yes	Yes	Yes
Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?			
Statistic =	Proportion of subjects achieving LDL-C target	Percent change from baseline in LDL-C	Percent change from baseline in LDL-C
Power =	90%	95%	92%
$\Delta$ =	0.15 (difference of proportions)	10 percentage points (difference between group means)	5 percentage points (difference between group means)
$\alpha$ =	two-tailed $\alpha$ of 0.05	two-tailed $\alpha$ of 0.05	two-tailed $\alpha$ of 0.05
<ul style="list-style-type: none"> <li>Was there an alternative analysis in case of violation of assumption; e.g., Lack of normality, proportional hazards assumption violation?</li> </ul>	No	No	No
<ul style="list-style-type: none"> <li>Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable?</li> </ul>	No	No	No
<ul style="list-style-type: none"> <li>Were the covariates pre-specified in the protocol?</li> </ul>	No covariates in the primary model for the primary endpoint	Yes	Yes
<ul style="list-style-type: none"> <li>Did the applicant perform sensitivity analyses?</li> </ul>	Yes, supportive analysis of PP population.	Yes, supportive analysis of PP population.	Yes, supportive analysis of PP population.
<ul style="list-style-type: none"> <li>How were the missing data handled?</li> </ul>	Non-responder imputation for missing data.	The double-blind period of 6 weeks has a lipid determination at baseline and at 6 weeks. By definition, subjects in the FAS would need to have both lipid determinations.	
<ul style="list-style-type: none"> <li>Was there a multiplicity adjustment involved?</li> </ul>	Not for the primary endpoint	Not for the primary endpoint	Not for the primary endpoint
<ul style="list-style-type: none"> <li>If yes, multiple arms?</li> </ul>	No	No	No
<ul style="list-style-type: none"> <li>Multiple endpoints?</li> </ul>	One primary endpoint	One primary endpoint	One primary endpoint
<ul style="list-style-type: none"> <li>Which method was used to</li> </ul>	N/A	N/A	N/A

Protocol Number (s):	P693	P079	P090
control for type I error?			
<ul style="list-style-type: none"> <li>Multiple secondary endpoints: Are they being included in the label? If yes, method to control for type I error.</li> </ul>	<p>Yes, multiple secondary endpoints are included in the label. The protocol did not pre-specify a method for controlling Type I error.</p>	<p>Yes, multiple secondary endpoints are included in the label.</p> <p>A “false discovery rate” (FDR) procedure was applied to pre-specified sets of secondary endpoints. Both unadjusted and FDR-adjusted p-values are reported.</p> <p>However, the FDR was not specified in a way that controls Type I error in the secondary endpoints reported in the proposed label.</p>	
<ul style="list-style-type: none"> <li>Were subgroup analyses performed?</li> </ul>	<p>Yes: gender, age, race plus subgroups of clinical interest.</p>	<p>Yes: gender, age, race plus subgroups of clinical interest.</p>	<p>Yes: gender, age, race plus subgroups of clinical interest.</p>
<ul style="list-style-type: none"> <li>Were there any discrepancies between the protocol / statistical analysis plan vs. the study report?</li> </ul>	<p>No</p>	<p>No</p>	<p>No</p>
<ul style="list-style-type: none"> <li>Overall, was the study positive?</li> </ul>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANICE A DERR  
01/06/2012

JON T SAHLROOT  
01/06/2012  
concur

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Today's date: 6/14/11

**NDA Number:** 200153

**Applicant:** MSP (Merck)

**Stamp Date:** 4/28/11

**Drug Name:** Atozet FDC  
(10 mg ezetimibe + 10, 20, 40 or 80 mg atorvastatin)

**NDA/BLA Type:** New NDA,

**PDUFA goal date:** 2/29/12

Note: 505(b)(2) application with the Pfizer "atorvastatin calcium" as the RLD

**Filing Date:** 6/28/11

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	Study P0693	Study P079	Study P090	Study 2154 (LTE)	Study 1417 (LTE)
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓	✓	✓	✓	✓
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓	✓	✓	✓	✓
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓	✓	✓	✓	✓
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓	✓	✓	✓	✓

Note: LTE = Long-term extension

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

Requests for 74-day letter:

For Study P0693, please provide analysis files with the following information, or, if this information is available in the submission, describe its location:

- Subject-specific: indicator variable(s) that code for each analysis population, such as full-analysis-set and per-protocol.
- Visit-specific:
  - indicator variable(s) that code for the primary endpoint in its final form
  - indicator variable(s) that code for the derivation status of the primary endpoint, i.e., whether it is measured or derived

<b>Content Parameter (possible review concerns for 74-day letter)</b>	Study P0693	Study P079	Study P090	Study 2154 (LTE)	Study 1417 (LTE)
Designs utilized are appropriate for the indications requested.	✓	✓	✓	✓	✓

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Study P0693	Study P079	Study P090	Study 2154 (LTE)	Study 1417 (LTE)
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓	✓	✓	✓	✓
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	N/A	N/A	N/A	N/A	N/A
Appropriate references for novel statistical methodology (if present) are included.	N/A	N/A	N/A	N/A	N/A
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓	✓	✓	✓	✓
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓	✓	✓	✓	✓

**Below are listed the clinical studies that are described in Part 14 (“Clinical Studies”) of the proposed package insert:**

**A. Clinical studies that have not been reviewed as part of the approval of Ezetimibe (Zetia™; NDA021445):**

Study P0693: “Add-On and Titration.” Study P0693 was ongoing at the time that Ezetimibe was approved. See the above 74-day letter requests.

- Patient population: Subjects with Heterozygous Familial Hypercholesterolemia (HeFH) or subjects with coronary heart disease or multiple cardiovascular risk factors and primary hypercholesterolemia not controlled by a starting dose of Atorva 10 mg.
- 621 subjects, randomized 1:1 to Atorva monotherapy or EZ 10 + Atorva coadministration therapy
- Up to 14 weeks of open-label Atorva 10 mg run-in, followed by randomization and 14 weeks of double-blind treatment in conjunction to Atorva 10 mg. Atorva dose was evaluated at week 5 and week 10 of the double-blind treatment period with the option of up-titration to a maximum daily dose of 40 mg.
- Primary efficacy endpoint was LDL-C change from baseline

Study P079: “TEMPO.” Study P079 was conducted after Ezetimibe was approved. No 74-day letter requests.

- Patient population: subjects who had been taking a stable dose of atorvastatin 20 mg for at least 6 weeks prior to visit 1.
- 196 subjects, randomized 1:1 to EZ-10+Atorva 20 mg or Atorva 40 mg.
- After a 1-week run-in period, the study had a 6-week double-blind treatment period.
- The primary efficacy endpoint was LDL-C change from baseline.

Study P090: “EZ-PATH.” Study P090 was conducted after Ezetimibe was approved. No 74-day letter requests.

- Patient population: Patients who have not reached optimal LDL-C goals on atorvastatin 40 mg alone

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

- 557 patients, randomized 1:1 to EZ 10 + Atorva 40 mg or EZ 10 + Atorva 80 mg
- Run-in period of 4-5 weeks with all patients on atorvastatin, followed by a double-blind treatment period of 6 weeks.
- Primary efficacy endpoint was LDL-C change from baseline

Study 2154. This is the long-term extension of Study P0692 (part of the approval of Ezetimibe).

Study P0692 “Atorvastatin Factorial.” No 74-day letter requests.

- Patient population: subjects with primary hypercholesterolemia.
- Factorial design with 10 arms, 628 subjects, approx 60 subjects/arm: placebo, EZ and Atorva monotherapies, and EZ+Azorva dose combinations. EZ dose is 10 mg, Atorva doses are 10, 20, 40 and 80 mg.
- 12 weeks of double blind treatment, preceded by 2 to 12 weeks of washout of lipid-lowering agents, and 4 weeks of single-blind placebo run-in.
- Primary efficacy endpoint was LDL-C change from baseline.

Study 2154: Long-term extension of Study P0692

- 12-month extension
- 246 subjects participated in the long-term extension
- double-blind assignment to medication (ezetimibe or placebo) based on the blinded treatment in Study P0692 as follows, from Study P0692 → Study 2154: placebo → placebo; ezetimibe (alone or in combination with atorvastatin) → ezetimibe; atorvastatin alone → ezetimibe or placebo in a 3:1 ratio. Atorvastatin was administered open-label to all patients. Atorvastatin was titrated based on an LDL-C target level, following a pre-specified protocol.

Study P1417. This is the long-term extension of Study P1030. Study P1030 was conducted in patients with Homozygous Familial Hypercholesterolemia (HoFH). No 74-day letter requests.

Study P1030

- 12 weeks of double-blind treatment
- 50 subjects
- 6 arms, factorial combination: ator 80 mg; EZ 10 mg + ator 40 mg; EZ 10 mg + ator 80 mg; simvastatin 80 mg; EZ 10 mg + sim 40 mg; EZ 10 mg + sim 80 mg

Study P1417

- 44 subjects
- up to 24 months duration
- open-label assignment to either Eze 10 mg + atorvastatin 40 mg or Eze 10 mg + simvastatin 40 mg. Subjects had the same statin therapy as they did in Study P1030.

### **B. Clinical studies that have been submitted and were previously reviewed as part of the approval of Ezetimibe:**

Study P0692 (described in previous section)

Study P1030 (described in previous section)

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/s/  
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JANICE A DERR  
06/21/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Today's date: 9/21/09

**NDA Number: 200153**

**Applicant:** MSP (Merck)

**Stamp Date:** September 2, 2009

**Drug Name:** (b) (4)  
(exetimibe/atorvastatin) FDC  
(10 mg eze + 10, 20, 40 or 80  
mg atorvastatin)

**NDA/BLA Type:** standard

**PDUFA date:** July 2, 2009

note: 505(b)(2) application with **Filing date:** October 30, 2009  
the Pfizer "atorvastatin calcium"  
as the RLD

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			For study P693 there are no data files, just data listings. We should request the analysis data files.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			For study P693 there are no data files, just data listings. We should request the analysis data files.

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Y \_\_\_**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			Low dropout rate, 5-10% across studies

**Further comments:**

The ISS report is included under m2\27\clin\sum in the file summary-clin-safety.pdf and the ISS database, along with statistical documentation, is included under M5\datasets\statistical-documentation\iss\analysis\. Based on finding this report and the associated database and documentation, I don't have requests for Merck concerning the ISS at the filing stage.

**The clinical Studies submitted with this NDA were previously reviewed in NDA's for Ezetimibe (Zetia) or Atorvastatin (Lipitor)**

**Short-Term Studies (6 to 14 weeks)**

“Atorvastatin Factorial” Study P 692:

- Patient population: subjects with primary hypercholesterolemia.
- Factorial design with 10 arms, 628 subjects, approx 60 subjects/arm: placebo, EZ and Atorva monotherapies, and EZ+Azorva dose combinations. EZ dose is 10 mg, Atorva doses are 10, 20, 40 and 80 mg.
- 12 weeks of double blind treatment, preceded by 2 to 12 weeks of washout of lipid-lowering agents, and 4 weeks of single-blind placebo run-in.
- Primary efficacy endpoint was LDL-C change from baseline.

Add-On Studies:

“EZ Add-on for statins” Study P2173:

- Patient population: subjects whose LDL-C levels did not meet their treatment goal in their ongoing statin therapy.
- 769 subjects, two study arms, EZ 10 mg and EZ placebo (1:1 randomization), added to ongoing statin therapy.
- 1 week of screening followed by 8 weeks of active double-blind treatment and a subsequent 6-week follow-up period, during which the subjects discontinued their blinded treatment while continuing their statin dosing regimen.
- Primary efficacy endpoint was LDL-C change from baseline.

“EASE” Study P040:

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

- Patient population: subjects whose LDL-C levels did not meet their treatment goal in their ongoing statin therapy.
- 3030 subjects, randomized 2:1 to EZ-10 or placebo, added to ongoing statin therapy.
- A 6-week double-blind treatment period.
- Primary efficacy endpoint was LDL-C change from baseline.

### Add-on Titration Studies:

#### “TEMPO” Study P079:

- Patient population: subjects who had been taking a stable dose of atorvastatin 20 mg for at least 6 weeks prior to visit 1.
- 196 subjects, randomized 1:1 to EZ-10+Atorva 20 mg or Atorva 40 mg.
- After a 1-week run-in period, the study had a 6-week double-blind treatment period.
- The primary efficacy endpoint was LDL-C change from baseline.

#### “EZ-PATH”, Study P090:

- Patient population: Patients who have not reached optimal LDL-C goals on atorvastatin 40 mg alone
- 557 patients, randomized 1:1 to EZ 10 + Atorva 40 mg or EZ 10 + Atorva 80 mg
- Run-in period of 4-5 weeks with all patients on atorvastatin, followed by a double-blind treatment period of 6 weeks.
- Primary efficacy endpoint was LDL-C change from baseline

#### “Zetia in the Elderly” Study P112

- Patient population: Elderly patients with hypercholesterolemia who have not reached LDL-C targets on Atorva 10 mg/day
- 1053 patients, randomized 1:1 to EZ 10 + Atorva 10 mg for 12 weeks or Atorva 20 mg for 6 weeks followed by Atorva 40 mg for 6 weeks.
- Run-in period followed by 12-week double-blind treatment period
- Primary efficacy endpoint was LDL-C change from baseline

#### “Add-On and Titration” Study P693

- Patient population: Subjects with Heterozygous Familial Hypercholesterolemia (HeFH) or subjects with coronary heart disease or multiple cardiovascular risk factors and primary hypercholesterolemia not controlled by a starting dose of Atorva 10 mg.
- 621 subjects, randomized 1:1 to Atorva monotherapy or EZ 10 + Atorva coadministration therapy
- Up to 14 weeks of open-label Atorva 10 mg run-in, followed by randomization and 14 weeks of double-blind treatment in conjunction to Atorva 10 mg. Atorva dose was evaluated at week 5 and week 10 of the double-blind treatment period with the option of up-titration to a maximum daily dose of 40 mg.
- Primary efficacy endpoint was LDL-C change from baseline

### **Long-Term Studies (52 weeks)**

“Blinded Comparator Extension” Study P154 (extension for P692)

“Open-label Extension” Study P1418 (extension for P693)

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA**

**Special Population Studies**

- “Homozygous Familial Hypercholesterolemia” Study P1030
- “HoFH open-label extension (extension to P1030)” Study P1417
- “Mixed hyperlipidemia” Study P692

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Reviewing Statistician Date

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Supervisor/Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200153	ORIG-1	MSP SINGAPORE CO LLC	(b) (4) (ezetimibe/atorvastatin calcium amorphous) Tablet Fixed dose combination

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/s/

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JANICE A DERR  
10/07/2009

JON T SAHLROOT  
10/07/2009