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APPLICATION NUMBER:
200153Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Priority or Standard Standard

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Reviewer Name(s) Iffat N. Chowdhury, MD
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Established Name Ezetimibe/ atorvastatin
(Proposed) Trade Name Liptruzet
Therapeutic Class Lipid lowering product
Applicant Merck Sharp & Dohme Corp.

Formulation(s) Fixed-dose combination
Dosing Regimen Once daily
Indication(s) Primary hypercholesterolemia
and homozygous familial
hypercholesterolemia
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Merck Sharp and Dohme Corporation (MSD), the applicant, submitted Liptruzet, a fixed dose combination (FDC) of ezetimibe and amorphous atorvastatin (EZ/AT 10/10, 10/20, 10/40, and 10/80 mg), for the treatment of patients with primary hyperlipidemia, mixed dyslipidemia, or patients with homozygous familial hypercholesterolemia (HoFH).

This is the applicant's third submission of NDA 200153. The Division of Metabolism and Endocrinology Products (DMEP) refused to file the first submission due to numerous chemistry, manufacturing, and control issues.

The applicant's second submission was on April 29, 2011 and the Division's Complete Response (CR) issued on February 29, 2012. The final decision not to approve the application was based on data from the pharmacokinetic/pharmacodynamic modeling which were not adequate to overcome failed bioequivalence results for the 10/20 mg and 10/40 mg EZ/AT FDC. Specifically, the 10/20 mg and the 10/40 mg dose combination tablets were not bioequivalent to the corresponding doses of ezetimibe + atorvastatin for atorvastatin C_{max}. Corrective actions to the CR included the option to re-formulate the 10/20 and 10/40 mg dosage strengths or to provide adequate clinical pharmacodynamic data.

The applicant resubmitted NDA 200153 on November 5, 2012 with data from two 12-week clinical trials, P185 and P190. These trials were submitted to demonstrate that FDC EZ/AT 10/20 mg and 10/40 mg were clinically equivalent to ezetimibe 10 mg co-administered with atorvastatin 20 mg or with atorvastatin 40 mg, respectively.

In study P185, the least square mean treatment difference for LDL-C between EZ/AT FDC 10/20 mg FDC and the co-administration of ezetimibe 10 mg plus atorvastatin 20 mg was -0.2% with a confidence interval (CI) from -1.7% to +1.3%. This trial satisfied the agreement that the two treatments would be considered equivalent if the 97.5% expanded CI for the mean difference in percent change from baseline in LDL-C after 6 weeks of treatment was contained within $\pm 4\%$.

In Study P190, the least square mean treatment difference for LDL-C between EZ/AT FDC 10/40 mg FDC and the co-administration of ezetimibe 10 mg plus atorvastatin 40 mg was -0.2% with a 97.5% CI from -1.9% to +1.4%. This trial also satisfied the equivalency requirements agreed upon before study initiation.

In addition, review of the safety data showed findings that were similar to the Core Safety Pool, which consisted of seven placebo and active controlled trials of ezetimibe co-administered with atorvastatin, reviewed during the second submission for NDA 200153.

Therefore, I find that the applicant has addressed the Complete Response issued on February 29, 2012. I recommend approval of NDA 200153.

1.2 Risk Benefit Assessment

In my assessment of the risk-benefit of this FDC product of ezetimibe and atorvastatin, I considered the efficacy and the safety data. The mean percent change in LDL-C from baseline to study endpoint with the FDC EZ/AT (10/20 mg or 10/40mg) was similar to the co-administration of 10 ezetimibe plus atorvastatin (20mg or 40 mg) of approximately 55%-59%. This is in comparison with atorvastatin 20 mg monotherapy (40% reduction) and atorvastatin 40 mg monotherapy (43% reduction). The ezetimibe component added approximately 15% LDL-C reduction to atorvastatin monotherapy.

The safety review did not show any novel toxicities associated with co-administration or the fixed dose combination of ezetimibe with atorvastatin. Treatment with EZ/AT FDC was generally well tolerated, with an adverse event profile similar to the atorvastatin monotherapy at corresponding doses.

Ezetimibe has an indication for combination use with a statin and is indicated for use in patient with primary hyperlipidemia. Furthermore, there is a FDC product of ezetimibe and simvastatin (Vytorin) currently on the market. Ezetimibe's indication with a statin and the already marketed simvastatin/ezetimibe FDC product bolstered my assessment in favor of the FDC EZ/AT product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Liptruzet is a fixed-dose combination drug product of two approved lipid-altering drugs, ezetimibe (Zetia®) and the amorphous formulation of atorvastatin (Lipitor®).

Ezetimibe inhibits the intestinal absorption of cholesterol and was approved in 2002 for the treatment of primary hypercholesterolemia, both as monotherapy and in combination with statins and fenofibrates. It is also approved for the treatment of hereditary sitosterolemia and in combination with atorvastatin or simvastatin for the treatment of HoFH. Ezetimibe is available only as a 10 mg tablet.

Atorvastatin is an HMG-CoA reductase inhibitor which blocks the rate-limiting enzyme in cholesterol synthesis. It has been marketed in the US since 1998 and has indications for treatment of primary hypercholesterolemia (both familial and non-familial forms) and mixed dyslipidemia. In addition to its lipid-lowering effects, atorvastatin is indicated to reduce the risk of mortality and cardiovascular morbidity in patients with or at high risk of coronary heart disease. Atorvastatin is available as a 10, 20, 40, or 80 mg tablet.

The ezetimibe/atorvastatin FDC was formulated in four tablet strengths: 10/10, 10/20, 10/40, 10/80 mg. The applicant proposed that the FDC be indicated for adjunctive therapy to diet for the reduction of elevated TC, LDL-C, Apo-B, TG and non-HDL-C and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia, or mixed dyslipidemia. In addition the product would be indicated for the reduction of elevated TC and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g, LDL apheresis).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are six classes of drugs used to treat dyslipidemias:

- HMG CoA reductase inhibitors (statins)
- fibric acid derivatives
- nicotinic acid derivatives
- cholesterol binding resins (bile acid sequestrants)
- cholesterol absorption inhibitors (ezetimibe)
- fish oils

These products have been approved as monotherapy and as combination therapy. A few have been approved as FDC products.

The most relevant currently available treatment is Vytorin®, the only other FDC drug product of ezetimibe and a statin (simvastatin). Vytorin® was approved in the US in 2004 to reduce elevated TC, LDL-C, Apo-B, TG, and non-HDL-C and to increase HDL-C in patients with primary hyperlipidemia or mixed hyperlipidemia. It is also indicated to reduce TC and LDL-C in patients with HoFH.

An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin® Efficacy International Trial) is examining whether Vytorin® reduces the risk for cardiovascular events compared with simvastatin alone. This trial of 18,000 patients is scheduled to be completed in September 2014. IMPROVE-IT will provide data regarding Vytorin®'s effect on the risk for cardiovascular disease events.

2.3 Availability of Proposed Active Ingredient in the United States

There are two active moieties in this FDC product —atorvastatin and ezetimibe. Atorvastatin is an HMG-CoA reductase inhibitor (statin). There have been a total of eight statins approved in the US over the last 30 plus years. Lovastatin was the first statin approved in the US in 1987 and the last statin, pitavastatin, was approved in 2008.

As a class of drugs, statins have been associated with myopathy and rare cases of rhabdomyolysis. According to findings from 21 clinical trials providing 180,000 person years of follow-up in patients treated with a statin or placebo, myopathy (defined as muscle symptoms plus CK >10XULN) occurred in 5 patients per 100,000 person-years and rhabdomyolysis in 1.6 patients per 100,000 person-years (placebo-corrected).¹

Statins have been associated with elevated liver aminotransaminases (ATs) and rarely hepatitis and liver failure. Asymptomatic liver AT elevations >3XULN are seen in <1% of patients on low and intermediated doses of statins and 2 to 3% at high doses.² The cause of this elevation in liver AT with statin therapy has not been determined, but in many if not most cases, statin-related transaminitis does not appear to herald significant liver injury, even with continued statin treatment.

The NDA review of ezetimibe revealed a slightly higher increase in liver ATs in the ezetimibe group compared to placebo but no cases of hepatitis were reported. Clinical AEs were more commonly reported in the hepato-biliary body system. Ezetimibe was associated with increased bile-cholesterol content in preclinical studies; however, it is unclear whether these findings result in an increased risk for developing pancreatitis.

2.4 Important Safety Issues With Consideration to Related Drugs

Please see the Clinical Review for NDA 200153 (dated 1/20/2012) for details related to safety issues with statins and ezetimibe.

1 McKenney JM, Davidson MH, Jacobson TA, and Guyton JR. Final Conclusions and Recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol 2006; 97 [suppl]:89C-94C).

2 Ibid.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The presubmission regulatory history is summarized in the following tables submitted by the applicant.

Table 1: Presubmission Regulatory History for NDA 200153/ (b) (4)

Event/Milestone/Activity	Date	Brief Summary
(b) (4)	05/13/2008	Original IND opened with Protocol No. 0145, a definitive BE study in healthy volunteers intended to demonstrate that the ezetimibe/ atorvastatin FDC tablet is bioequivalent to atorvastatin and ezetimibe when coadministered.
(b) (4)	08/5/2008	Agency confirmed the design of the definitive bioequivalence study including bracketing strategy appeared acceptable, pending submission of all relevant data to satisfy the requirements for the biowaiver for the 10/40mg FDC. Agency also agreed with the overall development strategy that a successful BE and food effect study would allow bridging the existing co-administration clinical efficacy and safety data to the FDC tablet.
IND 101, 953	06/30/2009	FDA provided comments regarding the nonclinical development program for a future NDA <ul style="list-style-type: none"> - It is recommended that the physicochemical characteristics of the atorvastatin used in the combination toxicology studies, the atorvastatin to be used in your FDC product, and the atorvastatin used in Lipitor be thoroughly compared. - Additional analytical characterization may be required on one or more of these substances if these data are not currently available. - If these data cannot be supplied or the data show that there are significant differences in impurity profiles between the three versions of atorvastatin, a bridging toxicology study in a single species may be required for marketing approval in the US.
Original NDA 200,153	09/02/2009	Original NDA to support the use of the ezetimibe/ atorvastatin combination tablet 10/10, 10/20, 10/40 and 10/80mg for the treatment of hypercholesterolemia and homozygous familial hypercholesterolemia.

Event/Milestone/Activity	Date	Brief Summary
FDA RFI	09/28/2009	FDA request for Information <ul style="list-style-type: none"> - Comparative CMC data for the atorvastatin used in the Tox studies, FDC product and Lipitor, - Master Production record, of the commercial product, - Dissolution profiles comparing the clinical batches and the to-be-marketed product and confirmation biobatches and to-be-marketed product used the same composition and process
Response to FDA RFI	10/27/2009	Response to FDA RFI
FDA Refusal to File	10/29/2009	NDA is considered to be incomplete and cannot be filed Filing deficiencies <ul style="list-style-type: none"> - All facilities involved in the manufacturing and testing of the commercial product need to be ready for GMP inspections. - Missing are the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54. - Missing are the stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data) as well as multipoint dissolution profiles - Missing is the information to bridge the performance of the clinically tested batches to the commercial products (e.g., multipoint in vitro dissolution profiles).

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Event/Milestone/Activity	Date	Brief Summary
General Advice letter	11/03/2009	FDA Non Filing issues to be addressed in a future submission includes: - 12-month primary stability data at the long term storage condition. The review of unsolicited amendment such as a stability update is not guaranteed. - In addition to the comparative impurity results submitted in your October 27, 2009 communication, missing are the physicochemical data as requested by FDA on June 30, 2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. - Justification for providing a combination toxicology study with atorvastatin and MK-6213 (a cholesterol absorption inhibitor which is not ezetimibe) in a 3-month toxicity study in dogs
Meeting Following Refusal to File	12/03/2009	Clarification meeting on the RTF issues and pathforward for the resubmission Merck indicated the NDA resubmission will have stability and dissolution data for the product manufactured by one chain of commercial facilities. In response to the sponsor's question about submitting prior-approval supplements for the alternate chains of manufacturing facilities, the agency indicated that it was not appropriate at this meeting to discuss the mechanism for submission of alternate manufacturing sites (CBE vs. Prior Approval).
General Correspondence	04/13/2011	Submission replaced the eCTD backbone xml file to delete previously submitted documents from the eCTD lifecycle for the purpose of providing a clean platform for the resubmission.
NDA 200-153 ATOZET	04/29/2011	Original NDA to support the use of 4 combination tablet strengths, with each strength containing ezetimibe 10 mg and atorvastatin 10, 20, 40 or 80mg, for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia .
FDA Acknowledgement Re-submission	05/09/2011	Acknowledgement of re- submission following RTF letter and of the request for full waiver of the pediatric studies

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Event/Milestone/Activity	Date	Brief Summary
FDA Filing Communication	07/06/2011	FDA determined that the application is sufficiently complete to permit a substantive review. The review classification for the application is Standard. Therefore, the user fee goal date is February 29, 2012, with the plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 1, 2012. FDA also has provided the potential review issues, including clarification on the location of analyses files; SAS transport files, and questions in relation to the dissolution data.
Request for Tradename review	07/07/2011	Separate submission of the tradename review request for ATOZET
Patent Information	07/18/2011	Submission of the Patent Information
	07/22/2011	Response to FDA comments in the review acceptance letter
Revised Pediatric waiver	07/29/2011	Revised Pediatric waiver included data showing that the vast majority of children and adolescents receiving lipid lowering therapy are taking statin monotherapy. Thus, it is likely that there would be a very limited number of pediatric patients prescribed a fixed-dose combination of ezetimibe/ atorvastatin and thus such a FDC would not represent a meaningful therapeutic benefit over existing therapies for pediatric patients.
Discipline Review Letter	08/24/2011	Focusing on CMC deficiencies and partial response to July 6, 2011 FDA letter
SUR	08/26/2011	Letter in lieu of 4 month Safety Update report
		(b) (4)
CMC response	09/22/2011	Complete response to CMC deficiencies issues
FDA letter on proprietary name request	09/26/2011	Conditional approval of the proposed proprietary name Atozet
RFI	10/04/2011	FDA request for additional information regarding the Biopharmaceutics sections
Response to RFI	10/11/2011	Response to FDA request dated October 4, 2011 that addressed questions on surfactant, discriminating capability of the proposed dissolution method, ezetimibe dissolution data.

Event/Milestone/Activity		Date	Brief Summary
Response to RFI		10/17/2011	Merck provided notice that on August 15, 2011, Pfizer filed an action for patent infringement against MSP in the United States District Court for The District of Delaware.
Transfer of ownership		10/31/2011	Transfer of ownership from MSP Singapore to MSD International GmbH
Communication of the PERC meeting outcome		12/07/2011	Full pediatric waiver was granted for Atozet
FDA communication of the outcome of the January 25, 2012 internal wrap up meeting		01/30/2012	No plans for labeling discussions
General Advice letter		01/31/2012	OSE review comments on the packaging components (carton and container labeling)
Complete Response letter		02/29/2012	The final decision was not to approve the application and a complete response was issued with the following deficiencies with recommendations for corrective action: <ul style="list-style-type: none"> - Data from the PK/ PD modeling were not adequate to overcome the failed bioequivalence results for the 10/20mg and 10/40mg ezetimibe/ atorvastatin FDC tablets that FDA believes will likely be the most commonly prescribed dosage strengths. - Among the corrective actions is listed the option to re-formulate the 10/20 and 10/40 mg dosage strengths or to provide adequate clinical pharmacodynamic data. - There were no comments on other aspects of the filing outside from a request to provide with the response an integrated safety update from all nonclinical and clinical studies on the FDC.
Meeting	Request	03/20/2012	The Division agreed on the adequacy of the clinical equivalence data to support registration of the 10/20 and 10/40 mg strengths and on the proposed structure and content of the safety update.
	Additional topic for feedback	04/12/ 2012	
	FDA preliminary comments	06/22/2012	

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was good. The submission was organized, and information was relatively easily found. No additional information was requested from the applicant.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in accordance with acceptable ethical standards and in compliance with good clinical practices.

3.3 Financial Disclosures

Form 3454 was completed with a list of clinical investigators certified as having an absence of financial interests and arrangements.

The following table lists the names of all identified clinical investigators/sub-investigators by product, protocol and site number for the covered clinical studies who have met the disclosure criteria regarding financial interests and arrangements as defined in 21 CFR 54.2(a,b,c,f).

Table 2: Clinical Investigators Requiring Financial Disclosures

Table of All Clinical Investigators/Subinvestigators Who Hold Financial Interest and/or Arrangements Requiring Disclosure		
Product/Protocol/Site	Investigator/ Subinvestigator	Financial Interests or Arrangements
	(b) (6)	Equity Interest: Amount: \$53,000.00 Comment: 1500 shares of stock valued at approximately \$53,000.00 as reported by investigator on 07-01-2011.
		Significant Payments of Other Sorts: Amount: \$36,305.05 Comment: \$36,305.05 received in payments from Merck for educational programs and advisory/consultant meetings regarding various drug developments as reported by investigator on 07-07-2011.
		Significant Payments of Other Sorts: Amount: \$39,150.00 Comment: \$39,150.00 for consulting services in 2010 (\$15,475.00 from Merck and \$23,675.00 from Schering-Plough) as reported by investigator on 08-04-2011.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new information submitted related to Chemistry, Manufacturing, and Controls with this submission.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There was no new information submitted related to pharmacology/toxicology with this submission. Please see this section in the previous clinical review and the pharmacology/toxicology report.

4.4 Clinical Pharmacology

There was no new information submitted related to clinical pharmacology with this submission. Please see this section in the previous clinical review and the clinical pharmacology report.

5 Sources of Clinical Data

In this drug development program, the phase III clinical trials supporting efficacy and safety were conducted with ezetimibe + atorvastatin co-administered as separate therapeutic agents. Furthermore, the atorvastatin formulation used in the trials was the crystalline formulation, not the amorphous formulation used in the applicant's FDC product. Therefore, bioequivalence trials were used to bridge the co-administration trials to the FDC EZ/AT product.

In the previous review cycle, the Division found that Study P145 (Bioequivalence Study) *did not* support bioequivalence of the doses of 10/20 mg and 10/40 mg ezetimibe/atorvastatin combination tablet to the ezetimibe + atorvastatin co-administration data. Specifically, the 10/20 mg and the 10/40 mg dose combination tablets were not bioequivalent to the corresponding doses of ezetimibe + atorvastatin for atorvastatin C_{max}.

Therefore, with this current submission the applicant submitted the results of P185 and P190 to overcome the failed bioequivalence study and establish the pharmacodynamic equivalence of the FDC 10/20 mg EZ/AT and 10/40 mg EZ/AT with the co-administration of ezetimibe 10 mg+ atorvastatin 20 mg and ezetimibe 10 mg + atorvastatin 40 mg, respectively.

5.1 Tables of Studies/Clinical Trials

Protocol Number	Study Title	N	Design	Patient Population	Relevant Treatments (n)
P185	A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/20 mg Fixed-Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 20 mg in Patients with Primary Hypercholesterolemia	406	25-week randomized, double blind 2-period, crossover study with a 5 week washout, a 2 week single-blind placebo run-in period, and two 6 week treatment crossover periods separated by a 6-week single-blind placebo washout period	Patients with hypercholesterolemia at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines)	Sequence 1: Co-admin EZ 10 mg and Atorva 20 mg to EZ/Atorva 10/20 mg FDC (n = 203) Sequence 2: EZ/Atorva 10/20 mg FDC to Co-admin EZ 10 + Atorva 20 (n = 203)
P190	A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/40 mg Fixed-Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 40 mg in Patients with Primary Hypercholesterolemia	328	25-week randomized, double blind 2-period, crossover study with a 5 week washout, a 2 week single-blind placebo run-in period, and two 6 week treatment crossover periods separated by a 6-week single-blind placebo washout period	Patients with hypercholesterolemia at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines)	Sequence 1: Co-admin EZ 10 mg and Atorva 40 mg to EZ/Atorva 10/40 mg FDC (n = 164) Sequence 2: EZ/Atorva 10/40 mg FDC to Co-admin EZ 10 + Atorva 40 (n = 164)

5.2 Review Strategy

Trials which are previously reviewed are not reported in this document; the recently completed trials P185 and P190 are reviewed here. Please see the clinical review related to the second review cycle for NDA 200153 (submitted on 4/26/2011) for details on other clinical trials related to Liptruzet.

5.3 Discussion of Individual Studies/Clinical Trials

Please see Section 6.

6 Review of Efficacy

Efficacy Summary

Efficacy results from the following trials are reported in this section: P185 and P190. These trials were submitted to demonstrate that FDC EZ/AT 10/20 mg and 10/40 mg are clinically “equivalent” to ezetimibe 10 mg co-administered with atorvastatin 20 mg or with atorvastatin 40 mg, respectively.

6.1 Indication

During the previous review cycle, the various disciplines (with the exclusion of clinical pharmacology) found that the applicant had submitted sufficient efficacy and safety data to support the following indication:

LIPTRUZET, which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments.

In this current review cycle, the applicant had to establish pharmacodynamic equivalence of the EZ/AT 10/20 mg FDC to the co-administration of ezetimibe 10 mg+ atorvastatin 20 mg. Similarly, the pharmacodynamic equivalence of the EZ/AT 10/40 mg FDC to the co-administration of ezetimibe 10 mg + atorvastatin 40 mg remained to be established.

6.1.1 Methods

Study P185

Study P185 was a 25-week randomized, double-blind, 2-period, crossover study comprising 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 (See Figure 1).

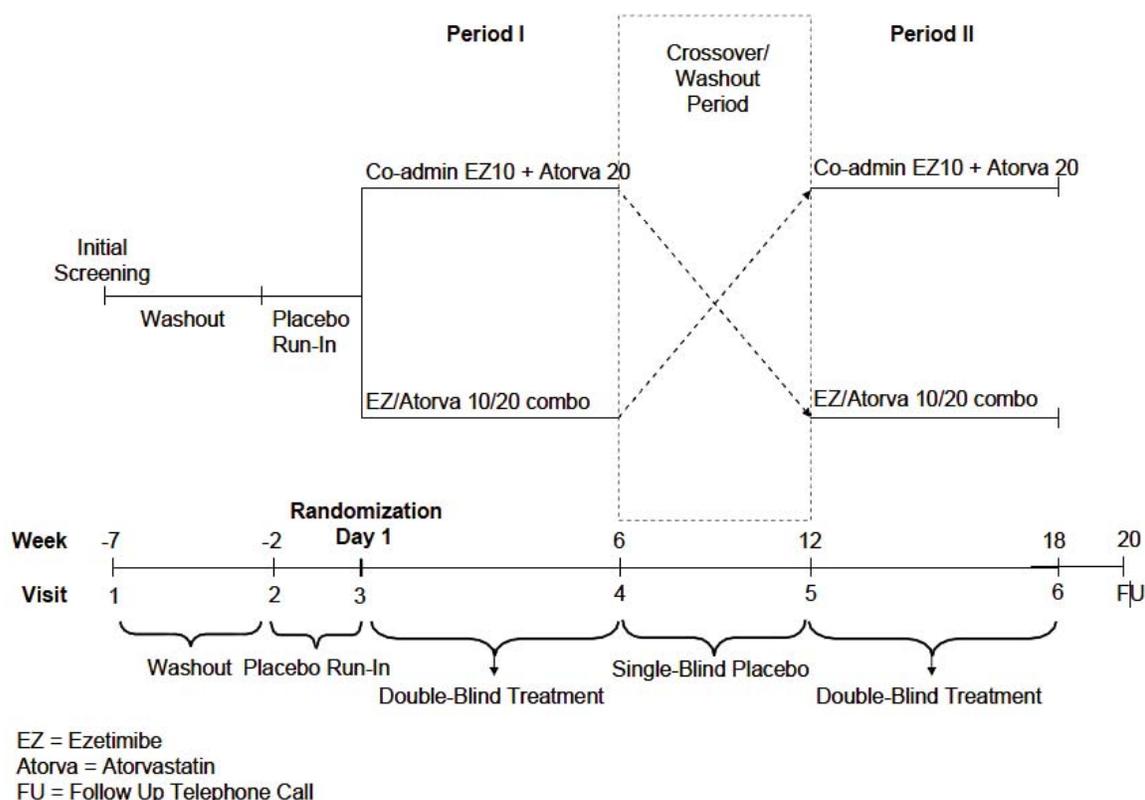


Figure 1: Study Design Study P185

Eligible patients could be at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines) who were naïve to lipid-lowering agents or were currently taking allowable statin or ezetimibe-statin combination therapy with acceptable LDL-C screening values. High-risk patients (CHD or CHD risk equivalent) were not eligible.

Patients were enrolled in a 7-week washout/run-in period. During the washout/run-in period, the patients received exercise and diet counseling and started placebo during the run-in from Week -2 to Day -1. Eligibility for randomization was determined at the

end of the run-in phase. Patients were randomized in a 1:1 ratio to one of the two blinded treatment arms.

Patients then received either a FDC tablet EZ/AT 10 mg/20 mg or ezetimibe 10 mg co-administered with atorvastatin 20 mg once daily for 6 weeks (Period I), then underwent washout for 6 weeks while taking single-blind placebo, and finally crossed over to the corresponding dose of co-administration or EZ/AT FDC tablet for an additional 6 weeks of treatment (Period II). Study endpoints were assessed at the end of Periods I and II. The LDL-C value measured at randomization served as the baseline for both Periods I and II.

The primary objective of this study was to demonstrate equivalent lipid-modifying efficacy of the ezetimibe/atorvastatin FDC tablet 10 mg/20 mg versus the corresponding dose of marketed ezetimibe 10 mg (Zetia®) co-administered with atorvastatin 20 mg (Lipitor®) in patients with primary hypercholesterolemia.

Study P190

Study P190 was a 25-week multicenter, randomized, double-blind, 2-period, crossover study comprising 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 (see Figure 2).

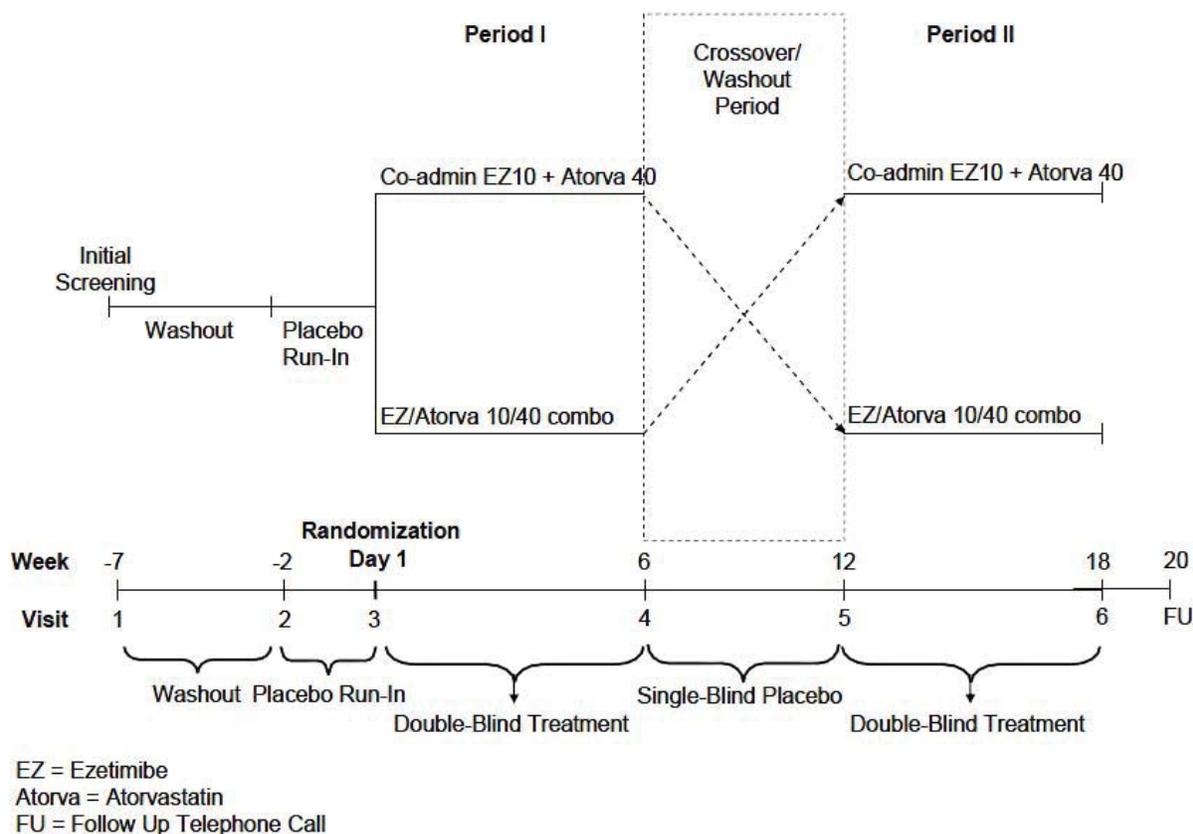


Figure 2: Study Design P190

Patients eligible for Study P190 could be at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines) and were naïve to lipid-lowering agents or currently taking allowable statin or ezetimibe-statin combination therapy with acceptable LDL-C screening values. 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 counsel, 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.

Patients were randomized in a 1:1 ratio to one of two blinded treatment arms. Patients received either an FDC tablet of ezetimibe/atorvastatin 10 mg/40 mg or ezetimibe 10 mg co-administered with atorvastatin 40 mg once daily for 6 weeks (Period I), underwent washout for 6 weeks while taking single-blind placebo, and then crossed over to the corresponding dose of co-administration or ezetimibe/atorvastatin FDC tablet for an additional 6 weeks of treatment (Period II).

Study endpoints were assessed at the end of Periods I and II. The LDL-C value measured at randomization served as the baseline for both Periods I and II.

6.1.2 Demographics

Study P185

The randomized population in Study 185 was mostly Caucasian (84%), female (61%), with a mean age of 56 years. The mean LDL-C was 162 mg/dL, TC was 247 mg/dL, HDL-C was 54 mg/dL and TG was 156 mg/dL. Age, gender, and race, and baseline lipid and lipoprotein parameters were generally comparable across the sequence groups.

Table 3: Baseline Demographics Study P185

	Co-admin EZ and Atorva 20 mg →EZ/Atorva 10/20 mg FDC n(%)	EZ/Atorva 10/20 mg FDC → Co-admin EZ and Atorva 20 mg n (%)	Total
Patients in Population	203	203	406
Gender			
Male	77 (37.9)	81 (39.9)	158 (38.9)
Female	126 (62.1)	122 (60.1)	248 (61.1)
Age (year)			
Mean (SD)	55.5 (9.94)	56.6 (8.94)	56.1 (9.46)
Median	56.0	58.0	56.0
Range	31-79	30-77	30-79
Race			
White	167 (82.3)	174 (85.7)	341 (84.0)
Black	28 (13.8)	26 (12.8)	54 (13.3)
Asian	4 (2.0)	2 (1.0)	6 (1.5)
Multi-racial	3 (1.5)	1 (0.5)	4 (1.0)
American Indian or Alaska Native	1 (0.5)	0	1 (0.2)

Source: Applicant's Clinical Summary Efficacy, Table 2.7.3,pg. 58.

Table 4: Baseline Lipid Parameters Study P185

Parameter	Co-admin EZ and Atorva 20 mg →EZ/Atorva 10/20 mg FDC n(%)	EZ/Atorva 10/20 mg FDC → Co-admin EZ and Atorva 20 mg n (%)	Total
Patients in Population	203	203	406
LDL-C (mg/dL)			
n	187	193	380
Mean (SD)	161(29)	163 (34)	162 (32)

Parameter	Co-admin EZ and Atorva 20 mg →EZ/Atorva 10/20 mg FDC n(%)	EZ/Atorva 10/20 mg FDC → Co-admin EZ and Atorva 20 mg n (%)	Total
Median	157	162	160
Range	98-247	94-336	94-336
Total Cholesterol (mg/dL)			
n	187	193	380
Mean (SD)	245 (34)	249 (38)	247 (36)
Median	241	248	242
Range	167-348	168-399	167-399
HDL-C (mg/dL)			
n	187	193	380
Mean (SD)	53 (15)	54 (15)	54 (15)
Median	50	52	52
Range	29-103	23-106	23-106
Triglycerides (mg/dL)			
n	187	193	380
Mean (SD)	153 (74)	159 (74)	156 (74)
Median (SD)	136 (98)	142 (100)	139 (100)
Range	40-449	54-432	40-449

Source: Applicant's Clinical Summary Efficacy, Table 2.7.3,pg. 59.

Study P190

The randomized population in Study P190 was mostly Caucasian (82%), female (57%), with a mean age of 55 years. The mean LDL-C was 163 mg/dL, TC was 249 mg/dL, HDL-C was 54 mg/dL and TG was 158 mg/dL. Age, gender, and race, and baseline lipid and lipoprotein parameters were generally comparable across the sequence groups..

Table 5: Baseline Demographics Study P190

	Co-admin EZ and Atorva 20 mg → FDC EZ/Atorva 10/40 mg n(%)	FDC EZ/Atorva 10/40 mg → Co-admin EZ and Atorva 40 mg n (%)	Total
Patients in Population	164	164	328
Gender			
Male	70 (43%)	72 (44%)	142 (43%)
Female	94 (57%)	92 (56%)	186 (57%)
Age (year)			
Mean (SD)	55 (9)	56 (10)	55 (9)

	Co-admin EZ and Atorva 20 mg → FDC EZ/Atorva 10/40 mg n(%)	FDC EZ/Atorva 10/40 mg → Co-admin EZ and Atorva 40 mg n (%)	Total
Median	56	57	56
Range	30-76	30-77	30-77
Race			
White	138 (84)	130 (79)	268 (82)
Black	25 (15)	28 (17)	53 (16)
Asian	0	2 (1)	2 (0.6)
Multi-racial	0	3 (2)	3 (1)
American Indian or Alaska Native	0	0	0

Source: Clinical Summary of Efficacy; Table 2.7.3, pg. 60.

Table 6: Baseline Lipid Parameters Study P190

Parameter	Co-admin EZ and Atorva 20 mg →EZ/Atorva 10/40 mg FDC n(%)	EZ/Atorva 10/40 mg FDC → Co-admin EZ and Atorva 40 mg n (%)	Total
Patients in Population	164	164	328
LDL-C (mg/dL)			
n	152	160	312
Mean (SD)	165 (32)	161 (27)	163 (31)
Median	162	157	159
Range	101-258	80-228	80-258
Total Cholesterol (mg/dL)			
n	152	160	312
Mean (SD)	252 (39)	245 (33)	248 (36)
Median	249	241	245
Range	168 - 362	176- 330	168-362
HDL-C (mg/dL)			
n	152	160	312
Mean (SD)	54 (13)	54 (14)	54 (14)
Median	51	53	53
Range	28-94	26-101	26-101
Triglycerides (mg/dL)			
n	152	160	312
Mean (SD)	166 (85)	151 (72)	158 (79)

Parameter	Co-admin EZ and Atorva 20 mg →EZ/Atorva 10/40 mg FDC n(%)	EZ/Atorva 10/40 mg FDC → Co-admin EZ and Atorva 40 mg n (%)	Total
Median (SD)	145 (91)	137 (85)	140 (84)
Range	44 - 481	39 – 406	39 - 481

Source: Summary of Clinical Efficacy, Table 2.7.3, pg. 61.

6.1.3 Subject Disposition

Study P185

In study P185, a total of 1092 patients were screened, of which 686 were excluded and 406 were randomized. The following table summarizes study disposition by Period I and Period II.

Approximately 92% completed Period I and 89% completed Period II. Eight percent discontinued the study in Period I, with approximately 4% of the discontinuations due to adverse events. In Period II, only 0.5% discontinued, with none due to an adverse event.

Table 7: Patient Disposition Study P185

	Co-admin EZ 10 mg and Atorva 20 mg-> EZ/Atorva 10 mg/20 mg fixed-dose combination		EZ/Atorva 10 mg/20 mg fixed-dose combination-> Co-admin EZ 10 mg and Atorva 20 mg		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					686	
Patients in Population	203		203		406	
Male	77	(37.9)	81	(39.9)	158	(38.9)
Female	126	(62.1)	122	(60.1)	248	(61.1)
Age Range (years)	31 to 79		30 to 77		30 to 79	
Study Disposition						
Period I						
Completed	187	(92.1)	192	(94.6)	379	(93.3)
Discontinued	16	(7.9)	11	(5.4)	27	(6.7)
Adverse Event	8	(3.9)	4	(2.0)	12	(3.0)
Lost to Follow-up	2	(1.0)	2	(1.0)	4	(1.0)
Protocol Violation	2	(1.0)	2	(1.0)	4	(1.0)
Study Terminated by Sponsor*	0	(0.0)	1	(0.5)	1	(0.2)
Withdrawal by Subject	4	(2.0)	2	(1.0)	6	(1.5)
Crossover Washout Period						
Completed	181	(89.2)	186	(91.6)	367	(90.4)
Discontinued	6	(3.0)	6	(3.0)	12	(3.0)
Adverse Event	1	(0.5)	4	(2.0)	5	(1.2)
Lost to Follow-up	2	(1.0)	0	(0.0)	2	(0.5)
Non-Compliance with Study Drug	1	(0.5)	0	(0.0)	1	(0.2)
Withdrawal by Subject	2	(1.0)	2	(1.0)	4	(1.0)
Period II						
Completed	180	(88.7)	184	(90.6)	364	(89.7)
Discontinued	1	(0.5)	2	(1.0)	3	(0.7)
Adverse Event	0	(0.0)	1	(0.5)	1	(0.2)
Withdrawal by Subject	1	(0.5)	1	(0.5)	2	(0.5)
EZ = ezetimibe. Each patient is counted once for Study Disposition. Only reasons that resulted in actual exclusions/discontinuations are listed. *Study Terminated by Sponsor is equivalent to Screen Failure as a reason for exclusion. Due to the rapid enrollment of this study, the target number of randomized patients was reached before screening was stopped. Thus, patients who were still being screened but had not yet been randomized were terminated from the study by the sponsor.						

Source: CSR P185.

Study P190

In study P190, a total of 570 patients were screened, of which 242 were excluded and 328 were randomized. The following table summarizes study disposition in P190.

Approximately 92% completed Period I and 84% completed Period II. Approximately 8.5% discontinued the study in Period I, with 3% of the discontinuations due to adverse events. In Period II, 1.8% discontinued, with 0.6% due to an adverse event.

Table 8: Patient Disposition Study P190

	Co-admin EZ 10 mg and Atorva 40 mg-> EZ/Atorva 10 mg/40 mg fixed-dose combination		EZ/Atorva 10 mg/40 mg fixed-dose combination-> Co-admin EZ 10 mg and Atorva 40 mg		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					242	
Patients in Population	164		164		328	
Male	70	(42.7)	72	(43.9)	142	(43.3)
Female	94	(57.3)	92	(56.1)	186	(56.7)
Age Range (years)	30 to 76		30 to 77		30 to 77	
Study Disposition						
Period I						
Completed	150	(91.5)	154	(93.9)	304	(92.7)
Discontinued	14	(8.5)	10	(6.1)	24	(7.3)
Adverse Event	5	(3.0)	3	(1.8)	8	(2.4)
Lost to Follow-up	2	(1.2)	0	(0.0)	2	(0.6)
Protocol Violation	2	(1.2)	2	(1.2)	4	(1.2)
Withdrawal by Patient	5	(3.0)	5	(3.0)	10	(3.0)
Crossover Washout Period						
Completed	141	(86.0)	150	(91.5)	291	(88.7)
Discontinued	9	(5.5)	4	(2.4)	13	(4.0)
Adverse Event	2	(1.2)	1	(0.6)	3	(0.9)
Lost to Follow-up	2	(1.2)	0	(0.0)	2	(0.6)
Non-Compliance with Study Drug	0	(0.0)	2	(1.2)	2	(0.6)
Protocol Violation	1	(0.6)	0	(0.0)	1	(0.3)
Withdrawal by Patient	4	(2.4)	1	(0.6)	5	(1.5)
Period II						
Completed	138	(84.1)	146	(89.0)	284	(86.6)
Discontinued	3	(1.8)	4	(2.4)	7	(2.1)
Adverse Event	1	(0.6)	4	(2.4)	5	(1.5)
Lost to Follow-up	1	(0.6)	0	(0.0)	1	(0.3)
Withdrawal by Patient	1	(0.6)	0	(0.0)	1	(0.3)
EZ = ezetimibe. Atorva = Atorvastatin						
Each patient is counted once for Study Disposition. Only reasons that resulted in actual exclusions/discontinuations are listed.						

Source: CSR, P190.

6.1.4 Analysis of Primary Endpoint(s)

Study P185

The primary hypothesis for P185 was that “in patients with primary hypercholesterolemia, EZ/AT 10 mg/20 mg FDC tablet is equivalent to ezetimibe 10 mg co-administered with atorvastatin 20 mg with respect to the percent change from baseline in LDL-C after 6 weeks of treatment.” It was agreed that the two treatments would be considered equivalent if the 97.5% expanded confidence interval (CI) for the mean difference in percent change from baseline in LDL-C after 6 weeks of treatment was contained within $\pm 4\%$.

The primary objective of P185 was “to evaluate the LDL-C-lowering efficacy of ezetimibe 10 mg co-administered with atorvastatin 20 mg compared to the EZ/AT combination tablet at 10 mg/20 mg in patients with primary hypercholesterolemia.”

Study endpoints were assessed at the end of Period I and II. The primary efficacy endpoint was percentage change from baseline in LDL-C after 6 weeks of treatment. The LDL-C concentration measured at Randomization was the Baseline LDL-C value. The following table summarizes the LDL-C changes across the treatment arms in P185.

Table 9: Percent Change in LDL-C from Baseline to Endpoint (Study P185)

Treatment Group	N	Mean (SD)		Percent Change From Baseline	
		Baseline	End of 6 Weeks of Treatment	Mean (SD)	LS Mean [†] (95% CI)
EZ/Atorva 10mg/20mg fixed-dose combination	353	162.5 (32.0)	73.4 (29.5)	-54.4 (17.4)	-54.0 (-55.8, -52.2)
Co-Admin EZ 10mg and Atorva 20mg	346	161.9 (32.4)	73.7 (28.4)	-53.7 (18.1)	-53.8 (-55.7, -52.0)
Comparison between the treatments					
			Difference in LS Means [†]		97.5% expanded CI
EZ/Atorva 10mg/20mg fixed-dose combination vs. Co-Admin EZ 10mg and Atorva 20mg			-0.2		-1.7, 1.3
[†] LS Means and 95% CI and p-value were obtained from fitting an ANCOVA repeated measures model with terms for treatment, baseline LDL-C, period and sequence. An unstructured covariance matrix was used. ANCOVA=Analysis of Covariance%; CI=Confidence Interval%; LS Mean=Least Squares Mean%; SD=Standard Deviation. Given the nominal 95% confidence interval, (L, U), the corresponding 97.5% expanded confidence interval is (min(0,L), max(0,U)). Equivalence is declared if the 97.5% expanded confidence interval for the mean difference between the fixed-dose combination and co-administration in percent change from baseline in LDL-C is contained within $\pm 4\%$. Note: The values measured at randomization will serve as the baseline for both Periods I and II.					

Source: Applicant’s CSR P185, Table 11-1, pg. 101.

Study P190

The primary hypothesis for P190 was that “in patients with primary hypercholesterolemia, EZ/AT 10 mg/40 mg combination tablet is equivalent to ezetimibe

10 mg co-administered with atorvastatin 40 mg with respect to the percent change from baseline in LDL-C after 6 weeks of treatment.” It was agreed that the two treatments would be considered equivalent if the 97.5% expanded CI for the mean difference in percent change from baseline in LDL-C after 6 weeks of treatment was contained within $\pm 4\%$.

The primary objective of P190 was “to evaluate the LDL-C-lowering efficacy of ezetimibe 10 mg co-administered with atorvastatin 40 mg compared to the EZ/AT combination tablet at 10 mg/40 mg in patients with primary hypercholesterolemia.”

Study endpoints were assessed at the end of Period I and II. The primary efficacy endpoint was percentage change from baseline in LDL-C after 6 weeks of treatment. The LDL-C concentration measured at Randomization was the Baseline LDL-C value. The following table summarizes the LDL-C changes across the treatment arms in P190.

Table 10: Percent Change in LDL-C from Baseline to End of Treatment (Study 190)

Treatment Group	N	Mean (SD)		Percent Change From Baseline	
		Baseline	End of 6 Weeks of Treatment	Mean (SD)	LS Mean [†] (95% CI)
EZ/Atorva 10mg/40mg fixed-dose combination	280	162.4 (30.2)	64.9 (25.8)	-59.3 (16.9)	-58.9 (-60.9, -56.9)
Co-admin EZ 10mg and Atorva 40mg	280	162.2 (30.2)	65.3 (26.2)	-59.1 (17.2)	-58.7 (-60.7, -56.7)
Comparison between the treatments					
			Difference in LS Means [†]		97.5% expanded CI
EZ/Atorva 10mg/40mg fixed-dose combination vs. Co-admin EZ 10mg and Atorva 40mg			-0.2		-1.9, 1.4
[†] LS Means and 95% CI and p-value were obtained from fitting an ANCOVA repeated measures model with terms for treatment, baseline LDL-C, period and sequence. An unstructured covariance matrix was used. ANCOVA=Analysis of Covariance%; CI=Confidence Interval%; LS Mean=Least Squares Mean%; SD=standard deviation. Given the nominal 95% confidence interval, (L, U), the corresponding 97.5% expanded confidence interval is (min(0,L), max(0,U)). Equivalence is declared if the 97.5% expanded confidence interval for the mean difference between the fixed-dose combination and co-administration in percent change from baseline in LDL-C is contained within $\pm 4\%$. Note: The values measured at randomization will serve as the baseline for both Periods I and II.					

Source: Applicant’s CSR P190, Table 11-1, pg. 95.

Comparison of LDL-C with studies from previous submission

Comparison of the results of P185 and P190 with trials submitted in the previous submission show similar results. For example, in Study P692, the least squares (LS) Mean Percent Change in LDL-C of EZ plus co-administration of all doses of atorvastatin

showed a difference of -54.53%. This is similar to the LS Mean Percent Change in LDL-C in P185 and P190.

Table 11: Mean Percent Change in Lipid Parameters from Baseline to Endpoint-Study P692 (from Core Safety Pool)

Lipid Variable	Atorvastatin Alone (n = 248)	EZ 10 mg + Atorvastatin (n = 255)	Ezetimibe 10 mg Alone (n=65)	p-value	
				EZ + Atorva vs Atorvastatin	EZ +Atorva vs Ezetimibe
Direct LDL-C	-42.41 (0.95)	-54.53 (0.94)	-18.43 (1.85)	p<0.01	p<0.01
Calculated LDL-C	-44.24 (0.97)	-56.31 (0.95)	-19.95 (1.88)	p<0.01	p<0.01
TC	-32.06 (0.75)	-41.13 (0.74)	-13.52 (1.53)	p<0.01	p<0.01
TG	-21.47 (1.55)	-29.47 (1.53)	-3.44 (3.02)	p<0.01	p<0.01
HDL-C	4.25 (0.74)	7.34 (0.73)	4.19 (1.43)	p<0.01	p=0.05
Apo B	-36.07 (0.93)	-45.37 (0.92)	-15.40 (1.82)	p<0.01	p<0.01
Non-HDL-C	-41.05 (0.93)	-52.33 (0.91)	-17.68 (1.80)	p<0.01	p<0.01
HDL ₂ -C	14.64 (2.31)	16.70 (2.31)	7.88 (4.51)	p=0.53	p=0.08
HDL ₃ -C	1.40 (1.11)	4.38 (1.10)	3.36 (2.16)	p=0.06	p=0.67
Apo A-1	0.91 (0.77)	2.00 (0.76)	2.43 (1.51)	p=0.31	p=0.80
Lp(a)	5.01 (9.98)	14.51 (9.80)	12.36 (19.7)	p=0.50	p=0.92
Direct LDL-C:HDL-C	-44.26 (1.06)	-56.81 (1.05)	-21.65 (2.06)	p<0.01	p<0.01
TC:HDL-C	-34.35 (0.88)	-44.51 (0.87)	-16.75 (1.71)	p<0.01	p<0.01

Source: CSR P692, pg. 4.

The results showed that co-administration of ezetimibe + atorvastatin produced consistent reductions in LDL-C that were greater than those achieved with either agent alone regardless of the treatment paradigm (i.e., co-initiation of the 2 agents or addition of ezetimibe to ongoing atorvastatin therapy), population characteristics, or treatment duration.

The statistical reviewer, Dr. Janice Derr conducted additional efficacy analyses specifically examining the treatment effects by Periods. An effect due to the Period was found to be statistically significant in Study P185 driven by a greater LDL-C lowering effect in Period 1 compared to Period 2 in Study 185. 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. The Period effect was not significant in Study P190.

To gain additional insight, Dr. Derr 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. Therefore, the statistical review concluded 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.

6.1.5 Analysis of Secondary Endpoints(s)

Other secondary efficacy variables included TC, HDL-C, TG, Apo B and non-HDL-C based on the currently approved indications for statins. The following two tables summarize these endpoints in Study P185 and P190.

Table 12: Summary of Percent Change from Baseline to Endpoint in Secondary Lipid Parameters Study P185

Lipid Endpoint	Percent Change from Baseline after 6 Weeks of Treatment				Pairwise Comparison	
	EZ/Atorva 10 mg/20 mg fixed-dose combination		Co-admin EZ 10 mg and Atorva 20 mg		EZ/Atorva 10mg/20mg fixed-dose combination vs. Co-admin EZ 10 mg and Atorva 20 mg	
	N	LS Mean (95% CI) [†]	N	LS Mean (95% CI) [†]	Difference in LS Means	97.5% expanded CI
LDL-C	353	-54.0 (-55.8, -52.2)	346	-53.8 (-55.7, -52.0)	-0.2	-1.7, 1.3
TC	353	-38.1 (-39.5, -36.8)	346	-38.5 (-39.8, -37.1)	0.3	-0.8, 1.4
HDL-C	353	5.4 (4.0, 6.7)	346	4.6 (3.2, 5.9)	0.8	-0.6, 2.2
Non-HDL-C	353	-50.1 (-51.8, -48.5)	346	-50.2 (-51.8, -48.5)	0.0	-1.3, 1.4
Apo-B	352	-42.6 (-44.2, -41.0)	345	-43.3 (-44.9, -41.7)	0.7	-0.6, 1.9
TG ^{††}	353	-28.3(-32.4, -24.0)	346	-29.9(-32.4, -27.3)	1.6	-3.2, 6.3

[†]For TG, based on cLDA model with terms for treatment, period and sequence. For all other lipid endpoints, based on an ANCOVA repeated measures model with terms for treatment, corresponding baseline lipid measurement, period and sequence. An unstructured covariance matrix was used.

^{††}Analyses were based on log-transformed data.;97.5% expanded CI calculated using the delta method.

cLDA=constrained Longitudinal Data Analysis; ANCOVA=Analysis of Covariance; CI=Confidence Interval; LS Mean=Least Squares Mean.

Given the nominal 95% confidence interval, (L, U), the corresponding 97.5% expanded confidence interval is (min(0,L), max(0,U)).

Equivalence is declared if the 97.5% expanded confidence interval for the mean difference between the combination and co-administration in percent change from baseline in LDL-C is contained within ±4%.

Source: CSR Study P185, Table 11-2, pg. 104.

Table 13: Summary of Percent Change from Baseline to Endpoint in Secondary Lipid Parameters Study P190

Lipid Endpoint	Percent Change from Baseline after 6 Weeks of Treatment				Pairwise Comparison	
	N	LS Mean (95% CI) [†]	N	LS Mean (95% CI) [†]	Difference in LS Means	97.5% expanded CI
	EZ/Atorva 10 mg/40 mg fixed-dose combination		Co-admin EZ 10 mg and Atorva 40 mg		EZ/Atorva 10mg/40mg fixed-dose combination vs. Co-admin EZ 10 mg and Atorva 40 mg	
LDL-C	280	-58.9 (-60.9, -56.9)	280	-58.7 (-60.7, -56.7)	-0.2	-1.9, 1.4
TC	280	-43.0 (-44.5, -41.5)	280	-42.9 (-44.4, -41.4)	-0.1	-1.4, 1.2
HDL-C	280	2.3 (0.8, 3.8)	280	2.6 (1.2, 4.1)	-0.3	-1.8, 1.2
Non-HDL-C	280	-55.4 (-57.2, -53.5)	280	-55.2 (-57.0, -53.4)	-0.2	-1.7, 1.4
Apo-B	278	-48.7 (-50.4, -47.0)	279	-48.3 (-50.0, -46.6)	-0.5	-1.9, 1.0
TG ^{††}	280	-36.2(-40.4, -31.6)	280	-36.2(-38.8, -33.5)	0.0	-4.9, 4.9

[†]For TG, based on cLDA model with terms for treatment, period and sequence. For all other lipid endpoints, based on an ANCOVA repeated measures model with terms for treatment, corresponding baseline lipid measurement, period and sequence. An unstructured covariance matrix was used.

^{††}Analyses were based on log-transformed data; 97.5% expanded CI calculated using the delta method.

cLDA=constrained Longitudinal Data Analysis; ANCOVA=Analysis of Covariance; CI=Confidence Interval; LS Mean=Least Squares Mean.

Given the nominal 95% confidence interval, (L,U), the corresponding 97.5% expanded confidence interval is (min(0,L), max(0,U)).

Equivalence is declared if the 97.5% expanded confidence interval for the mean difference between the combination and co-administration in percent change from baseline in LDL-C is contained within ±4%.

Source: CSR P190, Table 11-2, pg. 97.

The difference in means between treatment groups in P185 and P190 was small (generally contained within ±2%) for most of the secondary endpoints. The difference is most likely not clinically relevant.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Consistency of treatment effects in percent change from baseline in LDL-C at Week 6 was explored for certain subgroups: age, gender, and race.

Age in Study P185

The EZ/AT 10 mg/20 mg FDC tablet provided a generally consistent response relative to ezetimibe 10 mg co-administered with atorvastatin 20 mg for both age categories: less than 65 years and greater than or equal to 65 years. The FDC and the co-administration methods seemed to be more efficacious in patients ≥ 65 years.

Table 14: Subgroup Analysis by Age in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P185

Treatment Arm Category	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Age < 65 years					
Fixed Dose Combination EZ/AT 10mg/20mg	294	164 (31)	-53 (18)	-53 (-55, -51)	0 (-1.8, 1.7)
Co-admin EZ 10 mg + AT 20 mg	286	163 (32)	-53 (19)	-53 (-55, -51)	
Age ≥65 years					
Fixed Dose Combination EZ/AT 10mg/20mg	59	157 (35)	-60 (11)	-60 (-62, -57)	-0.9 (-3.6, 1.8)
Co-admin EZ 10 mg + AT 20 mg	60	157 (34)	-59 (11)	-59 (-61, -56)	

Source: CSR Study P185.

Gender in Study P185

Treatment with FDC EZ/AT was similar to the co-administration of ezetimibe 10 mg plus atorvastatin 20 mg within men and women subgroups. However, the FDC and the co-administration tablets seemed slightly more efficacious in women than in men.

Table 15: Subgroup Analysis by Gender in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P185

Treatment Arm Category	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Male Gender					
Fixed Dose Combination EZ/AT 10mg/20mg	136	157 (29)	-53 (17)	-52 (-56, -49)	-0.9 (-3.5, 1.8)
Co-admin EZ	136	157 (29)	-51 (20)	-52 (-55, -48)	

Treatment Arm Category Male Gender	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
10 mg + AT 20 mg					
Treatment Arm Category Female Gender					
Fixed Dose Combination EZ/AT 10mg/20mg	217	166 (34)	-55 (17)	-55 (-57, -53)	0.2 (-1.6, 2.0)
Co-admin EZ 10 mg + AT 20 mg	210	165 (34)	-55 (17)	-55 (-58, -53)	

Source: CSR Study P185.

Race in Study P185

Treatment with FDC EZ/AT was similar to the co-administration of ezetimibe 10 mg plus atorvastatin 20 mg within white and black subgroups. However, the FDC and the co-administration tablets was more efficacious in whites than in blacks (-56% vs. -45%). This result could be because there was a small number of blacks in the study (n=44).

There were too few patients in Asian and Other race categories to perform the expanded 97.5% CI.

Table 16: Subgroup Analysis by Race in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P185

Treatment Arm Category Race: White	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Fixed Dose Combination EZ/AT 10mg/20mg	300	163 (32)	-56 (16)	-55 (-57, -53)	-0.1 (-1.7, 1.5)
Co-admin EZ 10 mg + AT 20 mg	292	163 (33)	-55 (17)	-55 (-57, -53)	
Category Race: Black					
Fixed Dose	44	159 (30)	-45 (23)	-46 (-52, -40)	

Combination EZ/AT 10mg/20mg					-0.1 (-4.6, 4.3)
Co-admin EZ 10 mg + AT 20 mg	44	157 (29)	-45 (22)	-46 (-52, -40)	
Category Race: Asian					
Fixed Dose Combination EZ/AT 10mg/20mg	5	181 (43)	-47 (36)		
Co-admin EZ 10 mg + AT 20 mg	6	171 (46)	-49 (23)		
Category Race: Other					
Fixed Dose Combination EZ/AT 10mg/20mg	4	170 (28)	-64 (8)		
Co-admin EZ 10 mg + AT 20 mg	4	170 (28)	-56 (9)		

Source: CSR Study P185.

Age in Study P190

The EZ/AT 10 mg/40 mg FDC tablet provided a generally consistent response relative to ezetimibe 10 mg co-administered with atorvastatin 40 mg for both age categories: less than 65 years and greater than or equal to 65 years.

Table 17: Subgroup Analysis by Age in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P190

Treatment Arm	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Category					
Age <65 years					
Fixed Dose Combination EZ/AT 10mg/40mg	233	163 (31)	-59 (18)	-58 (-60, -56)	0.4 (-1.4, 2.3)
Co-admin EZ	233	164(31)	-59 (17)	-59 (-61, -56)	

Treatment Arm	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
10 mg + AT 40 mg					
Age Category ≥ 65 years					
Fixed Dose Combination EZ/AT 10mg/40mg	47	159 (24)	-63 (12)	-63 (-68, -59)	-3.1 (-6.8, 0.5)
Co-admin EZ 10 mg + AT 40 mg	47	155 (22)	-61 (16)	-60 (-64, -56)	

Source: CSR Study P190, Table 11-8; pg. 104.

Gender in Study P190

Treatment with FDC 10/40 EZ/AT was similar to the co-administration of ezetimibe 10 mg plus atorvastatin 40 mg within men and women subgroups. However, the FDC and the co-administration tablets seemed slightly more efficacious in men than in women.

Table 18: Subgroup Analysis by Gender in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P190

Treatment Arm Category Male Gender	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Fixed Dose Combination EZ/AT 10mg/40mg	125	160 (31)	-60 (15)	-60 (-63, -58)	-1.0 (-1.2, 3.2)
Co-admin EZ 10 mg + AT 40 mg	125	160 (31)	-62 (13)	-61 (-64, -59)	
Treatment Arm Category Female Gender					
Fixed Dose Combination EZ/AT 10mg/40mg	155	164 (30)	-59 (18)	-58 (-61, -55)	-1.2 (-3.6, 1.2)
Co-admin EZ	155	164 (30)	-57 (20)	-57 (-60, -54)	

Treatment Arm Category Male Gender	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
10 mg + AT 40 mg					

Source: CSR P190, Table 11-8, pg. 104.

Race in Study P190

Treatment with FDC 10/40 EZ/AT was similar to the co-administration of ezetimibe 10 mg plus atorvastatin 40 mg within white and black subgroups. However, the FDC and the co-administration tablets was more efficacious in whites than in blacks (-60% vs. -51%). There were too few patients in Asian and Other race categories to perform the expanded 97.5% CI.

Table 19: Subgroup Analysis by Race in Percent Change from Baseline LDL-C (mg/dL) after 6 Weeks of Treatment - P190

Treatment Arm Category Race: White	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Fixed Dose Combination EZ/AT 10mg/40mg	232	162 (31)	-61 (15)	-60 (-62, -58)	0.1 (-1.6, 1.7)
Co-admin EZ 10 mg + AT 40 mg	232	162 (31)	-61 (15)	-60 (-61, -58)	
Black					
Fixed Dose Combination EZ/AT 10mg/40mg	42	164 (29)	-51 (25)	-51 (-59, -44)	-2 (-8.7, 4.7)
Co-admin EZ 10 mg + AT 40 mg	42	166 (30)	-50 (24)	-49 (-57, -42)	
Asian					
Fixed Dose Combination EZ/AT 10mg/40mg	2	165 (36)	-69 (2)		

Treatment Arm Category Race: White	N	Baseline Mean (SD)	Percent Change From Baseline in LDL-C after 6 Weeks of Treatment		
			Mean (SD)	LS Mean (95% CI)	Difference in LS Mean (97.5% expanded CI)
Co-admin EZ 10 mg + AT 40 mg	2	165 (36)	-72 (2)		
Other					
Fixed Dose Combination EZ/AT 10mg/40mg	4	148 (14)	-60 (4)		
Co-admin EZ 10 mg + AT 40 mg	3	154 (7)	-58 (9)		
LS Mean and CI not presented for subgroups Asian and Other due to insufficient data					

Source: CSR Study 190, Table 11-8, pg. 104.

7 Review of Safety

Safety Summary

In the previous NDA review cycle, the applicant submitted data from nine blinded and two open-label trials of ezetimibe co-administered with atorvastatin. The Agency's review of these trials did not reveal any novel toxicities associated with co-administration of ezetimibe with atorvastatin. Treatment with the combination of ezetimibe and atorvastatin was generally well tolerated, with an adverse experience profile similar to that of atorvastatin monotherapy at corresponding doses.

In this current review cycle, the applicant completed two clinical equivalence trials (P185 and P190). These two trials were pooled for the safety review because they were identical in design except for the use of 20 mg atorvastatin in one and 40 mg in the other. The safety pool of P185 and P190 is referred to as the "Clinical Equivalence Safety Pool". The following sections detail how the safety review was conducted.

Of the 734 randomized patients in P185 and P190, 686 patients received treatment of EZ/AT FDC during Period I or Period II and 701 patients received treatment of co-administration of ezetimibe 10 mg and atorvastatin during Period I or Period II.

Adverse reactions were reported by 185 (27%) of the 686 patients during EZ/AT FDC treatment and 189 (27%) of the 701 patients during ezetimibe + atorvastatin co-administration treatment. One or more serious adverse experiences were reported by 5

patients (0.7%) during EZ/AT FDC treatment and 6 patients (0.9%) during ezetimibe + atorvastatin co-administration treatment. There were no deaths.

Adverse reactions that led to discontinuation were reported by 11 patients (1.6%) during EZ/AT FDC treatment and 18 patients (2.6%) during ezetimibe + atorvastatin co-administration treatment.

7.1 Methods

The Agency requested that the applicant compare the safety findings from the Clinical Equivalence Pool with the safety findings previously presented in NDA 200153. Therefore, the applicant submitted a “qualitative” comparison between the Clinical Equivalence Pool and the Core Safety Pool (7 trials 6-14 week in duration) from the previous NDA submission. Because of the differences in design of P185 and P190 with the trials in the Core Safety Pool (cross-over vs. parallel), a new ISS was not submitted.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 20: Clinical Trials in Clinical Equivalence Safety Pool

Protocol	Design	Patient Population	N
P185	25-week randomized, double-blind 2-period, crossover study with a 5 week washout, a 2 week single-blind placebo run-in period, and two 6 week treatment crossover periods separated by a 6-week single-blind placebo washout period	Patients with hypercholesterolemia at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines)	Sequence 1: Co-admin EZ 10 mg and Atorva 20 mg to EZ/Atorva 10/20 mg FDC (n = 203) Sequence 2: EZ/Atorva 10/20 mg FDC to Co-admin EZ10 + Atorva 20 (n = 203)
P190	25-week randomized, double-blind 2-period, crossover study with a 5 week washout, a 2 week single-blind placebo run-in period, and two 6 week treatment crossover periods separated by a 6-week single-blind placebo washout period	Patients with hypercholesterolemia at low, moderate, or moderately high risk (according to NCEP/ATP III guidelines)	Sequence 1: Co-admin EZ 10 mg and Atorva 40 mg to EZ/Atorva 10/40 mg FDC (n = 164) Sequence 2: EZ/Atorva 10/40 mg FDC to Co-admin EZ 10 + Atorva 40 (n = 164)

Table 21: Clinical Trial in Core Safety Pool (Second Review Cycle)

Protocol	Design	Patient Population	Relevant Treatments (Sample Size)
040	6-week, double-blind, randomized, placebo-controlled ezetimibe or placebo, added to ongoing statin (n=3030)	Patients with hypercholesterolemia not at LDL-C goal as defined by the NCEP ATP III guidelines	All Atorva (n= 401) EZ+All Atorva (n= 793)
2173	8-Week, double-blind, randomized, placebo-controlled, ezetimibe or placebo, added to ongoing statin (n=796)	Patients with primary hypercholesterolemia	All Atorva (n=162) EZ+ All Atorva (n= 146)
079	6-week , double-blind, randomized, parallel group titration trial, titration of atorvastatin from 20 mg to 40 mg or addition of EZ 10 mg to atorvastatin 20 mg (n=184)	Patients at moderate high risk for CHD who have not reached optional NCEP ATP III goal LDL-C level (<100 mg/dL) on atorvastatin 20 mg alone	All Atorva (n=98) EZ+ All Atorva (n=96)
090	6-week , double-blind, randomized, parallel group titration trial, titration of atorvastatin from 40 mg to 80 mg or addition of EZ 10 mg to atorvastatin 40 mg (n=579)	Patients at high risk for CHD who have not reached optional NCEP ATP III goal LDL-C levels (<70 mg/dL) on atorvastatin 40 mg alone	All Atorva (n= 289) EZ+ All Atorva (n= 286)
0692	12-week, double-blind, placebo-controlled, parallel-group, factorial study (n=628)	Patients with primary hypercholesterolemia, LDL-C \geq 145 mg/dL to \leq 250 mg/dL, and TG \leq 350 mg/dL	Placebo (n=60) EZ (n=65) All Atorva (n=248) EZ+ All Atorva (n= 255)
0693	14-week, double-blind, randomized, active-control, response-based atorvastatin dose titration vs EZ 10 mg plus atorvastatin 10 to 40 mg (n= 1847)	Patients with HEFH or CHD or multiple cardiovascular risk factors (greater than or equal to two) and primary hypercholesterolemia	All Atorva (n= 316) EZ+ All Atorva (n= 305)
112	12-week, double-blind, randomized, parallel arm, EZ 10	Elderly patients with hypercholesterolemia at high risk of CHD	All Atorva (n=525) EZ+ All Atorva (n= 526)

Protocol	Design	Patient Population	Relevant Treatments (Sample Size)
	mg added to atorvastatin 10 mg vs titration to atorvastatin 20 mg and to 40 mg		

7.1.2 Categorization of Adverse Events

Adverse events were defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the product (active drug or placebo), whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the product was also an adverse event.

Adverse events for the Clinical Equivalence Safety Pool were standardized using MedDRA, Version 15.0. Each term reported in a patient’s CRF was linked to a preferred term that served to consolidate reports of a similar nature; these preferred terms were used for safety analyses.

To assess the applicant’s categorization of events, I compared the verbatim terms to the coded preferred terms for studies P185 and P190 (Tables 5 and 6). In general, the reported adverse event term was appropriately mapped to a preferred term.

Table 22: Comparison of Reported Terms with Dictionary Derived Terms in Patients who Discontinued Study due to Adverse Event Study P185

Reported Term for the Adverse Event	Dictionary-Derived Term	ADVERSE EVENT DISCONTINUED
"COLON SPASMS"	Gastrointestinal pain	1 (0.09%)
ABDOMINAL CRAMPS	Abdominal pain	1 (0.09%)
BILATERAL LEG PAIN	Pain in extremity	1 (0.09%)
BRONCHITIS	Bronchitis	1 (0.09%)
CHEST PAIN	Chest pain	1 (0.09%)
CONSTIPATION	Constipation	1 (0.09%)
CONTUSIONS CHIN AND LEFT SHOULDER	Contusion	1 (0.09%)
CRAMPS,BILATERAL, FEET	Muscle spasms	1 (0.09%)
DEPRESSION	Depression	1 (0.09%)
DIARRHEA	Diarrhoea	2 (0.18%)
DIZZINESS	Dizziness	1 (0.09%)
DRY MOUTH	Dry mouth	1 (0.09%)
DYSPEPSIA	Dyspepsia	1 (0.09%)
FATIGUE	Fatigue	3 (0.27%)
FLATULENCE	Flatulence	2 (0.18%)
FRACTURED RIGHT ANKLE	Ankle fracture	1 (0.09%)
GASTRIC ULCER	Gastric ulcer	1 (0.09%)
HEAVY FEELING IN EYES BILATERAL	Asthenopia	1 (0.09%)
INDIGESTION	Dyspepsia	1 (0.09%)
INTERMITTENT BILATERAL LOWER LEG CRAMPS	Muscle spasms	1 (0.09%)
INTERMITTENT DYSPEPSIA	Dyspepsia	1 (0.09%)
INTERMITTENT HOT FLASHES	Hot flush	1 (0.09%)
JOINT PAIN	Arthralgia	1 (0.09%)
LOWER LEG CRAMPS	Muscle spasms	1 (0.09%)

Table 23: Comparison of Reported Terms with Dictionary Derived Terms in Patients who Discontinued Study due to Adverse Event Study P190

Reported Term for the Adverse Event	Dictionary-Derived Term	ADVERSE EVENT DISCONTINUED
(L) VENTRICLE ENLARGEMENT	Dilatation ventricular	1 (0.18%)
ACHES, PAIN OF THE HANDS AND FEET	Pain in extremity	1 (0.18%)
ACHINESS	Pain	1 (0.18%)
ANEMIA	Anaemia	1 (0.18%)
ATHEROSCLEROTIC DISEASE	Arteriosclerosis	1 (0.18%)
BILATERAL ARM ACHES	Pain in extremity	1 (0.18%)
CHEST CONGESTION	Respiratory tract congestion	1 (0.18%)
CHEST PAIN	Chest pain	1 (0.18%)
COMMON COLD	Nasopharyngitis	3 (0.53%)
COUGH	Cough	1 (0.18%)
DECREASED ENERGY LEVEL	Asthenia	1 (0.18%)
DEPRESSION	Depression	1 (0.18%)
DIZZINESS	Dizziness	2 (0.35%)
ECZEMA BILATERAL HANDS	Eczema	1 (0.18%)
ELEVATED ALKALINE PHOSPHATASE	Blood alkaline phosphatase increased	1 (0.18%)
ELEVATED ALT	Alanine aminotransferase increased	1 (0.18%)
ELEVATED AST	Aspartate aminotransferase increased	1 (0.18%)
ELEVATED BILIRUBIN, DIRECT	Bilirubin conjugated increased	1 (0.18%)
ELEVATED BILIRUBIN, TOTAL	Blood bilirubin increased	1 (0.18%)
ELEVATED CREATINE PHOSPHOKINASE	Blood creatine phosphokinase increased	1 (0.18%)
ELEVATED GAMMA GLUTAMYL TRANSFERASE	Gamma-glutamyltransferase increased	1 (0.18%)

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 734 patients were included in the Clinical Equivalence Safety Pool with 367 patients randomized to the sequence of EZ/ AT (20 mg or 40 mg) FDC followed by EZ10 mg + atorvastatin (20 mg or 40 mg) co-administration and 367 randomized to the sequence of ezetimibe 10 mg + atorvastatin (20 mg or 40 mg) co-administration followed by ezetimibe 10 mg/atorvastatin (20 mg or 40 mg) FDC. Therefore, there were 6 weeks of blinded experience comparing EZ/AT FDC to ezetimibe + atorvastatin co-administration therapy.

Table 24: Patient Exposure in Clinical Equivalence Safety Pool (P185 and P190)

	Fixed Dose Combination EZ/AT 10mg/All Atorva	Co-Administration EZ 10mg + All Atorva
Median Duration of Treatment (Weeks)	6	6
Number of Patients:		
< 2 Weeks	8	17
2 to < 4 Weeks	7	10
4 to 6 Weeks	496	503
>6 Weeks	175	171
All Atorva= Atorvastatin 20 or 40 mg pooled across all doses		

The mean treatment duration was 41.7 days (range: 1 to 56 days) for EZ/AT FDC and 41.2 days (range: 1 to 70 days) for ezetimibe + atorvastatin co-administration.

7.2.2 Explorations for Dose Response

Review of dose response of the different strengths of Liptruzet is addressed in the Clinical Review for NDA 200153 from the previous submission.

7.2.3 Special Animal and/or In Vitro Testing

See the pharmacology/toxicology review from the previous submission, NDA 200153 as well as NDA 21-455 in which ezetimibe was approved for monotherapy and co-administration therapy with statins.

7.2.4 Routine Clinical Testing

The methods and frequency of monitoring laboratory parameters were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant has adequately addressed enzymatic pathways for clearance of ezetimibe and atorvastatin in previous review cycles.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the Clinical Equivalence Safety Pool.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse experiences were reported by 5 patients (0.7%) during EZ/AT FDC treatment and 6 patients (0.9%) during ezetimibe + atorvastatin co-administration treatment.

Table 25: Number of Patients with Serious Adverse events by System Organ Class and Period - Clinical Equivalence Safety Pool

	EZ 10 mg/Atorva* fixed-dose combination			Co-admin EZ 10 mg and Atorva*		
	Period I	Period II	Total	Period I	Period II	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients in Population:	364	322	686	365	336	701
With one or more adverse events	4(1.1)	1(0.3)	5(0.7)	4(1.1)	2(0.6)	6(0.9)
With no adverse events	360(98.9)	321(99.7)	681(99.3)	361(98.9)	334(99.4)	695(99.1)
Cardiac disorders	2(0.5)	0(0.0)	2(0.3)	2(0.5)	2(0.6)	4(0.6)
Angina Unstable	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Coronary Artery Disease	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.1)
Myocardial Infarction	1(0.3)	0(0.0)	1(0.1)	0(0.0)	1(0.3)	1(0.1)
Stress Cardiomyopathy	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Ventricular Extrasystoles	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Gastrointestinal disorders	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Colitis Ischaemic	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Hepatobiliary disorders	0(0.0)	1(0.3)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Cholecystitis Acute	0(0.0)	1(0.3)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Infections and infestations	0(0.0)	1(0.3)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Sepsis	0(0.0)	1(0.3)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Metabolism and nutrition disorders	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Hypokalaemia	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0.3)	0(0.0)	1(0.1)	1(0.3)	0(0.0)	1(0.1)
Basal Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Squamous Cell Carcinoma	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)

* Atorvastatin 20 mg or 40 mg

Source: Clinical Summary of Safety, Table 2.7.4:13, pg. 39.

7.3.3 Dropouts and/or Discontinuations

Overall, the incidence of AEs leading to discontinuations was similar between the EZ/AT FDC, the ezetimibe plus atorvastatin co-administration, and the Core Safety Pool in the previous submission to this NDA. Approximately 1.6% of patients in the EZ/AT FDC discontinued due to an AE as compared to 2.6% in the co-administration of ezetimibe plus atorvastatin. This is in comparison with 2.7% of patients who discontinued due to an AE in the Core Safety Pool.

The major body system class contributing to discontinuations was the Musculoskeletal and Connective Tissue Disorders. There was also a difference between the groups with the Musculoskeletal and Connective Tissue Disorders; the co-administration of ezetimibe plus atorvastatin reported a 1% total discontinuation rate in this body system class as compared to the EZ/AT FDC which reported a discontinuation rate of 0.4%.

The following table summarizes the adverse events leading to study discontinuation in the Clinical Equivalence Safety Pool.

Table 26: Number (%) of Patients with Adverse Events Leading to Discontinuation - Clinical Equivalence Safety Pool

	EZ 10 mg/Atorva* fixed-dose combination			Co-admin EZ 10 mg and Atorva*		
	Period I	Period II	Total	Period I	Period II	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients in Population:	364	322	686	365	336	701
With one or more adverse events	10(2.7)	1(0.3)	11(1.6)	14(3.8)	4(1.2)	18(2.6)
With no adverse events	354(97.3)	321(99.7)	675(98.4)	351(96.2)	332(98.8)	683(97.4)
Cardiac disorders	1(0.3)	0(0.0)	1(0.1)	1(0.3)	1(0.3)	2(0.3)
Myocardial Infarction	1(0.3)	0(0.0)	1(0.1)	0(0.0)	1(0.3)	1(0.1)
Ventricular Extrasystoles	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Gastrointestinal disorders	2(0.5)	0(0.0)	2(0.3)	3(0.8)	0(0.0)	3(0.4)
Abdominal Discomfort	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Abdominal Pain	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Abdominal Pain Upper	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Flatulence	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Gastrointestinal Pain	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
General disorders and administration site conditions	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Fatigue	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Hepatobiliary disorders	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Hyperbilirubinaemia	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Investigations	0(0.0)	1(0.3)	1(0.1)	0(0.0)	2(0.6)	2(0.3)
Alanine Aminotransferase Increased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.1)
Aspartate Aminotransferase Increased	0(0.0)	1(0.3)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Blood Creatine Phosphokinase Increased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.1)
Musculoskeletal and connective tissue disorders	3(0.8)	0(0.0)	3(0.4)	6(1.6)	1(0.3)	7(1.0)
Muscle Spasms	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.3)	2(0.3)
Muscular Weakness	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Myalgia	1(0.3)	0(0.0)	1(0.1)	3(0.8)	0(0.0)	3(0.4)
Pain In Extremity	2(0.5)	0(0.0)	2(0.3)	1(0.3)	0(0.0)	1(0.1)
Nervous system disorders	2(0.5)	0(0.0)	2(0.3)	1(0.3)	0(0.0)	1(0.1)
Dizziness	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Migraine	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Paraesthesia	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Psychiatric disorders	1(0.3)	0(0.0)	1(0.1)	1(0.3)	0(0.0)	1(0.1)
Depression	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Loss Of Libido	1(0.3)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)
Respiratory, thoracic and mediastinal disorders	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)
Nasal Congestion	0(0.0)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.1)

* Atorvastatin 20 mg or 40 mg

Source: Clinical Summary of Safety Appendix 2.7.4:22, pg. 129.

7.3.4 Significant Adverse Events

Muscle-Related Events

In this review, myopathy is defined as the presence of muscle symptoms in association with CPK elevations to levels $\geq 10XULN$. Rhabdomyolysis is defined as the presence of myopathy plus end-organ damage such as renal compromise. Typically, the CPK elevation in rhabdomyolysis is $\geq 50XULN$.

The following table summarizes CPK by categorical elevations. For CPK $>10XULN$, there was 1 of 680 patient (0.1%) in the FDC EZ/AT treatment arm as compared to zero in the co-administration arm.

Table 27: Number (%) of Patients with Post-baseline Values for Creatine Phosphokinase (CPK) – Clinical Equivalence Safety Pool

	FDC EZ 10/ All Atorva			Co-Administration EZ 10 mg + All Atorva		
	Period I m/n (%)	Period II m/n (%)	Total m/n (%)	Period I m/n (%)	Period II m/n (%)	Total m/n (%)
Patients	364	322	686	365	336	701
CPK						
3XULN to <5XULN	2/358 (0.6)	2/322 (0.6)	4/680 (0.6)	5/358 (1.4)	4/336 (1.2)	9/694 (1.3)
3XULN to <10XULN	1/358 (0.3)	2/322 (0.6)	3/680 (0.4)	1/358 (0.3)	2/336 (0.6)	3/694 (0.4)
$\geq 10XULN$	1/358 (0.3)	0	1/680 (0.1)	0	0	0
$\geq 10XULN$ with muscle symptoms	1/358 (0.3)	0	1/680 (0.1)	0	0	0

All Atorva= Atorvastatin 20 mg or 40 mg

Source: Summary of Clinical Safety, Table 2.7.4:34, pg. 66.

The Core Safety Pool (original NDA 200153) showed incidences of CPK $\geq 10xULN$ in the atorvastatin monotherapy treatment group of 0.1% versus 0.0% in the ezetimibe + atorvastatin co-administration group, with a pattern consistent with the findings of the Clinical Equivalence Safety Pool.

Table 28: Number (%) of Patients with Post-baseline CPK by Dose- Clinical Equivalence Safety Pool

	EZ 10 mg / Atorva 20 mg fixed-dose Combination	Co-admin EZ 10 mg and Atorva 20 mg	EZ 10 mg / Atorva 40 mg fixed-dose Combination	Co-admin EZ 10 mg and Atorva 40 mg
3xULN to < 5xULN	2/378 (0.5)	5/384 (1.3)	2/302 (0.7)	4/310 (1.3)
5xULN to < 10xULN	3/378 (0.8)	2/384 (0.5)	0(0.0)	1/310 (0.3)
≥10xULN	1/378 (0.3)	0(0.0)	0(0.0)	0(0.0)
≥10xULN with muscle symptoms	1/378 (0.3)	0(0.0)	0(0.0)	0(0.0)
≥10xULN with muscle symptoms considered drug-related	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Summary of Clinical Safety, Table 2.7.4:35, pg. 67.

Increased CPK was reported as an AE in 7 of 686 patients (1.0%) during EZ/AT FDC treatment and 6 of 701 patients (0.9%) during ezetimibe + atorvastatin co-administration.

The one patient in the FDC EZ/AT 20 mg who reportedly had a CPK >10ULN was further described as follows: This patient was a 59 yo white man who, on Day 49 of Period I, had a CPK elevation of 2,841 IU/L. The CPK elevation had been preceded by an AE of musculoskeletal discomfort. It was noted the patient was very active and had recently done some strenuous weight lifting during a workout. Follow-up value obtained 5 days after the event was 237 IU/L.

7.3.5 Submission Specific Primary Safety Concerns

Liver-Related Events

The Liver Expert Panel of the National Lipid Association (NLA) affirms that there is a relation between statin therapy and elevations in serum aminotransferase levels (ALT and AST). This has been consistently demonstrated in clinical trials performed during statin phase 2 and 3 development programs and in long-term, end point trials. The prescribing information for each statin cites these associations.

Aminotransferase elevations >3 times the upper limit of normal generally occur in <1% of patients across the dose range for marketed statins; the exceptions are aminotransferase elevations of this magnitude that occur in 2%–3% of patients receiving atorvastatin 80 mg/ day or the combination of ezetimibe and a statin.³

³ Cohen DE, Anania FA, and Chalasani N. An Assessment of Statin Safety by Hepatologists. Am J Cardiol 2006;96 [sup]:77C-81C.

Significant liver damage appears to be extremely uncommon with statins, especially when one considers the magnitude of their use worldwide. One study estimates that the incidence of statin-associated liver failure is about 1 per million person-years of use. Of the 51,741 patients who underwent liver transplantation in the United States between 1990 and 2002, there were 3 patients in whom the procedure was performed for acute liver failure presumably caused by statins. Of these 3 patients, 2 had acute liver failure while receiving cerivastatin and 1 had liver failure that was apparently associated with simvastatin. After an extensive review of the literature, the Liver Expert Panel could find no direct evidence of death due to liver failure caused by statin therapy.³

In the Clinical Equivalence Safety Pool, consecutive ALT or AST elevations $\geq 3xULN$ in patients with post-baseline laboratory measurements were reported by 3 (0.4%) of 680 patients during EZ/AT FDC treatment and 3 (0.4%) of 694 patients during ezetimibe + atorvastatin co-administration treatment. No patients were identified with hepatitis-related adverse experiences in the Clinical Equivalence Safety Pool and no patients were identified as potential Hy's law cases (see following table).

The Core Safety Pool showed incidences of consecutive ALT or AST elevations $\geq 3xULN$ in the atorvastatin monotherapy treatment group of 0.5% versus 0.6% in the ezetimibe + atorvastatin co-administration group, with a pattern consistent with the findings of the Clinical Equivalence Safety Pool.

The Core Safety Pool showed incidences of any hepatitis-related adverse experience in the atorvastatin monotherapy treatment group of 0.1% versus 0.0% in the ezetimibe + atorvastatin co-administration group. The Core Safety Pool also showed incidences of potential Hy's Law cases in the atorvastatin monotherapy treatment group of 0.0% versus 0.1% in the ezetimibe + atorvastatin co-administration group.

Table 29: Number (%) of Patients with Post-baseline ALT and AST- Clinical Equivalence Safety Pool

	EZ 10 mg/Atorva* fixed-dose combination			Co-admin EZ 10 mg and Atorva*		
	Period I m/n (%)	Period II m/n (%)	Total m/n (%)	Period I m/n (%)	Period II m/n (%)	Total m/n (%)
Patients in Population	364	322	686	365	336	701
ALT						
2xULN to <3xULN	6/358 (1.7)	6/322 (1.9)	12/680 (1.8)	5/358 (1.4)	5/336 (1.5)	10/694 (1.4)
≥3xULN	1/358 (0.3)	2/322 (0.6)	3/680 (0.4)	2/358 (0.6)	2/336 (0.6)	4/694 (0.6)
≥3xULN, consecutive †	1/358 (0.3)	1/322 (0.3)	2/680 (0.3)	2/358 (0.6)	1/336 (0.3)	3/694 (0.4)
≥5xULN	0(0.0)	1/322 (0.3)	1/680 (0.1)	1/358 (0.3)	0(0.0)	1/694 (0.1)
≥5xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AST						
2xULN to <3xULN	0(0.0)	0(0.0)	0(0.0)	1/358 (0.3)	3/336 (0.9)	4/694 (0.6)
≥3xULN	1/358 (0.3)	1/322 (0.3)	2/680 (0.3)	1/358 (0.3)	0(0.0)	1/694 (0.1)
≥3xULN, consecutive †	1/358 (0.3)	0(0.0)	1/680 (0.1)	1/358 (0.3)	0(0.0)	1/694 (0.1)
≥5xULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥5xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
ALT and/ or AST						
2xULN to <3xULN	6/358 (1.7)	6/322 (1.9)	12/680 (1.8)	6/358 (1.7)	7/336 (2.1)	13/694 (1.9)
≥3xULN	2/358 (0.6)	2/322 (0.6)	4/680 (0.6)	2/358 (0.6)	2/336 (0.6)	4/694 (0.6)
≥3xULN, consecutive †	2/358 (0.6)	1/322 (0.3)	3/680 (0.4)	2/358 (0.6)	1/336 (0.3)	3/694 (0.4)
≥5xULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥5xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
≥10xULN, consecutive †	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

* Atorvastatin 20 mg or 40 mg

Source: Clinical Summary of Safety, Table 2.7.4:24, pg. 53.

Narratives of Patients with Consecutive Elevations in ALT or AST at Least 3XULN

EZ 10 mg/ AT 20 mg FDC

1. Patient AN20160: 59 yo white male, on Day 49 (end of Period I) had an AST elevation >3X ULN (AST 168 mIU/mL, ALT 98 mIU/mL). Total bilirubin was within normal range. Follow-up lab values on Day 54 showed that AST decreased to 34 mIU/mL. Patient continued to Period II with ALT of 30 mIU/ml and AST of 30 mIU/mL reported on Day 127.
2. Patient AN20201: 37 yo white male, on Day 133 (end of treatment Period II) patient experienced ALT elevation ≥3x ULN (ALT 135 mIU/mL, AST 54 mIU/mL)

in the EZ/AT 10/20 mg FDC treatment group. Total bilirubin was within the normal range. Follow-up laboratory values were performed at Day 137; ALT had decreased 97 mIU/mL

EZ 10 mg+ AT 20 mg Co-administration

1. Patient AN20159: 54 yo white female, on Day 43 (end of treatment Period I) patient experienced ALT and AST elevations $\geq 3x$ ULN (ALT 212 mIU/mL, AST 170 mIU/mL) in the EZ 10 mg + Atorva 20 mg co-administration treatment group. Total bilirubin was within the normal range. Follow-up laboratory values were performed at Day 49; ALT was 92 mIU/mL) and AST was 44 mIU/mL). Patient continued into study Period II (combination treatment) with ALT of 20 mIU/mL and AST of 23 mIU/mL reported on Day 86 and ALT of 24 mIU/mL and AST of 22 mIU/mL on Day 128.

EZ 10 mg/ AT 40 mg FDC

1. Patient AN20230: 69 yo white female, on Day 48 (end of treatment Period I) patient experienced ALT elevation $\geq 3x$ ULN (ALT 112 mIU/mL, AST 45 mIU/mL) in the EZ/Atorva 10/40 mg FDC treatment group. Total bilirubin was within the normal range. Follow-up laboratory values were performed at Day 52; ALT was 49 mIU/mL). Patient continued into study Period II (co-administration treatment) with ALT of 76 mIU/mL and AST of 44 mIU/mL reported on Day 90 and ALT of 55 mIU/mL and AST of 35 mIU/mL on Day 127.

EZ 10mg + AT 40 mg Co-administration

1. Patient AN20295: 47 yo white male, on Day 43 (end of treatment Period I) patient experienced ALT elevation $\geq 3x$ ULN (ALT 159 mIU/mL, AST 90 mIU/mL) in the EZ 10 mg + Atorva 40 mg co-administration treatment group. Total bilirubin was within the normal range. Follow-up laboratory values were performed at Day 85; ALT was 43 mIU/mL). Patient continued into study Period II (combination treatment) with ALT of 109 mIU/mL and AST of 68 mIU/mL reported on Day 127.
2. Patient AN20327: 57 yo white female, on Day 119 (end of treatment Period II) patient experienced ALT elevation $\geq 3x$ ULN (ALT 99 mIU/mL, AST 90 mIU/mL) in the EZ 10 mg + Atorva 40 mg co-administration treatment group. Total bilirubin was within the normal range. Follow-up laboratory values were performed at Day 121;. ALT was 86 mIU/mL).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the adverse event safety profile in the Clinical Equivalence Safety Pool for ezetimibe/atorvastatin FDC was similar to co-administration of ezetimibe + atorvastatin, and both were also generally consistent with the data for ezetimibe + atorvastatin co-administration in the Core Safety Pool presented in the original NDA 200153.

Table 30: Number (%) of Patients with Adverse Events \geq 2.0% in Any Treatment Arm by System Organ Class- Clinical Equivalence Safety Pool

	EZ10 mg/ All Atorva* fixed-dose combination	Co-administration EZ 10 mg and all Atorva
	n (%)	n (%)
Number of Patients in Population	686	701
With one or more adverse events	185 (27)	189 (27)
With no adverse events	501 (73)	512 (73)
Gastrointestinal disorders	35 (5)	34 (4.9)
Infections and infestations	55 (8)	53 (7.6)
Nasopharyngitis	11 (1.6)	16 (2.3)
Upper Respiratory Tract Infection	15 (2.2)	12 (1.7)
Injury, poisoning and procedural complications	14 (2.0)	18 (2.6)
Investigations	15 (2.2)	20 (2.9)
Musculoskeletal and connective tissue disorders	46 (6.7)	49 (7.0)
Arthralgia	12 (1.7)	15 (2.1)
Nervous system disorders	19 (2.8)	13 (1.9)

Source: Summary of Safety, Table 2.7.4:10, pg 35.

7.4.2 Laboratory Findings

Liver (ALT, AST) and muscle (CPK) related laboratory results are discussed in Section 7.3.5.

Renal Biochemistry

Renal function as assessed by BUN and serum creatinine showed no clinically meaningful differences between the EZ/AT FDC and ezetimibe + atorvastatin co-administration treatment groups.

Table 31: Number of Patients Exceeding Predefined Limits for Renal Function - Clinical Equivalence Safety Pool

	EZ 10 mg/ Atorva* fixed-dose combination	Co-admin. EZ 10 mg and Atorva*	Difference in Proportions (EZ/Atorva* fixed-dose combination minus Co-admin. EZ 10 mg and Atorva*)	
			Observed Difference	Calculated Difference (95% CI) [§]
	m/n (%)	m/n (%)		
Serum blood urea nitrogen (mg/dL) < 5	0.0	0.0		0.00 (-0.53,0.53)
Serum blood urea nitrogen (mg/dL) > 30m	2/680 (0.3)	6/694 (0.9)	-0.6	-0.58 (-1.45,-0.04)
Serum creatinine (mg/dL) > 2	0.0	1/694 (0.1)		-0.14 (-0.79,0.39)

* Atorvastatin 20 mg or 40 mg
[§] Calculated difference and confidence interval calculated using the efficient score method associated with the modified McNemar's test.
 Confidence interval calculated if incidence of event in either treatment group is >1%.
[†] Patients must have taken at least one dose of study medication and have at least one postbaseline measurement to be included in the analysis.
 %=m/n x 100 = (Number of patients with elevated test / number of patients tested) x 100.
 Baseline is treated as the values measured at randomization. Should this be missing, the last non-missing pre-randomization measurement is used.

Source: Clinical Summary of Safety, Table 2.7.4:37, pg. 69.

7.4.3 Vital Signs

Although the applicant did not pool the data for vital sign parameters, no effects on blood pressure or pulse were observed in the reports for the individual studies P185 and P190.

7.4.4 Electrocardiograms (ECGs)

Although the applicant did not pool the data for ECGs, no effects on ECG parameters were observed in the reports for the individual studies P185 and P190.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

No data were submitted in the current review cycle on immunogenicity. Repeat dose toxicity studies were submitted and reviewed by the pharmacology toxicology reviewer in previous submissions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the Clinical Equivalence Safety Pool, the incidence rates of AEs across different doses of EZ + AT did not follow a dose dependent relationship.

However, in the Core Safety Pool, there was a slight difference in the AE incidence between EZ + AT 80 mg and the other three doses of the EZ/AT co-administration doses.

Table 32: Summary of Adverse Events by Dose- Core Safety Pool

Number (%) of Patients	EZ + Atorvastatin 10mg N=1207	EZ + Atorvastatin 20mg N=693	EZ + Atorvastatin 40mg N=741	EZ + Atorvastatin 80mg N=208
≥ 1 Adverse Event	398 (33.0)	203 (29.3)	227 (30.6)	78 (37.5)
Serious Adverse Event	29 (2.4)	13 (1.9)	18 (2.4)	5 (2.4)
Discontinued due to Adverse Event	33 (2.7)	9 (1.3)	14 (1.9)	7 (3.4)

Source: Clinical Review NDA 200153, Table 50, pg. 93.

7.5.2 Time Dependency for Adverse Events

Please see previous Agency reviews for the Zetia NDA for these analyses.

7.5.3 Drug-Demographic Interactions

This section was previously reviewed in the Clinical Review for NDA 200153. The conclusion was that for patients <65 and those >65 years, the AEs in the co-administration group (all doses) was similar to the all atorvastatin monotherapy group.

7.5.4 Drug-Disease Interactions

This section was previously addressed in the Clinical Review for NDA 200153 (second review cycle). Please see that review for complete details.

7.5.5 Drug-Drug Interactions

This section was previously addressed in the Clinical Review for NDA 200153 (second review cycle). Please see that review for complete details.

7.6 Additional Safety Evaluations

This section/ subsections (7.6.1-7.6.4) was previously addressed in the Pharmacology/toxicology review and the Clinical Review for NDA 200153 (second cycle). Please see those reports for complete details.

8 Postmarket Experience

Post-marketing experience with ezetimibe and atorvastatin are discussed in the Clinical Review for NDA 200153 (second cycle).

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

As both ezetimibe and atorvastatin are approved drugs marketed in the US and there were no significant safety issues identified with the co-administration of ezetimibe and atorvastatin, an Advisory Committee meeting was not considered necessary.

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/s/

IFFAT N CHOWDHURY
04/10/2013

ERIC C COLMAN
04/10/2013

Summary Review for Regulatory Action

Date	February 14, 2012
From	Eric Colman, MD, Deputy Division Director
NDA#	200153
Applicant Name	MSP Singapore Company
Date of Submission	Original September 2, 2009; Resubmission April 29, 2011
PDUFA Goal Date	February 29, 2012
Proprietary Name / Established (USAN) Name	Atozet/Ezetimibe/Atorvastatin
Dosage Forms / Strength	10/10, 10/20, 10/40, and 10/40 mg Tablets
Proposed Indication(s)	Treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Janice Derr, PhD
Pharmacology Toxicology Review	Indra Antonipillai, PhD
CMC Review/OBP Review	Joseph Leginus, PhD/Deepika Lakhani, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Johnny Lau, PhD
OSI	Michael Skelly, PhD
OSE/DMEPA	Anne Tobenkin, PharmD

OND=Office of New Drugs
 CMC=Chemistry, Manufacture, and Control
 OBP=Office of Biopharmaceutics
 OSI=Office of Scientific Investigations
 OSE=Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

Signatory Authority Review Template

1. Introduction

This memorandum summarizes the findings and recommendations from the scientific and regulatory disciplines assigned to this application. I am not aware of any substantive differences of opinion between disciplines on the recommended regulatory action.

2. Background

This is a 505b2 New Drug Application (NDA) for a fixed-dose combination (FDC) of ezetimibe and atorvastatin (hereafter *eze/atorva*). The NDA was originally submitted on 2 September 2009. Due to chemistry, manufacturing, and controls (CMC) deficiencies, a refuse-to-file action was taken on 20 October 2009. The applicant addressed these deficiencies and resubmitted the application on 29 April 2011.

The applicant is seeking the following indications for *eze/atorva*: 1) to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C and to increase HDL-C in patients with primary or mixed hyperlipidemia; and 2) to reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments.

The proposed dosage range is 10/10 mg to 10/80 mg once daily anytime of the day with or without food. The recommended starting dose is 10/10 mg or 10/20 mg once daily.

Ezetimibe is an inhibitor of dietary cholesterol absorption. This compound was approved in 2002 with the tradename Zetia® to reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; to reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor; to reduce elevated sitosterol in patients with homozygous sitosterolemia; and to reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin. The original ezetimibe NDA contained clinical data, including lipoprotein lipid levels, with ezetimibe coadministered with atorvastatin crystalline.

Atorvastatin is an HMG-CoA reductase inhibitor (statin) originally approved in 1996. Atorvastatin is indicated to reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors; to reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors; to reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD; to reduce elevated total-C, LDL-C, Apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia and mixed dyslipidemia; to reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia; reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia; and reduce elevated total-C, LDL-C, and Apo B levels in boys and

postmenarchal girls, 10 to 17 years of age, with heterozygous hypercholesterolemia after failing an adequate trial of diet therapy. A generic atorvastatin was approved by the Agency in the latter part of 2011.

A fixed-dose combination of ezetimibe and 10 to 80 mg of simvastatin (Vytorin®) was approved by the Agency in 2004.

It is important to note that the applicant has not provided the Agency with any pharmacodynamic data with the to-be-marketed eze/atorva FDC product, which contains an atorvastatin calcium amorphous formulation manufactured by Dr. Reddy's Laboratories. All clinical studies that examined lipid parameters in this NDA were conducted with co-administration of ezetimibe with the atorvastatin calcium crystalline formulation (Lipitor®) manufactured by Pfizer.

Thus, this application relies entirely on bioequivalence (BE) bridging data to establish the efficacy and safety of eze/atorva FDC to coadministration of the reference drugs ezetimibe (Zetia®) and atorvastatin crystalline. The applicant does own or have right of reference to the latter drug.

3. CMC/Biopharmaceutics

All of the original CMC deficiencies that led to the refuse-to-file action have been satisfactorily addressed by the applicant in their resubmission. I concur with the conclusions reached by the CMC reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding CMC issues.

The biopharmaceutics reviewer, Dr. Lakhani, recommends approval of this application. I concur that there are no outstanding biopharmaceutics issues that would prevent approval of this application.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Antonipillai, nonclinical studies conducted with ezetimibe and atorvastatin (Lipitor) under the ezetimibe NDA adequately characterize the safety of these two drugs. The applicant submitted a 3-month toxicity/toxicokinetics study of atorvastatin amorphous in dogs and 2 gene-toxicity studies. These studies adequately qualified the impurities/excipients of the atorvastatin amorphous formulation. No safety issues were identified in these studies. Dr. Antonipillai recommends approval of this application and indicates that there are no outstanding nonclinical pharmacology or toxicology issues. I concur.

5. Clinical Pharmacology

In a pivotal BE study (P145), 288 healthy volunteers participated in either Part 1, 2, or 3 of the study, as shown below:

- 1) Single doses of coadministration of 10 mg EZE tablet plus 10 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/10 mg FDC tablet under fasting conditions
- 2) Single doses of coadministration of 10 mg EZE tablet plus 20 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/20 mg FDC tablet under fasting conditions
- 3) Single doses of coadministration of 10 mg EZE tablet plus 80 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/80 mg FDC tablet under fasting conditions

Serial plasma samples were obtained pre-dose and 96 hours post-dose to determine unconjugated and total ezetimibe levels and pre-dose and 48 hours post-dose to determine plasma levels of atorvastatin and its ortho- and para-hydroxy metabolites.

As depicted in the following table excerpted from Dr. Lau’s review, the estimated geometric mean ratio (GMR) and its 90% confidence interval for the atorvastatin component from the eze/atorva 10/20 mg FDC was (b) (4). To demonstrate bioequivalency, the 90% confidence interval must be 0.80, 1.25. Hence, these data indicate that the eze/atorva 10/20 mg FDC is not bioequivalent to coadministered ezetimibe 10 mg and atorvastatin 20 mg.

Study P145 – Relative Pharmacokinetic Parameters for Atorvastatin and Ezetimibe

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI) FDC Tablet/ Coadministration (b) (4)
		FDC Tablet	Coadministration	
Atorvastatin	AUC _{0-∞} (ng*hr/mL)			
	C _{max} (ng/mL)			
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL)			
	C _{max} (ng/mL)			

The 10/10 mg and 10/80 mg eze/atorva FDC doses were bioequivalent to coadministered ezetimibe 10 mg and atorvastatin 10 mg and 80 mg.

In a second pivotal BE trial (P183), 96 healthy volunteers received, under fasting conditions, eze/atorva 10/40 mg FDC and coadministered ezetimibe 10 mg and atorvastatin 40 mg during a randomized, 2-period, crossover study.

Plasma drug and metabolite samples were obtained as outlined above in study P145. As shown in the below table, which can be found in Dr. Lau’s review, the eze/atorva 10/40 mg FDC was not BE to coadministered ezetimibe 10 mg and atorvastatin 40 mg. The GMR for the C_{max} for the atorvastatin component of the eze/atorva FDC was below the benchmark of 0.80.

Study P183 – Relative Pharmacokinetic Parameters for Atorvastatin and Ezetimibe

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI) FDC Tablet/ Coadministration
		FDC Tablet	Coadministration	

Atorvastatin	AUC _{0-∞} (ng*hr/mL) C _{max} (ng/mL)	(b) (4)
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL) C _{max} (ng/mL)	

In sum, the two pivotal BE studies submitted by the applicant demonstrate that the eze/atorva 10/20 mg and 10/40 mg FDC formulations are not BE to coadministered ezetimibe 10 mg and atorvastatin 20 mg or atorvastatin 40 mg. Because the applicant did not submit clinical lipid data with the to-be-marketed eze/atorva FDC, the results of the pivotal BE are central to the regulatory action taken on this NDA.

The below figure from Dr. Lau’s review provides a summary of the BE data, including information on the effect of food on the pharmacokinetic parameters of the eze/atorva FDC.

Comparison of Atorvastatin (A) and Ezetimibe (E) PK Among Formulations

Comparison (Trial No.)	Cmax(90%CI)	AUC(90%CI)	Assessment
(b) (4)			

Food reduces the rate and extent of absorption of the atorvastatin component of the eze/atorva FDC.

The applicant provided information from mathematical PK/PD modeling in an attempt to convince the Agency that the reductions in atorvastatin Cmax observed with the eze/atorva FDC 10/20 mg and 10/40 mg doses would not meaningfully influence levels of LDL-C. The clinical pharmacology reviewers do not, for a variety of reasons, agree with the applicant that

the modeling data negate or supersede the BE data from Studies P145 and P183. I agree with their assessment.

The clinical pharmacology discipline recommends that this application receive a Complete Response action due to the failed BE for the atorvastatin component of the eze/atorva 10/20 mg and 10/40 mg FDC dosage strengths. Further, they recommend that the applicant reformulate these two dosage strengths in order to satisfy the accepted BE benchmarks. I concur with these recommendations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Drs. Chowdhury and Derr have reviewed the efficacy data and Dr. Chowdhury has completed a safety review of the submitted clinical data.

The applicant has proposed inclusion in the Clinical Studies section of the eze/atorva FDC labeling of data from studies P692, P2154, P693, P079, and P090, P1030, and P1417. The applicant has also proposed inclusion of cardiovascular outcomes data from the approved atorvastatin labeling.

Study P692 was 12 weeks in duration and was conducted in subjects with primary hyperlipidemia. The results established that ezetimibe and atorvastatin (10-80 mg) each contribute to the LDL-C lowering effects of the two drugs used in combination. Study P1030 was a 12-week study of ezetimibe and atorvastatin in patients with homozygous familial hyperlipidemia (HoFH). Data from these two studies were previously reviewed by the Agency under the ezetimibe NDA. The results from the studies can be found in the ezetimibe labeling.

This memorandum summarizes Drs. Chowdhury and Derr's conclusions of the efficacy data from studies P693, P079, P090, P2154, and P1417.

Studies P693, P079, and P090 were 14-week (P693) and 6-week investigations (other two studies) that examined the LDL-C lowering efficacy of ezetimibe coadministered with atorvastatin 10 mg vs. atorvastatin 20 mg (P693); ezetimibe coadministered with atorvastatin 20 mg vs. atorvastatin 40 mg (P079); and ezetimibe coadministered with atorvastatin 40 mg vs. atorvastatin 80 mg (P090).

All studies included a run-in phase prior to randomization, during which subjects received atorvastatin at the lower dose of the co-administration arm. In study P693, at randomization subjects either continued on atorvastatin 10 mg monotherapy or received ezetimibe 10 mg in addition to atorvastatin 10 mg. In subjects not reaching LDL-C goal at Week 4/5 or 9/10, the dose of atorvastatin was doubled. In studies P079 and P090, at randomization subjects either continued to receive atorvastatin at the run-in dose plus ezetimibe 10 mg or received double

the run-in dose of atorvastatin. All studies were conducted in a double-blind manner; study P693 included an open-label 10 mg atorvastatin arm.

The primary endpoint in study P693 was the proportion of subjects with an LDL-C < 100 mg/dl at Week 14. The primary endpoint in studies P079 and P090 was the mean percent change in LDL-C from baseline to Week 6.

A total of nearly 1400 subjects with primary hyperlipidemia took part in these three studies. The mean baseline LDL-C level in study P693 was approximately 186 mg/dl. The proportion of subjects who achieved an LDL-C < 100 mg/dl was 7.3% in the atorvastatin 20 mg arm and 22% in the ezetimibe + atorvastatin 10 mg arm ($p < 0.01$). The mean baseline LDL-C level in study P079 was about 119 mg/dl. The mean percent change in LDL-C at Week 6 was -11.0% in the atorvastatin 40 mg arm and -31.0% in the ezetimibe + atorvastatin 20 mg arm ($p < 0.001$). The mean baseline LDL-C level in P090 was approximately 89 mg/dl. The mean percent change in LDL-C at Week 6 was -11.0% in the atorvastatin 80 mg arm and -27% in the ezetimibe + atorvastatin 40 mg arm ($p < 0.001$).

The run-in phases during which all subjects received atorvastatin therapy explains why the mean changes in LDL-C from randomization to Endpoint are smaller than expected if the measurements were made prior to the run-in period.

Study P2154 was a 12-month extension of the 12-week study P692. A total of 246 subjects volunteered to enroll into study P2154: 45 to placebo + atorvastatin and 201 to ezetimibe + atorvastatin. After 6 weeks, the dose of atorvastatin could be titrated up by doubling the dose to a maximum of 80 mg. The goal was to achieve the subject's target based on the National Cholesterol Education Program (NCEP) guidelines. The mean percent change in LDL-C from baseline (in study P692) to Month 12 was -49% in the pooled ezetimibe + atorvastatin arm and -39% in the pooled atorvastatin arm.

Study P1417 was a 24-month open-label extension to study P1030. Forty-four subjects with HoFH enrolled into this extension study. Thirty-five of these subjects received open-label ezetimibe co-administered with atorvastatin 40 mg (the remaining seven received simvastatin). The dose of atorvastatin was doubled if the LDL-C goal of < 100 mg/dl was not achieved after at least 1 month of treatment. The mean percent change in LDL-C from entry into the extension to Month 24 was -15%.

8. Safety

The safety profile of ezetimibe, when used along or in combination with a statin, is reasonably well characterized. In placebo-controlled clinical trials of ezetimibe monotherapy, the most commonly-reported adverse reactions included upper respiratory tract infection, diarrhea, arthralgia, sinusitis, and pain in extremity.

The safety profile of atorvastatin is similarly well characterized. Statins, including atorvastatin, are associated with myopathy ranging from mild muscle aches to clinically significant rhabdomyolysis. These lipid-lowering drugs are also associated with hepatic transaminitis. The

risk for drug-induced liver injury, however, is considered very low. Recently-reported data indicate that statins, with the possible exception of pravastatin, may lead to increases in serum glucose levels, as assessed by HbA1c levels.

As highlighted in the ezetimibe labeling, co-administration of ezetimibe with a statin is associated with a higher incidence of hepatic transaminitis compared with ezetimibe or statin monotherapy.

Data from seven clinical studies were pooled for an overall analysis of safety. Duration of exposure in these studies ranged from 6 to 14 weeks. Treatment arms included placebo, ezetimibe, atorvastatin, and ezetimibe + atorvastatin. Approximately 4500 subjects were included in these studies.

The incidence of consecutive ALT ≥ 3 xULN was 0.4% in all atorvastatin groups combined, 0.5% in all ezetimibe + atorvastatin groups combined, and 0% in ezetimibe monotherapy and placebo groups. One subjects randomized to ezetimibe + atorvastatin (10 mg) had consecutive ALT ≥ 10 xULN. The incidence of CPK 3xULN to <5 xULN was 1.5% in the ezetimibe monotherapy group, 0.6% in the all atorvastatin groups combined, 0.5% in the all ezetimibe + atorvastatin groups combined, and 0% in the placebo group. One subjects from the ezetimibe + atorvastatin 40 mg group and one subject from the all atorvastatin group had had a CPK value ≥ 10 xULN with muscle symptoms. There were no cases of clinically significant rhabdomyolysis.

All told, Dr. Chowdhury's review of a relatively large database of short and long-term exposure did not reveal any novel toxicities associated with co-administered use of ezetimibe with atorvastatin.

9. Advisory Committee Meeting

An advisory committee meeting was not considered necessary for this application given that both products are approved and there are no clinical or regulatory issues that require input from our advisory committee.

10. Pediatrics

The applicant was granted a full waiver for pediatric studies because the FDC product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and it is not likely to be used in a substantial number of pediatric patients.

Pediatric studies were conducted with ezetimibe and atorvastatin, under their respective NDAs.

11. Other Relevant Regulatory Issues

Dr. Chowdhury reviewed the financial disclosure information provided by the sponsor and concluded that there were no financial interests or arrangements between the applicant and the clinical investigators.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed tradename, Atozet, and found it acceptable. The tradename will be re-evaluated during the next review cycle.

The Office of Scientific Investigations conducted inspections of the clinical and analytical portions of studies P145 and P183, both of which examined the bioequivalency of eze/atorva versus co-administration of the marketed components. Aside from a recommendation that data from one subject in study P145 be excluded from the overall analysis because one or more of this individual's plasma samples were misidentified at the clinical site, there were no notable issues related to the inspections. According to Dr. Lau, the misidentified sample was for the ezetimibe component of the 10/20 mg FDC. It is Dr. Lau's judgment that the misidentification of a single ezetimibe plasma sample will not affect the overall results from study P145.

12. Labeling

Because the application is not being approved during this review cycle, no labeling reviews by the clinical or clinical pharmacology reviewers have been conducted. Based on a consult from DMEPA, the Division has conveyed recommendations regarding the proposed container and carton labels.

13. Decision/Action/Risk Benefit Assessment

Because the atorvastatin components of the 10/20 mg and 10/40 mg eze/atorva FDC product were not bioequivalent to 20 mg and 40 mg atorvastatin (Lipitor) used in combination with ezetimibe, the applicant has not established an adequate bridge to the reference listed product.

Although the 10/10 mg and 10/80 mg dosage strengths of the eze/atorva FDC product are bioequivalent to co-administered ezetimibe with 10 mg and 80 mg atorvastatin, given that the primary rationale for the eze/atorva FDC product is patient convenience, I do not recommend approval of two of the four dosage strengths. Based on prescription-use data for Vytorin®, a fixed-dose combination of ezetimibe and simvastatin, the 10/20 mg and 10/40 mg eze/atorva FDC strengths would no doubt be the most commonly prescribed dosages. The unavailability of two dosage strengths undermines the primary rationale for the proposed FDC product. This is particularly true considering that the applicant proposed eze/atorva 10/20 mg as a starting dose.

Therefore, I agree with the clinical pharmacology reviewer's recommendation that this application receive a Complete Response. In order to satisfy the bioequivalency/bridging requirements, the applicant would need to successfully reformulate the 10/20 mg and 10/40 mg dosage strengths. Alternatively, the applicant could provide clinical data demonstrating that the LDL-C lowering effects of the 10/20 mg and 10/40 mg eze/atorva FDCs are

“equivalent” or “non-inferior” to the LDL-C lowering effects of 10 mg ezetimibe co-administered with 20 mg and 40 mg of marketed atorvastatin.

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/s/

ERIC C COLMAN
02/29/2012

CLINICAL REVIEW

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Application Number(s) 200,153
Priority or Standard Standard

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Division / Office DMEP/OND II

Reviewer Name(s) Iffat N. Chowdhury, MD
Review Completion Date 1/20/2012

Established Name Ezetimibe/atorvastatin
(Proposed) Trade Name Atozet
Therapeutic Class Lipid lowering product
Applicant MSP

Formulation(s) Fixed-dose combination
Dosing Regimen Once daily
Indication(s) Primary hypercholesterolemia
and homozygous familial
hypercholesterolemia
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

MSP Singapore Company (MSP), the applicant, submitted Atozet, a fixed dose combination (FDC) of ezetimibe and amorphous atorvastatin, for the treatment of patients with primary hyperlipidemia, mixed dyslipidemia, or patients with homozygous familial hypercholesterolemia (HoFH).

This is the applicant's second submission of NDA 200,153. The sponsor's first submission of this NDA was on September 2, 2009. However, the Division of Metabolism and Endocrinology Products (DMEP) refused to file the NDA the first time due to numerous chemistry, manufacturing, and control issues including the unavailability of the manufacturing and testing facilities for GMP inspections.

The final recommendation for this review cycle is that daily doses of Atozet (ezetimibe/atorvastatin 10/10 mg, 10/20 mg, 10/40 mg, 10/80 mg) not be approved based on the lack of bioequivalence data for the 10/20 mg and 10/80 mg doses.

1.2 Risk Benefit Assessment

The recommendation for a Complete Response (CR) is based on the failure to establish bioequivalence of the ezetimibe/ atorvastatin 10 mg/20 mg FDC to the co-administration of ezetimibe 10 mg + atorvastatin 20 mg. Similarly, there was a failure to establish bioequivalence of the ezetimibe/ atorvastatin 10 mg/40 mg FDC to the co-administration of ezetimibe 10 mg + atorvastatin 40 mg. In both cases, the failure was due to the atorvastatin component of the FDC; the C_{max} of atorvastatin was (b) (4) in the FDC as compared to individual atorvastatin tablets.

In addition, there was a food-effect in which food decreased atorvastatin AUC_{0-inf} and C_{max} 11% and 35%, respectively.

The two remaining strengths of Atozet, 10 mg/10mg and 10 mg/80 mg were bioequivalent to the corresponding co-administered doses of ezetimibe + atorvastatin.

In this NDA, there were no other clinical data for the four strengths of the ezetimibe/ atorvastatin FDC, other than the pivotal bioequivalence trial which was necessary to bridge all the clinical data on co-administration of ezetimibe + atorvastatin. Therefore a CR was the logical recommendation.

Consideration was given to approving the two strengths of Atozet (10/10mg and 10/80mg) for which bioequivalence was established. However, it was felt that there would be dose titration problems if only the lowest strength and the highest strength of this FDC were approved. For example, patients already on a stable regimen of atorvastatin 40 mg and ezetimibe co-administration would not be able to switch over to the corresponding dose of the FDC. Confusion-free labeling for only the lowest and highest dose of Atozet would not be feasible.

Consideration was given to approving only the 10/80 mg dose of Atozet for patients with HoFH. However, approving only one strength of the FDC for a very small segment of the population when the individual tablets were readily available was not deemed to be a large public health benefit.

Another option would be to approve all strengths of Atozet and label for administration under fasting conditions. However, this would mean that the established requirement of meeting bioequivalence would have to be relaxed. As both ezetimibe and a generic version of atorvastatin are available, waiving the Agency's requirements to approve this FDC is not a compelling action.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Atozet® is a fixed-dose combination drug product of two approved lipid-altering drugs, ezetimibe (Zetia®) and the amorphous formulation of atorvastatin (Lipitor®).

Ezetimibe inhibits the intestinal absorption of cholesterol and was approved in 2002 for the treatment of primary hypercholesterolemia, both as monotherapy and in combination with statins and fenofibrates. It is also approved for the treatment of

hereditary sitosterolemia and in combination with atorvastatin or simvastatin for the treatment of HoFH. Ezetimibe is available only as a 10 mg tablet.

Atorvastatin is an HMG-CoA reductase inhibitor which blocks the rate-limiting enzyme in cholesterol synthesis. It has been marketed in the US since 1998 and has indications for treatment of primary hypercholesterolemia (both familial and non-familial forms) and mixed dyslipidemia. In addition to its lipid-lowering effects, atorvastatin is indicated to reduce the risk of mortality and cardiovascular morbidity in patients with or at high risk of coronary heart disease. Atorvastatin is available as a 10, 20, 40, or 80 mg tablet.

The ezetimibe/atorvastatin FDC was formulated in four tablet strengths: 10/10, 10/20, 10/40, 10/80 mg. The applicant proposes that the FDC be indicated for adjunctive therapy to diet for the reduction of elevated TC, LDL-C, Apo-B, TG and non-HDL-C and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia, or mixed dyslipidemia. In addition the product would be indicated for the reduction of elevated TC and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g, LDL apheresis).

2.2 Tables of Currently Available Treatments for Proposed Indications

The drugs used to treat dyslipidemias are of six classes: HMG CoA reductase inhibitors (statins), fibric acid derivatives, nicotinic acid derivatives, cholesterol binding resins (bile acid sequestrants), cholesterol absorption inhibitors (ezetimibe) and fish oils. These products have been approved as monotherapy and as combination therapy. A few have been approved as FDC products.

The most relevant currently available treatment is Vytorin®, the only other FDC drug product of ezetimibe and a statin (simvastatin). Vytorin® was approved in the US in 2004 to reduce elevated TC, LDL-C, Apo-B, TG, and non-HDL-C and to increase HDL-C in patients with primary hyperlipidemia or mixed hyperlipidemia. It is also indicated to reduce TC and LDL-C in patients with HoFH.

In 2008, the results of the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial were released. ENHANCE was a randomized, double-blind, active-controlled trial conducted in patients with heterozygous familial hypercholesterolemia (HeFH). A total of 725 patients were randomized 1:1 to receive either Vytorin® 10/80 or simvastatin 80 mg for 2 years. The primary efficacy outcome was the change in ultrasound-determined carotid artery thickness (cIMT).

Following two years of treatment, cIMT increased by 0.011 mm in the Vytorin® group and by 0.006 mm in the simvastatin group. The difference in the changes in cIMT between the two groups was not statistically significant. However, the levels of LDL-C

decreased by 56% in the Vytorin® group and decreased by 39% in the simvastatin group. The difference in the reductions in LDL-C between the two groups was statistically significant.

After review of the ENHANCE trial data, the Agency determined that there were several possible explanations for why the larger reduction in LDL-C observed in the Vytorin® group did not translate into significant improvement in cIMT. These included:

- enrollment of a patient population who received prior lipid-altering or statin therapy which may have reduced the ability to demonstrate a reduction or improvement in cIMT with Vytorin® compared with simvastatin therapy
- the 2-year duration of ENHANCE which may have been too short to demonstrate a favorable effect of cholesterol lowering on cIMT
- some other unknown properties of ezetimibe that may negate the beneficial effects of LDL-C lowering on cIMT.

An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin® Efficacy International Trial) is examining whether Vytorin® reduces the risk for cardiovascular events compared with simvastatin alone. This trial of 18,000 patients is scheduled to be completed in 2013. IMPROVE-IT will provide data regarding Vytorin®'s effect on the risk for cardiovascular disease events.

2.3 Availability of Proposed Active Ingredient in the United States

HMG-CoA reductase inhibitors are anti-hyperlipidemic agents whose development originated with the discovery of mevastatin (Compactin®) in 1976 and mevinolin (lovastatin – Mevacor®) in 1979. Over the last 20 years, a total of 8 statins have come to the market worldwide. Lovastatin was approved in the US in 1987, pravastatin (Pravachol®) was approved in 1991, followed by simvastatin (Zocor®) and fluvastatin (Lescol®). A 'second generation' of more effective and more potent statins followed with the approval of cerivastatin (Baycol®) in 1997 (subsequently withdrawn in 2001 due to myotoxicity) and atorvastatin (Liptor®) in 1998. Rosuvastatin (Crestor®) was approved in 2003 and pitavastatin (Livalo®) was approved in 2008.

2.4 Important Safety Issues With Consideration to Related Drugs

As a class of drugs, statins have been associated with myopathy and rare cases of rhabdomyolysis. According to findings from 21 clinical trials providing 180,000 person years of follow-up in patients treated with a statin or placebo, myopathy (defined as muscle symptoms plus CK >10XULN) occurred in 5 patients per 100,000 person-years and rhabdomyolysis in 1.6 patients per 100,000 person-years (placebo-corrected).

Statins have been associated with elevated liver aminotransaminases (ATs) and rarely hepatitis and liver failure. Asymptomatic liver AT elevations >3XULN are seen in <1% of patients on low and intermediated doses of statins and 2 to 3% at high doses. The

cause of this elevation in liver AT with statin therapy has not been determined, but in many if not most cases, statin-related transaminitis does not appear to herald significant liver injury, even with continued statin treatment.

The NDA review of ezetimibe revealed a slightly higher increase in liver ATs in the ezetimibe group compared to placebo but no cases of hepatitis were reported. Clinical AEs were more commonly reported in the hepato-biliary body system. Recent post-marketing reports for ezetimibe have included cases of anaphylaxis-like side-effects and pancreatitis. Ezetimibe was associated with increased bile-cholesterol content in preclinical studies; however, it is unclear whether these findings result in an increased risk for developing pancreatitis. Gallbladder-related AEs were selectively reported and these findings are summarized in the safety section.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This NDA was initially refused for filing by the Agency on 29 October 2009 for several CMC deficiencies. The applicant resubmitted this NDA on 26 April 2011 with responses to each filing deficiency and other agency comments. The four filing deficiencies cited by the Agency are listed below:

1. You indicate that the manufacturing and testing facilities are currently not ready for GMP inspections. Therefore, this NDA is considered to be incomplete and cannot be filed until all facilities involved in the manufacturing and testing of the commercial product are ready for GMP inspections.

Applicant's Response: All facilities involved in the manufacturing and testing of commercial product are ready for GMP inspections.

2. Provide the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54.

Applicant's Response: The unexecuted master production records are provided in Sec. 3.2.R.4 FDA Filing.

3. Your primary stability batches were manufactured at an R&D facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data as well as multipoint dissolution profiles.)

Applicant's Response: Three months of long term and accelerated stability data have been generated on batches manufactured at the commercial manufacturing

site and are provided in Sec. 3.2.P.8.3.1 and Sec. 3.2.P.8.3.2, respectively. Data are presented from three batches of each strength that were placed on stability for the primary stability study (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg). These data include multipoint dissolution profiles.

4. The application did not include any information to bridge the performance of the clinically tested batches to the commercial products (e.g. multipoint in vitro dissolution profiles).

Applicant's Response: Multipoint dissolution profiles generated on the bioequivalence batches of each strength have been compared with batches manufactured at the commercial site and the data are provided in Sec. 3.2.P.8.1.6.7. In addition, the 10 mg/10 mg, 10 mg/20 mg, and 10 mg/80 mg bioequivalence batches were also part of the primary stability study. The dissolution data for ezetimibe and atorvastatin show similar release profiles between the bioequivalence batches and commercial product. The four bioequivalence batches (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg) were the only clinically tested batches of the fixed dose combination product.

The applicant's responses to these CMC filing deficiencies will be evaluated by the CMC reviewer.

2.6 Other Relevant Background Information

On November 7, 2005, Pfizer Global Research and Development, Inc. filed a Citizen's Petition (Docket No. FDA-2005-P-0315) regarding the approval of any ANDA containing amorphous atorvastatin in the USA. Pfizer Inc. was concerned that applicants would seek approval of polymorphs of atorvastatin that are different from, and may be inferior in quality to, Lipitor®. According to Pfizer, these physical forms of atorvastatin may be susceptible to higher levels of impurities, may degrade more quickly and have inferior stability compared to Lipitor®.

On November 30, 2011, the Agency issued a response to the above cited Citizen's Petition. The Agency stated that it believed that its existing recommendations to industry on assessing active ingredient sameness and stability of polymorphic forms of drug substances, as well as those on comprehensive chemistry, manufacturing, and controls and impurities, are adequate to enable an ANDA applicant to address any potential drug product stability, degradation, and impurity issues associated with the amorphous form of atorvastatin.

Furthermore, the Agency's existing policies and review practices are sufficient for a critical evaluation of the variables that have the potential to affect drug product quality of drug products containing amorphous atorvastatin. Any such evaluation would be based

on current scientific data and information, the Agency's knowledge of the drug, the Agency's scientific experience and expertise, and the nature and extent of the data and information provided by an ANDA applicant to support approval of a drug product containing amorphous atorvastatin. The Agency also declined to pursue the development of standards for identity for atorvastatin through a public process.¹

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

On 7 September 2011, this clinical reviewer requested additional information from the applicant regarding missing AE fields from the ISS:

FDA Comment:

"There are missing dictionary derived terms for the following reported adverse events in the ISS for NDA 200,153 accounting for 822 events in 621 subjects. This is a concern because a large number of adverse events that were reported by patients were not mapped to the dictionary-derived term. The missing terms may affect the common adverse events analysis. How does the company account for it?"

The applicant responded on 22 September 2011:

MSP Response:

"Of the 822 missing events identified, most (814) of these are records which should have been deleted, as they represent empty fields not associated with data that should have been included in the dataset.

In total, there are 8 records, effecting 7 patients, associated with an adverse event (AE) reported verbatim term which did not get mapped to a MedDRA dictionary term. Thus each of the MedDRA associated fields for these 8 records are missing. All other reported AEs in the database have populated MedDRA fields.

In 5 of these 7 patients (involving 6 reported verbatim terms), the matching MedDRA terms for these reported verbatim terms coded to MedDRA terms already in the database for these patients. For 2 patients (007000121 and 010005094), the missing reported verbatim terms (heat and cold intolerance, and red papulous skin irritation, respectively) mapped to MedDRA terms (temperature intolerance, and rash papular) which were not previously included in the database.

Below are the 8 reported verbatim terms now mapped to MedDRA 13.1. The addition of these two events to the database has a minimal impact on the analyses as temperature intolerance, and rash papular are not uncommon events, nor serious or unexpected in the general

¹ Response to Docket No. FDA-2005-P-0315, Food and Drug Administration, November 30, 2011.

population. Therefore Merck is of the opinion that these additional events would not affect the conclusions regarding the safety of the product.”

Table 1: Response to FDA Request

study	subject ID	trt	Reported	Dictionary	Body System or Organ Class
P-02173	001005016	EZ 10 mg + Atorva 80 mg	ARTHRALGIA WHICH GRADUALLY INCREASED ON TREATMENT RAPIDLY RETURNED TO BASELINE SEVERITY IMMEDIATELY	ARTHRALGIA	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
P-02173	001005021	Atorva 80 mg	ELEVATED ACT	ALANINE AMINOTRANSFERASE INCREASED	INVESTIGATIONS
P-02173	007000121	EZ 10 mg + Atorva 20 mg	HEAT AND COLD INTOLERANCE	TEMPERATURE INTOLERANCE	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
P-02173	009005073	Atorva 40 mg	SINUSITIS MAXILLARIS ET FRONTALIS	SINUSITIS	INFECTIONS AND INFESTATIONS
P-02173	010005094	Atorva 20 mg	RED PAPULOUS SKIN IRRITATIONS	RASH PAPULAR	SKIN AND SUBCUTANEOUS TISSUE DISORDERS
P-02173	030005271	Atorva 40 mg	ANGINA PECTORIS ALSO AT REST	ANGINA PECTORIS	CARDIAC DISORDERS
P-02173	030005271	Atorva 40 mg	AUGNA PECTORIS ALSO IN TEST	ANGINA PECTORIS	CARDIAC DISORDERS
P-02173	047000790	EZ 10 mg + Atorva 20 mg	LEFT CALF SWOLLEN & TENDER	PAIN IN EXTREMITY	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Source: Submission to NDA 200, 153, 9/22/2011.

According to the table submitted by the applicant, the majority (5 out of 8) of the missing data were from patients on atorvastatin monotherapy. This reviewer determined that the missing data from Study P2173 would not affect the overall safety conclusions of the FDC ezetimibe + atorvastatin.

3.2 Compliance with Good Clinical Practices

The clinical development program in Europe and US was conducted to the standards set out in the current good clinical practice (GCP) guidelines. According to the applicant, no debarred investigators were used in the conduct of these studies.

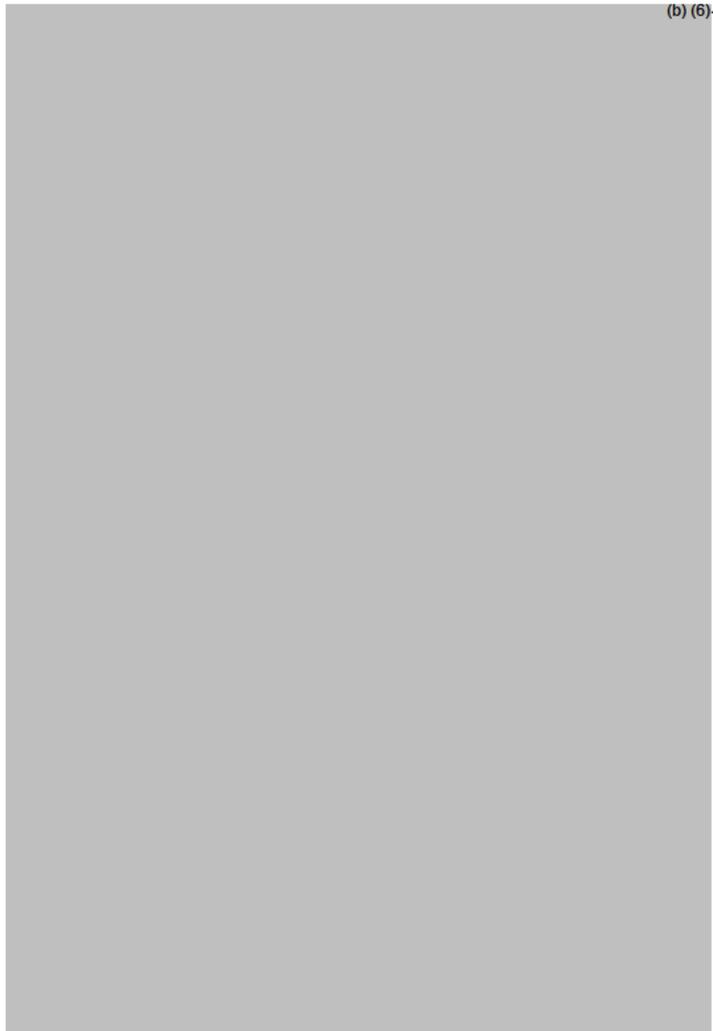
3.3 Financial Disclosures

Form 3454 was completed with a list of clinical investigators certified not to have engaged in financial interests or engagements.

The following table lists the names of all identified clinical investigators/sub-investigators by product, protocol and site number for the covered clinical studies who have met the disclosure criteria regarding financial interests and arrangements as defined in 21 CFR 54.2(a,b,c,f).

Table 2: Table of Clinical Investigators Who Hold Financial Interests or Arrangements Requiring Disclosure

Table D-1 Table of All Clinical Investigators/Subinvestigators Who Hold Financial Interests or Arrangements Requiring Disclosure		
Product/Protocol/Site	Investigator/ Subinvestigator	Financial Interests or Arrangements
	(b) (6)	Significant Payments of Other Sorts: Amount: \$35,000.00 (Approximately \$35,000.00 in speaker fees as reported by investigator on 03-02-2009.)
		Significant Payments of Other Sorts: Amount: \$36,000.00 (Approximately \$36,000.00 in speaker honorarium as reported by investigator on 03-21-2007.)
		Significant Payments of Other Sorts: Amount: \$33,000.00 (Approximately \$33,000.00 in speaker honorarium as reported by investigator on 04-15-2009.)
		Significant Payments of Other Sorts: Amount: \$50,000.00 (Approximately \$50,000.00 in speaker honorarium as reported by investigator on 05-19-2006.)

	<p>(b) (6) Significant Payments of Other Sorts: Amount: \$41,004.00 (Merck payments in the amount of \$29,504.00 and Schering-Plough payments in the amount of \$11,500.00 for educational programs and advisory/consultant meetings as reported by investigator on 03-17-2009.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$39,398.00 (Merck payments in the amount of \$28,398.00 and Schering-Plough payments in the amount of \$11,000.00 for educational programs and advisory/consultant meetings as reported by investigator on 11-19-2008.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$38,900.00 (Merck: \$11,700.00 for out of town and \$9,000.00 for local educational programs and advisory/consultant meetings. Schering-Plough: \$14,600.00 for out of town and \$3,600.00 for local educational programs and advisory/consultant meetings per 2006 tax records as reported by investigator on 03-16-2007.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$38,900.00 (Merck: \$11,700.00 for out of town and \$9,000.00 for local educational programs and advisory/consultant meetings. Schering-Plough: \$14,600.00 for out of town and \$3,600.00 for local educational programs and advisory/consultant meetings per 2006 tax records as reported by investigator on 02-02-2007.)</p>

(b) (6)	<p>Significant Payments of Other Sorts: Amount: \$140,007.00 (Payments in the amount of \$140,007.00 received in 2008 for speakers' bureau, consultant, grant/research, and advisory board as reported by investigator on 09-23-2009.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$244,081.00 (Payments in the amount of \$104,074.00 in 2007 and \$140,007.00 in 2008 for speaking and consulting honorarium as reported by investigator on 06-22-2009.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$208,000.00 (Payments in the amount of \$105,000.00 in 2007 and \$103,000.00 in 2008 for speaking and consulting honorarium as reported by investigator on 02-27-2009.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$100,000.00 (Approximately \$100,000.00 in 2005 for honorarium and consulting fees as reported by investigator on 08-04-2006.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$86,296.00 (Payments in the amount of \$30,420.00 in 2007 and \$55,876.00 in 2008 for speaking honoraria as reported by investigator on 07-13-2009.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$57,425.00 (Payments in the amount of \$21,178.00 in 2008 and \$36,247.00 in 2007 for speaking honoraria as reported by investigator on 10-13-2008.)</p>
	<p>Significant Payments of Other Sorts: Amount: \$30,000.00 (Payments from Merck and Schering-Plough for consulting and speaking estimated at \$30,000.00 as reported by investigator on 04-24-2009.)</p>
<p>Significant Payments of Other Sorts: Amount: \$27,000.00 (Approximately \$27,000.00 in speaker and consultant honoraria as reported by investigator on 02-12-2008.)</p>	

Source: Applicant's Financial Disclosures, Table D-1.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

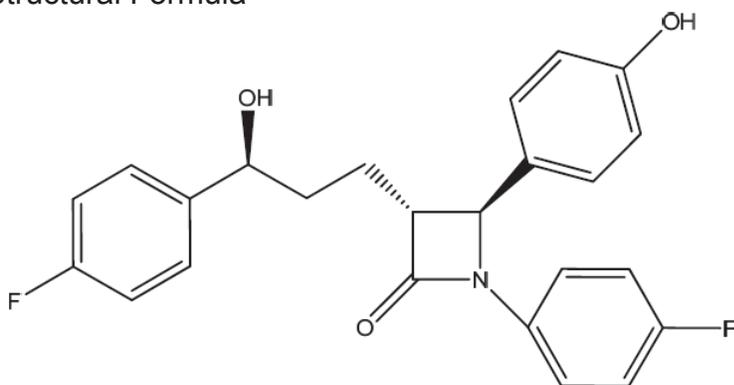
4.1 Chemistry Manufacturing and Controls

Please see the review by Dr. Joseph Leginus for complete details.

Ezetimibe

Chemical Name: 1-(4-Fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone

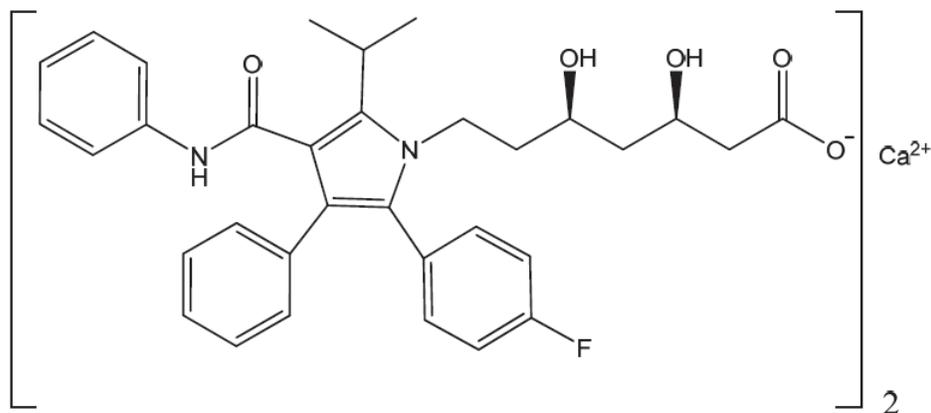
Structural Formula



Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. It is a white, crystalline powder that is freely to very soluble in ethanol, methanol and acetone and practically insoluble in water.

Atorvastatin

Chemical name:[R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1)



Atorvastatin Calcium (amorphous)

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, an enzyme involved in cholesterol biosynthesis. The amorphous

atorvastatin formulation is a white to off-white powder that is very slightly soluble in water, practically insoluble in acetonitrile and freely soluble in methanol. Information for amorphous atorvastatin calcium has been provided in Dr. Reddy's Type II DMF 18468 and is incorporated by reference herein. DMF 18468 was reviewed on 10- Jun-2008 and found to be adequate by the chemistry reviewer.

Dr. Deepika Lakhani reviewed the applicant's proposed in-vitro dissolution test for the ezetimibe/ atorvastatin FDC tablets and found all four dose strengths to be acceptable.

4.2 Clinical Microbiology

Clinical microbiology review not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth.

4.3 Preclinical Pharmacology/Toxicology

Please see the review by the Pharmacology/Toxicology reviewer.

4.4 Clinical Pharmacology

The clinical pharmacology program for this combination tablet consisted of four biopharmaceutical studies:

- Pilot biocomparison study – this pilot study was done to select an amorphous atorvastatin (b) (4) for use in the combination tablet (P9396-001)
- Descriptive food effect study of the combination tablet (Study 146)
- Two definitive bioequivalence studies – comparing the combination tablets to marketed agents dosed concomitantly (Studies 145 and 183)

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 recommends that this NDA submission receive a "Complete Response" because the *atorvastatin component* of the 10/20 ezetimibe/ atorvastatin FDC is not bioequivalent to the co-administration of ezetimibe + atorvastatin 20 mg. Similarly, the *atorvastatin component* of the 10/40 ezetimibe/ atorvastatin FDC is not bioequivalent to co-administration of ezetimibe + atorvastatin 40 mg.

The clinical pharmacology reviewer, Dr. Johnny Lau recommends that the applicant reformulate the 10 mg ezetimibe/20 mg atorvastatin and 10 mg ezetimibe/40 mg atorvastatin FDC tablets so as to demonstrate bioequivalence for both atorvastatin and ezetimibe to the co-administration of corresponding individual ezetimibe + atorvastatin tablets.

4.4.1 Mechanism of Action

Atorvastatin, an HMG-CoA reductase inhibitor, inhibits cholesterol biosynthesis, which leads to induction of the LDL-C receptor, thereby increasing removal of LDL-C from the blood and thus lowering circulating LDL-C levels. Ezetimibe reduces intestinal cholesterol absorption on average by 54 to 65% leading to a reduction in hepatic cholesterol stores and an increase in clearance of cholesterol from the blood, presumably also through up-regulation of the LDL-C receptor. Thus, the mechanism of cholesterol absorption inhibition is complementary to that of statins, but also shares the same common final pathway by ultimately leading to decreases in LDL-C through increases in hepatic clearance.

4.4.2 Pharmacodynamics

The applicant submitted a pharmacokinetic/ pharmacodynamic (PK/PD) model. The clinical pharmacology team rejects the conclusion of the PK/PD model based on the following:

-
-
-
-
-

(b) (4)

4.4.3 Pharmacokinetics

According to the clinical pharmacology reviewer, Dr. Lau, the ezetimibe + atorvastatin 10/10 mg and ezetimibe + atorvastatin 10/80 mg FDC tablets are bioequivalent for both ezetimibe and atorvastatin components to the co-administration of corresponding individual ezetimibe + atorvastatin tablets.

The ezetimibe component of the ezetimibe/ atorvastatin 10/20 mg and ezetimibe/ atorvastatin 10/40 mg FDC tablets is bioequivalent to the co-administration of corresponding individual ezetimibe + atorvastatin tablets.

However, the atorvastatin component of the ezetimibe/ atorvastatin 10/20 mg and ezetimibe/atorvastatin 10/40 mg FDC tablets are not bioequivalent to the co-administration of corresponding individual ezetimibe+ atorvastatin tablets.

According to the clinical pharmacology reviewer, the 90% confidence interval (CI) for atorvastatin show that the atorvastatin component of the ezetimibe 10mg /atorvastatin 20mg FDC is not bioequivalent to the co-administration of the individual 10 mg ezetimibe plus 20 mg atorvastatin calcium tablets since the 90% CIs for C_{max} are outside of the 0.8 and 1.25 bioequivalence goalpost. The resulting atorvastatin $AUC_{0-\infty}$ and C_{max} of ezetimibe/ atorvastatin 10/20 mg FDC tablet is (b) (4) than those of the co-administration of individual 10 mg ezetimibe plus 20 mg atorvastatin tablets (See Table 3).

Table 3: Comparisons ezetimibe/atorvastatin 10/20 mg FDC versus the co-administration of individual 10 mg ezetimibe plus 20 mg atorvastatin

Analyte	Parameter	Least Square Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Co-administration	FDC Tablet/ Co-administration
Atorvastatin	$AUC_{0-\infty}$ (ng*hr/mL)	(b) (4)		
	C_{max} (ng/mL)			
Unconjugated Ezetimibe	AUC_{0-last} (ng*hr/mL)			
	C_{max} (ng/mL)			

Source: Clinical Pharmacology Review, Table 4, pg. 14.

The 90% CI of atorvastatin show that the atorvastatin component of ezetimibe/atorvastatin 10/40 mg FDC tablet is not bioequivalent to the co-administration of individual 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets since the 90% CIs for C_{max} are outside of the 0.8 and 1.25 bioequivalence goalpost. The resulting atorvastatin $AUC_{0-\infty}$ and C_{max} of ezetimibe/ atorvastatin 10/40 mg FDC tablet is (b) (4) than those of the co-administration of individual 10 mg ezetimibe plus 40 mg atorvastatin tablets (Table 4).

Table 4: Comparisons ezetimibe/atorvastatin 10/40 mg FDC versus the co-administration of individual 10 mg ezetimibe plus 40 mg atorvastatin

Analyte	Parameter	Least Square Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Co-administration	FDC Tablet/ Co-administration
Atorvastatin	$AUC_{0-\infty}$ (ng*hr/mL)	(b) (4)		
	C_{max} (ng/mL)			

Analyte	Parameter	Least Square Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Co-administration	FDC Tablet/ Co-administration
		(b) (4)		
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL) C _{max} (ng/mL)	(b) (4)		

Source: Clinical Pharmacology Review, Table 6, pg. 16.

Food decreased atorvastatin AUC_{0-∞} and C_{max} 11% and 35%, respectively, of the ezetimibe/ atorvastatin 10/80 mg FDC tablet. Food decreased unconjugated ezetimibe AUC_{0-last} 2% and increased unconjugated ezetimibe C_{max} 10%, of the ezetimibe/ atorvastatin 10/80 mg FDC tablet.

5 Sources of Clinical Data

In this drug development program, the clinical trials supporting efficacy and safety were conducted with ezetimibe + atorvastatin co-administered as separate agents. Furthermore, the atorvastatin formulation used was the crystalline formulation, not the amorphous formulation used in the applicant's FDC product.

The applicant relies on the results of Study P145 (Bioequivalence Study) to support the bridging of the full dose range of 10/10 mg, 10/20 mg, 10/40 mg, and 10/80 mg ezetimibe/atorvastatin combination tablet to the ezetimibe + atorvastatin co-administration clinical trial data.

5.1 Table of Clinical Trials

There were eleven phase 3 clinical trials submitted to this NDA. These trials are summarized in the following table.

Table 5: Summary of Phase 3 Clinical Trials

Protocol Number	Title	N	Design	Treatment Arms: (n)
Short-Term Studies				
P0692 (Factorial study) Previously submitted to Zetia NDA	A Phase 3 Double Blind Efficacy and Safety Study of ezetimibe (10 mg) in Addition to Atorvastatin Compared to Placebo in Patients with Primary Hypercholesterolemia	628	12-week active treatment, factorial design, 10 treatment groups	EZ 10 mg = 65 Placebo = 60 All Atorva = 248 EZ 10 mg + All Atorva = 255
Only Atorvastatin Groups enrolled in P2173 (Add-on study) Previously submitted to Zetia NDA	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety, and Tolerability of Ezetimibe When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known CHD, or Multiple CVD Risk Factors	729	8-week active treatments, EZ or placebo added to ongoing statin therapy	All Atorva = 162 EZ 10 mg + All Atorva = 146
Only Atorvastatin Groups enrolled in P040 (Add-on study) Previously submitted to Zetia NDA	A Multi-center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, 6-Week Study to Evaluate the Efficacy and Safety of Ezetimibe 10 mg/day When Added to Ongoing Therapy With a Statin Versus Statin Therapy Alone, in Patients with Hypercholesterolemia Who Have Not Reached National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Target LDLCholesterol Level	3030	6-week active treatments, EZ or placebo added to ongoing statin therapy	All Atorva = 401 EZ 10 mg + All Atorva = 793
P079 (Add-on study)	A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate and Compare the	196	6-week active treatment, dose titration	EZ 10 mg + Atorva 20 mg: 98 Atorva 40 mg: 98

Protocol Number	Title	N	Design	Treatment Arms: (n)
	Efficacy and Safety of Ezetimibe Added on to Atorvastatin 20 mg Versus Up Titration to Atorvastatin 40 mg in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart Disease .		2 treatment groups	
P090 (Add-on study)	A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate and Compare the Efficacy and Safety of Ezetimibe Added On to Atorvastatin 40 mg Versus Up Titration to Atorvastatin 80 mg in Hypercholesterolemic Patients at High Risk for Coronary Heart Disease Not Adequately Controlled on Atorvastatin 40 mg	579	6-week active treatment, add-on, 2 treatment groups	EZ 10 mg + Atorva 40 mg: 288 Atorva 80 mg: 291
P112 Previously submitted to the Zetia NDA	A Multicenter, Randomized, Double-Blind, Parallel Arm, 12-Week Study to Evaluate the Efficacy and Safety of Ezetimibe 10 mg When Added to Atorvastatin 10 mg Versus Titration to Atorvastatin 20 mg and to 40 mg in Elderly Patients With Hypercholesterolemia at High Risk for CHD	1053	6-week active treatment, dose titration 2 treatment groups	Atorva 10 mg + EZ: 526 Atorva 20 mg/Atorva 40 mg: 527
P693 (Add-on study)	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Cardiovascular Risk Factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin	621	14-week active treatments, dose titration 2 treatment groups	All Atorva = 316 EZ 10 mg + All Atorva = 305
Long-Term Studies				

Protocol Number	Title	N	Design	Treatment Arms: (n)
P2154 (Blinded extension to P692)	Long-Term, Safety and Tolerability Study of Ezetimibe (SCH 58235) or Placebo in Addition to Atorvastatin in Subjects With Primary Hypercholesterolemia	246	12-month active treatment extension, 2 treatment groups	EZ 10 mg + All Atorva: 201 All Atorva: 45
P1418 (Open-label extension to P693) Previously submitted to the Zetia NDA	Long Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Atorvastatin in Subjects With Coronary Heart Disease or Multiple Risk Factors and With Primary Hypercholesterolemia Not Controlled By a Starting Dose (10 mg) of Atorvastatin	432	12-month, open-label extension	EZ 10 mg + All Atorva: 432
Special Population Studies				
Only Atorvastatin Groups enrolled in P1030 Previously submitted to the Zetia NDA	A Phase III Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia	50	12-week active treatment, parallel design	EZ 10 mg + All Atorva: 24 All Atorva: 12
Only Atorvastatin Groups enrolled in P1417	Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia	44	24-month, open-label extension	EZ 10 mg + All Atorva: 35

Source: Applicant's Clinical Summary, Table 2.7.3-hypercholesterolemia:2,pg.31.

5.2 Review Strategy

The four clinical pharmacology trials, P9396-001, P145, P146, and P183 are reviewed by the clinical pharmacology reviewer, Dr. Johnny Lau. Section 4.4 briefly summarizes the clinical pharmacology findings, while an in-depth analysis can be found in Dr. Lau's report.

Dr. Janice Derr, statistical reviewer, will focus on the efficacy results of the clinical trials described in the proposed labeling. Please see her review for details.

Dr. Joseph Leginus will conduct the chemistry review for this NDA. Please see his review for a thorough assessment.

This clinical review analyzes both the efficacy and the safety results of the Phase 3 clinical trials. The efficacy review is organized according to the proposed indications and the clinical trials that support that indication.

1. Primary Hyperlipidemia (familial and non-familial): The studies supporting this claim and that are described in the proposed labeling are P692, P2154, P693, P079, and P090.

2. Mixed Dyslipidemia: The studies supporting this claim and that are mentioned in the labeling are the same as above, P692, P2154, P693, P079, and P090

3. HoFH: The studies supporting this claim are P1030 and P1417.

Trials which were previously reviewed are not reported further in this document. These trials include P2173, P1418, P040, P112, and P1030. Although P692 was previously reviewed by the Agency, it is reviewed again in this document because it is so frequently referenced by the applicant in their proposed labeling. Study P1417, an open-label extension of P1030 is reviewed in this document for safety in Section 7.

The safety review is organized by the safety data pooled by the applicant; thus the short-term trials are pooled in one data set and the longer duration trials that are pooled in another (see Section 7).

5.3 Discussion of Individual Studies/Clinical Trials

See analysis under Section 6.

6 Review of Efficacy

Efficacy Summary

Efficacy results from the following trials are reported in this section:

P692, P2154, P693, P079, and P090

These trials were submitted to support the indication for primary hyperlipidemia and mixed dyslipidemia populations.

For the primary efficacy endpoint, LDL-C, the addition of ezetimibe to ongoing atorvastatin therapy reduced LDL-C to a greater extent than doubling the dose of atorvastatin (nominal p-value <0.001).

For the secondary endpoint of TG, the addition of ezetimibe to ongoing atorvastatin therapy reduced TG to a greater extent than doubling the dose of atorvastatin (nominal p-value <0.001)

For the secondary endpoint of HDL-C, favorable increases were not significantly greater with the addition of ezetimibe to ongoing atorvastatin therapy compared to doubling the dose of atorvastatin.

6.1 Indication

The applicant intends this NDA submission to support the approval of four (b) (4) tablet formulations containing ezetimibe 10 mg and either atorvastatin 10, 20, 40, or 80 mg (referred to as ezetimibe/atorvastatin 10/10, 10/20, 10/40, or 10/80 mg) for the treatment of patients with primary hypercholesterolemia, mixed hyperlipidemia, and HoFH. The applicant's proposed indication is as follows:

ATOZET, which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. (1.1)
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments. (1.2)

6.1.1 Methods

The applicant conducted bioequivalence studies of the FDC of ezetimibe/ amorphous atorvastatin to bridge to eleven other clinical trials in which ezetimibe was co-administered with atorvastatin. The clinical pharmacology team will review the bioequivalence studies.

This efficacy review is organized according to the proposed indications and the clinical trials that support the particular indication.

1. Primary Hyperlipidemia (familial and non-familial): The studies supporting this claim and that are described in the proposed labeling are P692, P2154, P693, P079, and P090.

*Trials in the primary hyperlipidemia and mixed dyslipidemia populations which were previously reviewed are not reported further in this document. These trials include P2173, P1418, P040, and P112.

2. Mixed Dyslipidemia: The studies supporting this claim and that are mentioned in the labeling are the same as above, P692, P2154, P693, P079, and P090

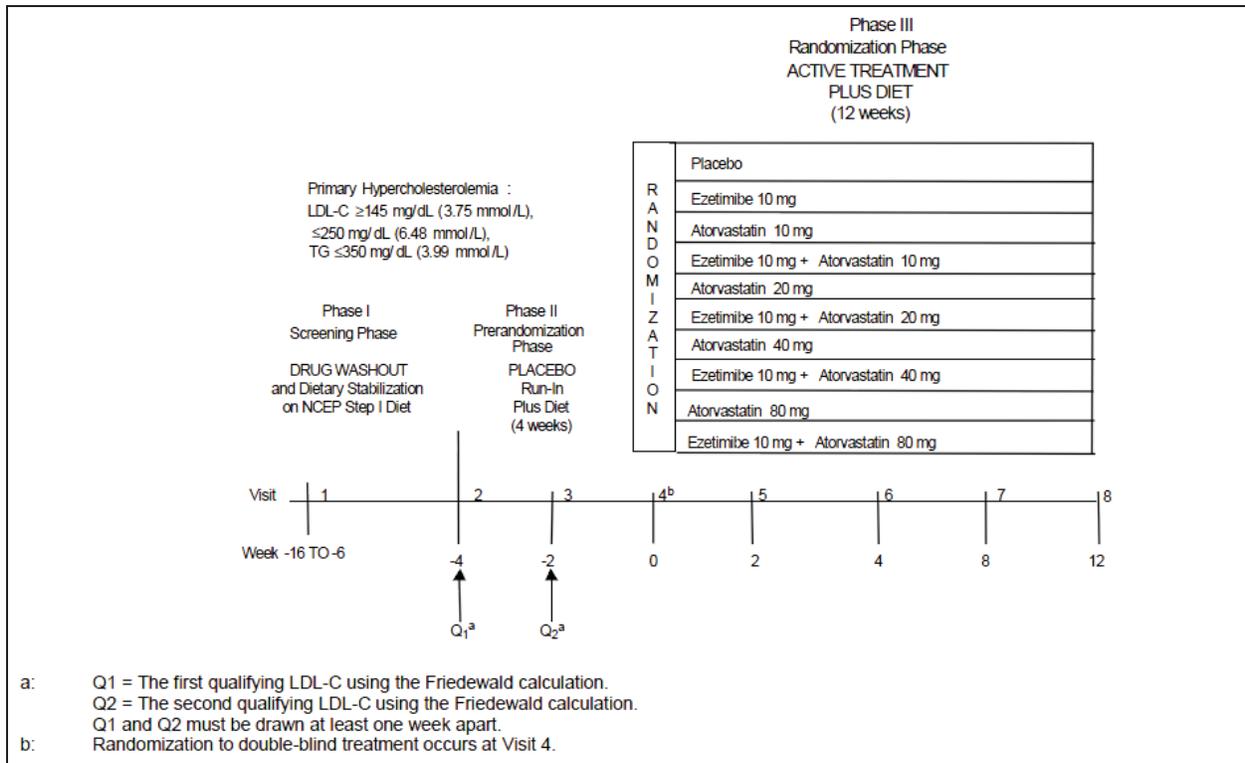
3. HoFH: The studies supporting this claim are P1030 and P1417. Study P1030 has been previously reviewed by the Agency and study results are included in the current approved Zetia labeling. P1417, an open-label extension of P1030 is reviewed for safety in Section 7.

Primary Hyperlipidemia and Mixed Dyslipidemia

Factorial Study P692

P692 was a multicenter, double-blind, placebo-controlled study that evaluated the efficacy of ezetimibe and atorvastatin, co-administered and alone, in men and women, aged 18 to 79 years, with primary hypercholesterolemia defined as an LDL-C ≥ 145 and ≤ 250 mg/dL and TG ≤ 350 mg/dL. After a 4-week placebo/diet run-in period, eligible patients were randomized equally to one of 10 treatment groups for 12 weeks: placebo, ezetimibe, atorvastatin 10, 20 40, or 80 mg, or ezetimibe + atorvastatin 10, 20, 40, or 80 mg.

Figure 1: Study Design P692

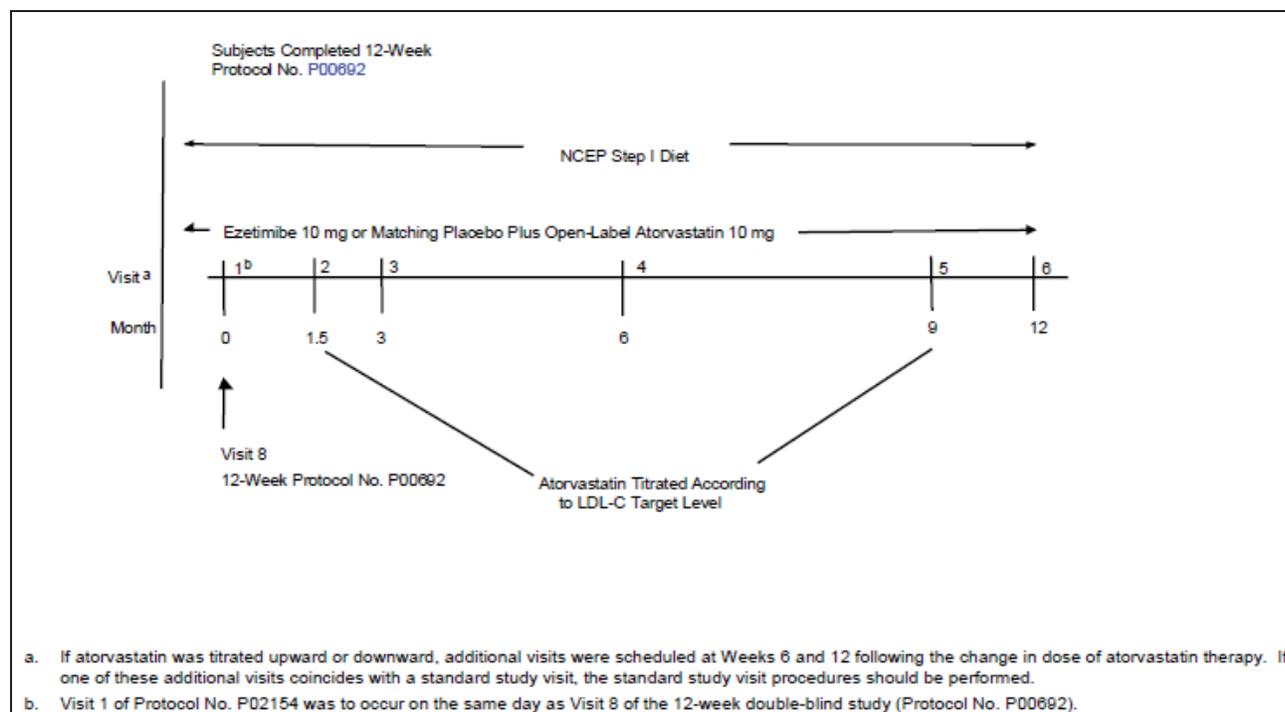


Source: Study Report P692.

P2154 (Extension of P692)

Study P2154 was a blinded extension of P692. For all subjects the initial dose upon entry was double-blind ezetimibe 10 mg daily or matching placebo plus open label atorvastatin 10 mg. The atorvastatin dose could be doubled if the target level of LDL-C was not achieved after \geq 6 weeks of treatment. The maximum dose was ezetimibe 10 mg QD or matching placebo plus atorvastatin 80 mg QD.

Figure 2: Study Design P2154



Source: Study Report P2154.

Add-On Studies- P693, P079, and P090

Three other studies were supportive of the indication for treatment in the primary hyperlipidemia and mixed dyslipidemia populations: studies P693, P079, and P090.

Study P693 was a double-blind, randomized study of ezetimibe 10 mg co-administered with atorvastatin in adult subjects with HeFH, or with CHD, or with multiple cardiovascular risk factors (greater than or equal to two) and primary hypercholesterolemia not controlled by a starting dose (10 mg daily) of atorvastatin.

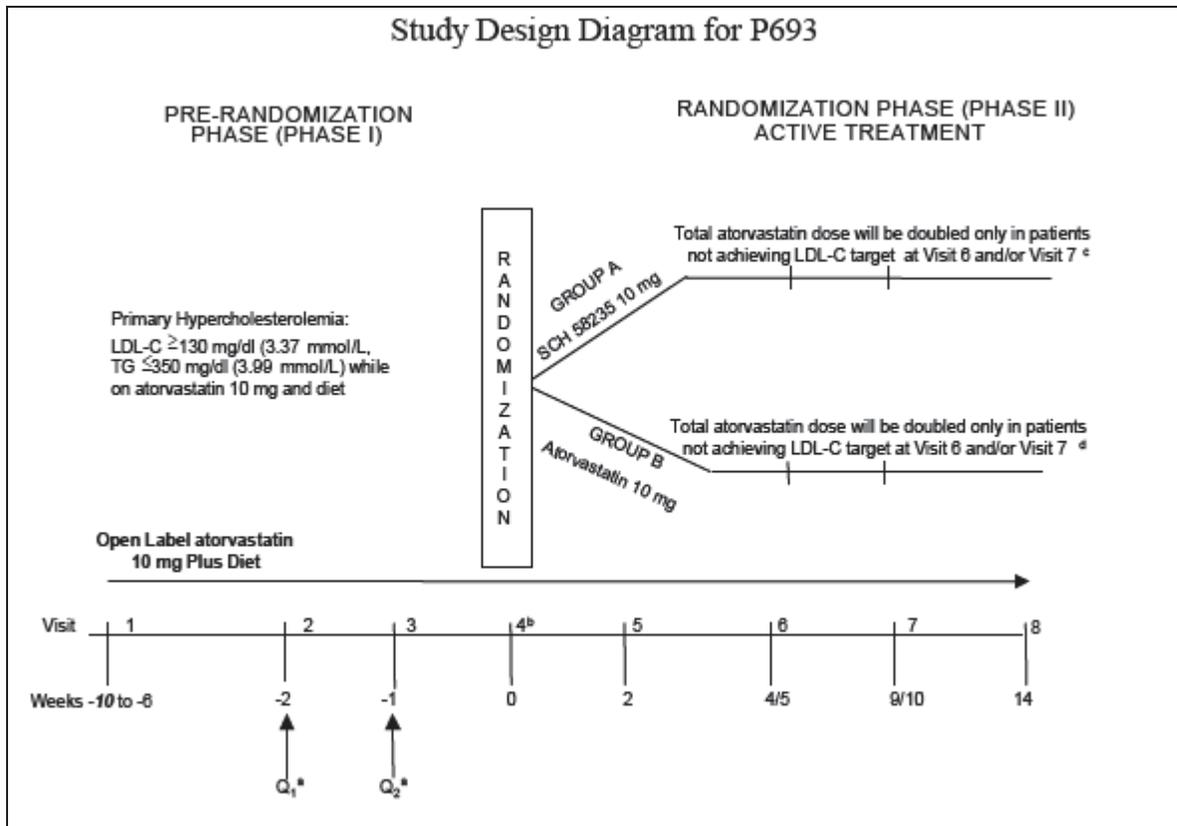
The study was designed to investigate whether ezetimibe 10 mg co-administered with atorvastatin (10 to 40 mg) for 14 weeks, resulted in more patients meeting a target LDL-C level (≤ 100 mg/dL) than treatment with atorvastatin (20 to 80 mg) alone.

The study was also designed to evaluate the efficacy of adding ezetimibe 10 mg daily to ongoing atorvastatin 10 mg daily in the morning for 4 consecutive weeks versus doubling the atorvastatin dose to 20 mg daily.

A total of 621 patients aged 18 to 82 years, with LDL-C concentrations ≥ 130 mg/dL and TG ≤ 350 mg/dL after a 4-week active run-in on atorvastatin 10 mg were enrolled into the study.

Eligible patients were randomized equally to 1 of 2 groups for a 14-week active treatment period. During the first 4 weeks following randomization, patients received either ezetimibe 10 mg or atorvastatin 10 mg in addition to their ongoing dose of atorvastatin 10 mg. After Week 4 of active treatment, patients who had not achieved their LDL-C target had their atorvastatin doses doubled at specified time periods.

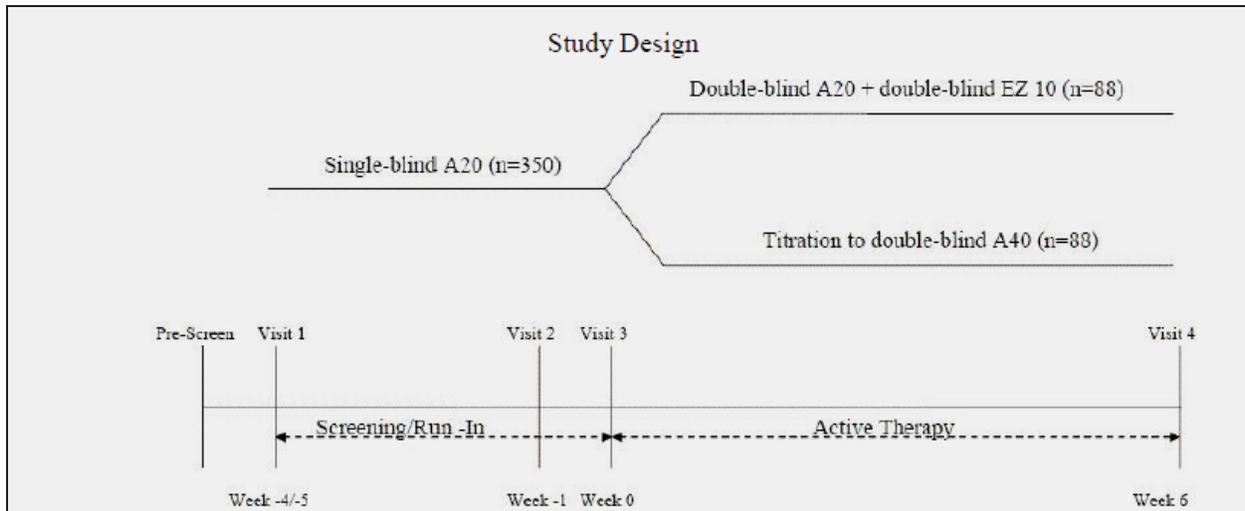
Figure 3: Study Design for P693



Source: Study Report P693.

Study P079 was a double-blind, randomized, parallel-group titration study that evaluated the efficacy and safety of adding ezetimibe to atorvastatin 20 mg therapy as compared to up-titrating to atorvastatin 40 mg in men and women, age 18 to 93, with hypercholesterolemia, moderate risk of CHD, and not at NCEP ATP III LDL-C goals. Eligible patients were run-in for 4-5 weeks on single-blind atorvastatin 20 mg, and then received either ezetimibe in addition to their atorvastatin 20 mg, or were up-titrated to atorvastatin 40 mg for 6 weeks. This study involved 196 patients at 72 centers worldwide.

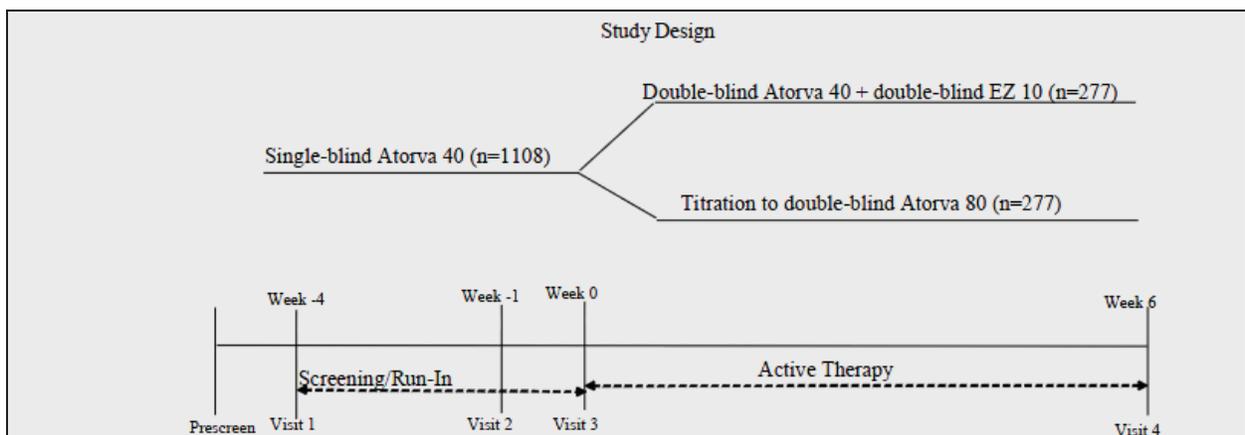
Figure 4: Study Design P079



Source: Study Report P079.

Study P090 was a double-blind, randomized, parallel-group titration study that evaluated the efficacy and safety of adding ezetimibe to atorvastatin 40 mg therapy as compared to up-titrating to atorvastatin 80 mg in men and women, age 31 to 80, with hypercholesterolemia, high risk of CHD, and not at NCEP ATP III LDL-C goals. Eligible patients were run-in for 4-5 weeks on single-blind atorvastatin 40 mg, and then received either ezetimibe in addition to their atorvastatin 40 mg, or were up-titrated to atorvastatin 80 mg for 6 weeks. This study involved 579 patients at 96 centers in the United States and Canada.

Figure 5: Study Design P090



Source: Study Report P090.

Efficacy endpoints

Mean percent change in plasma LDL-C concentrations from baseline to study endpoint or to predefined on-treatment periods was the primary efficacy variable in all the above described studies.

Other efficacy variables included plasma concentrations of TC, Apo B, HDL-C, Apo A-1, TGs, non-HDL-C, ratios of LDL-C:HDL-C and TC:HDL-C, lipoprotein(a) [Lp(a)] and hs-CRP.

6.1.2 Demographics

Primary Hyperlipidemia and Mixed Dyslipidemia

Factorial Study P692

Demographic data and baseline lipid and lipoprotein concentrations are shown in the following two tables. Age, gender, and race, and baseline lipid and lipoprotein parameters were generally comparable across the treatment groups within the study.

Table 6: Baseline Demographics- P692

Characteristic	Placebo (N=60)	EZ 10 mg (N=65)	All Atorva (N=248)	EZ 10 mg + All Atorva (N=255)
Age				
Mean	56.9	56.7	57.8	58.7
Median	57.5	58	59	59
Min-Max	18-79	27-82	21-84	26-86
Number (%) <65 years	41 (68)	47 (72)	171 (69)	174 (68)
Number (%) ≥65 years	19 (32)	18 (28)	77 (31)	81 (32)
Gender (n, %)				
Female	31 (52)	36 (55)	153 (62)	148 (58)
Male	29 (48)	29 (45)	95 (38)	107 (42)
Race (n, %)				
Black	6 (10)	3 (5)	18 (7)	9 (4)
Caucasian	49 (82)	57 (88)	205 (83)	222 (87)
American Indian	0	1 (2)	4 (2)	3 (1)
Asian	2 (3)	2 (3)	6 (2)	6 (2)
Hispanic	3 (5)	2 (3)	14 (6)	15 (6)
Other	0	0	1 (<1)	0
EZ = ezetimibe.				
All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.				

Source: Summary of Clinical Efficacy, Table 2.7.3, pg. 47.

Demographic and baseline lipid values were generally consistent across the individual treatment groups. Mean baseline calculated LDL-C concentrations ranged from 176.5 to 184.7 mg/dL.

Table 7: Baseline Lipid Concentrations- P692

Lipid Variable Mean	Placebo (N=60)	EZ 10 mg (N=65)	All Atorva (N=248)	EZ 10 mg + All Atorva (N=255)
Calculated LDL-C (mg/dL)	180.2	176.7	181.3	181.7
Direct LDL-C (mg/dL)	178.1	175.3	179.9	179.9
Total Cholesterol (mg/dL)	261.9	259.1	268.5	267.3
Apo B (mg/dL)	168.1	166.5	167.6	170.3
HDL-C (mg/dL)	50.4	50.6	53.7	50.8
Apo A-I (mg/dL)	152.5	154.8	163.0	155.8
TG [†] (mg/dL)	156.8	159.1	167.7	174.6
Non-HDL-C (mg/dL)	211.5	208.5	214.9	216.5
Direct LDL-C: HDL-C (mg/dL)	3.7	3.7	3.5	3.7
Total Cholesterol: HDL-C (mg/dL)	5.5	5.4	5.3	5.6
Lp(a) (mg/dL)	32.9	27.8	32.7	29.3
CRP [†] (mg/dL)	-	-	-	-

EZ = ezetimibe.
 All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.
[†] CRP not evaluated for this study

Source: Summary of Clinical Efficacy, Table 2.7.3, pg. 48.

P2154 (Extension of P692)

Demographic and baseline lipid values were generally consistent across the individual treatment groups. Baseline values were as recorded for P692.

Table 8: Baseline Demographics and Lipid Profiles P2154- Extension of P692

Characteristic	Atorvastatin n=45	EZ 10 mg+ Atorvastatin n=201
Age		
Mean	58.5	57.6
Min	34	26
Max	76	86
Gender		
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%)

Characteristic	Atorvastatin n=45	EZ 10 mg+ Atorvastatin n=201
LDL-C		
Mean	184.6 mg/dL	180.6 mg/dL
HDL-C		
Mean	51.5 mg/dL	52.4 mg/dL
Total Cholesterol		
Mean	269.8 mg/dL	267.7 mg/dL
TG		
Mean	163.7 mg/dL	172.3 mg/dL

Source: Study Report P2154. Note: Baseline values were as recorded at baseline in P692.

Add-On Studies P079, and P090

Table 9: Baseline Demographics and Lipid Profile- P079 and P090

Characteristic	P079		P090	
	Atorva 40 mg (N=98)	EZ 10 mg + Atorva 20 mg (N=98)	Atorva 80 mg (N=291)	EZ 10 mg + Atorva 40 mg (N=288)
Age (mean)	58.0	56.4	62.0	60.6
Gender				
Female	49 (50%)	40 (41%)	113 (39%)	115 (40%)
Male	49 (50%)	58 (59%)	178 (61%)	173 (60%)
Race				
Caucasian	60 (61%)	58 (59%)	232 (80%)	237 (82%)
Black	9 (9%)	3 (3%)	29 (10)	32 (11)
Asian	8 (8%)	7 (7%)	8 (3)	4 (1)
Other	21 (21%)	29 (30%)	22 (8)	15 (5)
Mean LDL-C	117.9 mg/dL	119.9 mg/dL	89.9 mg/dL	88.8 mg/dL
Mean Total Cholesterol	200.0 mg/dL	202.6 mg/dL	165.3 mg/dL	165.2 mg/dL
Mean TG	152.4 mg/dL	158.3 mg/dL	141.0 mg/dL	144.6 mg/dL
Mean HDL-C	51.7 mg/dL	51.1 mg/dL	47.2 mg/dL	47.4 mg/dL

In P090, the average LDL-C was much lower than in P079 (89 mg/dL vs. 119 mg/dL). According to the applicant this difference was due to the eligibility criteria of the two studies:

- P079 enrolled patients at moderately high risk for CHD who had not reached optional NCEP ATP III goal LDL-C level (<100 mg/dL) on atorvastatin 20 mg alone.
- Study P090 enrolled patients at high risk for CHD who had not reached optional NCEP ATP III goal LDL-C levels (<70 mg/dL) on atorvastatin 40 mg alone.

Add-On Study P693

The baseline demographic data and lipid concentrations for Study P693 are shown in the following two tables. In contrast to P079 and P090, but similar to P692, the baseline LDL-C is higher in P693 with an average LDL-C of 186 mg/dL.

Table 10: Baseline Demographics- P693

Characteristic	All Atorva (N=316)	EZ 10 mg + All Atorva (N=305)
Age		
Mean	51.6	53
Median	53	54
Min-Max	18-80	18-82
Number (%) <65 years	266 (84)	240 (79)
Number (%) ≥65 years	50 (16)	65 (21)
Gender (n, %)		
Female	145 (46)	146 (48)
Male	171 (54)	159 (52)
Race (n, %)		
Caucasian	289 (91)	279 (91)
Black	4 (1)	6 (2)
Asian	6 (2)	4 (1)
Hispanic	17 (5)	15 (5)
Other	0	1 (<1)
EZ = ezetimibe. All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.		

Table 11: Baseline Efficacy Variables- P693

Lipid Variable Mean	All Atorva (N=316)	EZ 10 mg + All Atorva (N=305)
Calculated LDL-C (mg/dL)	186.8	185.9
Direct LDL-C (mg/dL)	187.2	186.2
Total Cholesterol (mg/dL)	264.2	262
Apo B [†] (mg/dL)	-	-
HDL-C (mg/dL)	49.9	50
Apo A-I [†] (mg/dL)	-	-
TG (mg/dL)	137.3	130.6
Non-HDL-C (mg/dL)	214.3	212.1
LDL-C: HDL-C (mg/dL)	4	3.9
Total Cholesterol: HDL-C (mg/dL)	5.6	5.5
Lp(a) (mg/dL)	n=312 ^a	n=304 ^a
CRP [†] (mg/dL)	35.4	34.2
CRP [†] (mg/dL)	-	-

EZ = ezetimibe
 All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.
 a = "n" values are given in those cases where information is missing for one or more subjects in either treatment group.
 † Lipid variable not evaluated for this study

6.1.3 Subject Disposition

Primary Hyperlipidemia and Mixed Dyslipidemia

Factorial Study P0692

A high number of patients discontinued before Randomization in P692; out of 1703 patients enrolled, 1075 or 63% dropped out of the study before receiving randomized treatment assignment. Most of these patients did not meet protocol eligibility, i.e., lipid parameters.

Of the 628 patients who received randomized treatment, 576 (92%) completed the study. The primary reason for discontinuation was due to AEs, approximately 5% of patients assigned to randomized treatment. The percentage of patients discontinuing due to AEs was similar in the combination treatment group as compared to the atorvastatin monotherapy or ezetimibe monotherapy.

Table 12: Disposition following Randomization-P692

Disposition of Subjects	Placebo	EZ 10 mg	All Atorva	EZ 10 + All Atorva	Treatment Assignment in P00692							
					Atorva 10 mg	EZ 10 + Atorva 10	Atorva 20 mg	EZ 10 + Atorva 20	Atorva 40 mg	EZ 10 + Atorva 40	Atorva 80 mg	EZ 10 + Atorva 80
Received Randomized Treatment Assignment	60 (100)	65 (100)	248 (100)	255 (100)	60 (100)	65 (100)	60 (100)	62 (100)	66 (100)	65 (100)	62 (100)	63 (100)
Completed Treatment	55 (92)	60 (92)	229 (92)	232 (91)	55 (92)	64 (98)	56 (93)	58 (94)	59 (89)	57 (88)	59 (95)	53 (84)
Discontinued Treatment	5 (8)	5 (8)	19 (8)	23 (9)	5 (8)	1 (2)	4 (7)	4 (6)	7 (11)	8 (12)	3 (5)	10 (16)
Adverse event	3 (5)	3 (5)	13 (5)	15 (6)	4 (7)	1 (2)	3 (5)	2 (3)	4 (6)	5 (8)	2 (3)	7 (11)
Lost to follow-up	0	0	2 (<1)	1 (<1)	0	0	1 (2)	0	1 (2)	1 (2)	0	0
Subject did not wish to continue	2 (3)	0	3 (1)	5 (2)	1 (2)	0	0	1 (2)	1 (2)	1 (2)	1 (2)	3 (5)
Noncompliance with protocol	0	2 (3)	1 (<1)	2 (<1)	0	0	0	1 (2)	1 (2)	1 (2)	0	0

EZ 10 = ezetimibe 10 mg; Atorva XX = dose of atorvastatin in milligrams; All Atorva = pool of all doses of atorvastatin;
 EZ 10+All Atorva = pool of all doses of atorvastatin coadministered with ezetimibe 10 mg.
 Source Data: [Section 14.4.3.3](#).

Source: Study Report P692, Table7, pg.91.

P2154 (Extension of P692)

The following table summarizes the disposition of patients who received randomized treatment in P692 and their subsequent enrollment/completion status in P2154.

Table 13: Disposition of Patients Between P692 and P2154

Disposition of Subjects	Treatment Assignment in P00692				
	Placebo	Ezetimibe 10 mg	Atorvastatin	EZ 10 mg+ Atorvastatin	Total
Received Randomized Treatment Assignment in P00692 (Double-Blind)	60 (100)	65 (100)	248 (100)	255 (100)	628 (100)
Discontinued P00692	5 (8)	5 (8)	19 (8)	23 (9)	52 (8)
Adverse Event	3 (5)	3 (5)	13 (5)	15 (6)	34 (5)
Lost to Follow-Up	0	0	2 (<1)	1 (<1)	3 (<1)
Subject Did Not Wish to Continue	2 (3)	0	3 (1)	5 (2)	10 (2)
Noncompliance with Protocol	0	2 (3)	1 (<1)	2 (<1)	5 (<1)
Completed P00692 but Did Not Continue in P02154	35 (58)	30 (46)	129 (52)	136 (53)	330 (53)
Completed P00692 and Received Treatment Assignment in P02154	20 (33)	30 (46)	100 (40)	96 (38)	246 (39)

Atorvastatin = all doses of atorvastatin; EZ 10 mg + Atorvastatin = all doses of atorvastatin coadministered with ezetimibe 10 mg.

Source: Study Report P2154, Table 6, pg. 64.

Of the 246 patients who enrolled in P2154, 9% on ezetimibe+ atorvastatin co-administration discontinued due to an AE as compared to 7% on atorvastatin monotherapy.

Table 14: Disposition of Patients- P2154

Disposition of Subjects	Atorvastatin (N=45)	EZ 10 mg + Atorvastatin (N=201)
Completed Study P02154	39 (87)	166 (83)
Discontinued Study P02154	6 ^a (13)	35 (17)
Adverse Event	3 ^a (7)	19 (9)
Lost to Follow-Up	0	2 (<1)
Subject Did Not Wish to Continue	2 (4)	8 (4)
Noncompliance with Protocol	1 (2)	6 (3)

a: Subject 21/1308, who was randomized to coadministration therapy, initiated treatment in P02154 on atorvastatin monotherapy due to a dispensing error, and is reported in the monotherapy group (see [Section 10.2.](#) for details).

Atorvastatin = all doses of atorvastatin; EZ 10 mg + Atorvastatin = all doses of atorvastatin coadministered with ezetimibe 10 mg.

Source: Study Report P2154, Table 7, pg. 65.

Add-On Studies P079 and P090

The following table summarizes the patient disposition in P079. Of those patients who discontinued, none did so due to an AE on ezetimibe + atorvastatin co-administration. In contrast, there were two patients in the atorvastatin monotherapy who discontinued due to an AE.

Table 15: Disposition of Patients- P079

	<u>Atorva 20 mg ± EZ 10 mg</u>	<u>Atorva 40 mg</u>	<u>Total</u>
SCREENING FAILURES:			<u>1,151</u>
RANDOMIZED:	98	98	196
Male (age range)	58 (21-80)	49 (31-80)	107
Female (age range)	40 (21-80)	49 (31-80)	89
COMPLETED:	92	91	183
DISCONTINUED:	6	7	13
Adverse Event	0	2	2
Deviation from Protocol	4	3	7
Lost to Follow Up	2	2	4

Source: Study Report, P079,

The table below summarizes the patient disposition in P090. Of those patients who discontinued the study, approximately 1.4% on ezetimibe + atorvastatin did so due to an AE. In comparison, approximately 2.4% on atorvastatin 80 mg monotherapy discontinued due to an AE.

Table 16: Disposition of Patients- P090

	Atorvastatin 40 mg +EZ		Atorvastatin 80 mg		Total	
	n	(%)	n	(%)	n	(%)
SCREENED					2120	
SCREENING FAILURES:					1541	
RANDOMIZED:	288		291		579	
Male (age range)	173 (31 to 79)		178 (34 to 77)		351 (31 to 79)	
Female (age range)	115 (32 to 80)		113 (40 to 79)		228 (32 to 80)	
COMPLETED:	279 (96.9)		278 (95.5)		557 (96.2)	
DISCONTINUED:	9 (3.1)		13 (4.5)		22 (3.8)	
Adverse experience	4 (1.4)		7 (2.4)		11 (1.9)	
Deviation from protocol	0 (0.0)		1 (0.3)		1 (0.2)	
Withdrew Consent	4 (1.4)		3 (1.0)		7 (1.2)	
Lost to Follow Up	1 (0.3)		1 (0.3)		2 (0.3)	
Other	0 (0.0)		1 (0.3)		1 (0.2)	

Source: Study Report, P090.

Add-On Study P693

In P693, out of 1847 patients initially enrolled, 1226 or 66% dropped out of the study before receiving randomized treatment assignment. Most of these patients did not meet protocol eligibility, i.e., lipid parameters.

Of the 621 patients who received randomized treatment, 568 (91%) completed the study. The primary reason for discontinuation was due to AEs, approximately 4% of patients assigned to randomized treatment. The percentage of patients discontinuing due to AEs was similar in the combination treatment group as compared to the atorvastatin monotherapy.

Table 17: Disposition of Patients- P0693

Disposition of Subjects	Atorvastatin Monotherapy	EZ 10 mg + Atorvastatin Coadministration
Received Randomized Treatment Assignment	316	305
Completed Treatment	290 (92)	278 (91)
Discontinued Treatment	26 (8)	27 (9)
Adverse event	14 (4)	13 (4)
Lost to follow-up	1 (<1)	3 (<1)
Subject did not wish to continue	6 (2)	2 (<1)
Noncompliance with protocol	5 (2)	9 (3)
EZ = ezetimibe.		
Source Data: Section 14.4.3.2.		

Source: Study Report P693, Table 7, pg. 94.

6.1.4 Analysis of Primary Endpoint(s)

Primary Hyperlipidemia and Mixed Dyslipidemia

Study P692

In P692, the primary efficacy analysis was the percent change from baseline in LDL-C to study endpoint. The primary hypothesis was that the addition of ezetimibe 10 mg/day to atorvastatin would result in a significantly greater reduction in LDL-C compared with atorvastatin monotherapy and ezetimibe monotherapy.

The primary efficacy results are summarized by atorvastatin dose in the following table.

Table 18: Mean Percent Change in LDL-C from Baseline to Endpoint-P692

Clinical Review
 Iffat N. Chowdhury, MD
 {NDA 200,153
 {Atozet, ezetimibe/atorvastatin}

	Placebo n = 60	EZ 10 mg n = 65	Atorva 10 mg n = 60	EZ 10 + Atorva 10 n = 65	Atorva 20 mg n = 60	EZ 10 + Atorva 20 n = 62	Atorva 40 mg n = 66	EZ 10 + Atorva 40 n = 65	Atorva 80 mg n = 62	EZ 10 + Atorva 80 n = 63
Baseline	(n = 60)	(n = 65)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 66)	(n = 65)	(n = 62)	(n = 63)
Mean value in mg/dl [mmol/l]	178.06 [4.60]	175.28 [4.53]	183.60 [4.75]	174.83 [4.52]	174.64 [4.52]	182.70 [4.72]	179.30 [4.64]	181.26 [4.69]	182.19 [4.71]	181.14 [4.68]
Endpoint	(n = 60)	(n = 65)	(n = 59)	(n = 65)	(n = 60)	(n = 62)	(n = 64)	(n = 63)	(n = 62)	(n = 62)
Mean value in mg/dl [mmol/l]	188.42 [4.87]	142.63 [3.69]	118.29 [3.06]	85.91 [2.22]	105.30 [2.72]	83.95 [2.17]	102.34 [2.65]	82.49 [2.13]	88.44 [2.29]	72.85 [1.88]
Mean percent change from baseline (SEM)	5.88 (1.92)	-18.43 ^a (1.85)	-35.45 (1.94)	-50.37 (1.85)	-39.77 (1.92)	-53.70 (1.89)	-43.05 (1.86)	-54.33 (1.88)	-51.35 (1.89)	-59.70 (1.89)
Difference from same dose of atorvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-14.92** (-20.18, -9.66) [versus Atorva 10]	N/A	-13.93** (-19.23, -8.63) [versus Atorva 20]	N/A	-11.28** (-16.47, -6.09) [versus Atorva 40]	N/A	-8.34** (-13.60, -3.09) [versus Atorva 80]
Difference from next higher dose of atorvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-10.60** (-15.84, -5.36) [versus Atorva 20]	N/A	-10.65** (-15.86, -5.43) [versus Atorva 40]	N/A	-2.98 (-8.21, 2.25) [versus Atorva 80]	N/A	N/A

Source: Study Report P692, Table 15. pg.114.

On placebo, LDL-C increased by approximately 6% as compared to ezetimibe monotherapy which decreased LDL-C by 18% from baseline. Atorvastatin monotherapy at 10 mg, 20 mg, 40 mg, and 80 mg decreased LDL-C by approximately 36%, 40%, 43%, and 51%, respectively.

The addition of ezetimibe to each dose of atorvastatin decreased LDL-C further when compared to the corresponding dose of atorvastatin monotherapy. For example, the addition of ezetimibe to atorvastatin 10 mg further decreased LDL-C by approximately 15%. At the atorvastatin 80 mg dose, the addition of ezetimibe further decreased LDL-C by approximately 8%. The incremental mean percent change observed with the co-administration of ezetimibe to each dose of atorvastatin was statistically significant (p<0.01) in all cases when compared with each corresponding dose of atorvastatin monotherapy.

Study P2154 (extension to P692)

The following table summarizes the LDL-C results for P2154.

Table 19: Mean Percent Change in LDL-C from Baseline to Endpoint- P2154

	Atorvastatin ^a					EZ 10 mg + Atorvastatin				
	n	Actual ^b	Change ^b	% Change	SD of % Change	n	Actual ^b	Change ^b	% Change	SD of % Change
Calculated LDL-C										
Baseline	45	185.56 (4.81)	--	--	--	201	181.08 (4.69)	--	--	--
Week 6	43	117.40 (3.04)	-68.65 (-1.78)	-36.78	12.13	191	84.75 (2.19)	-96.07 (-2.49)	-52.94	13.49
Month 3	40	114.90 (2.98)	-70.44 (-1.82)	-37.87	10.27	189	86.65 (2.24)	-94.78 (-2.45)	-52.00	12.70
Month 6	38	114.63 (2.97)	-69.51 (-1.80)	-37.33	10.04	181	87.02 (2.25)	-93.97 (-2.43)	-51.76	12.70
Month 9	39	113.77 (2.95)	-71.17 (-1.84)	-38.18	12.66	173	90.01 (2.33)	-91.52 (-2.37)	-50.36	16.08
Month 12	39	112.00 (2.90)	-72.94 (-1.89)	-39.18	9.35	169	85.75 (2.22)	-95.30 (-2.47)	-52.49	13.02
Endpoint	45	113.09 (2.93)	-72.47 (-1.88)	-38.58	12.43	201	93.27 (2.42)	-87.81 (-2.27)	-48.44	18.81
Direct LDL-C										
Baseline	45	184.63 (4.77)	--	--	--	201	180.59 (4.67)	--	--	--
Month 12	38	118.58 (3.07)	-64.14 (-1.66)	-34.78	10.13	163	90.75 (2.35)	-90.33 (-2.34)	-49.69	12.88
Endpoint	43	118.12 (3.05)	-64.87 (-1.68)	-34.89	13.00	194	97.48 (2.52)	-83.20 (-2.15)	-45.93	18.43

a: Subject 21/1308, who was randomized to coadministration therapy, initiated treatment in P02154 on atorvastatin monotherapy due to a dispensing error, and is reported in the monotherapy group (see [Section 10.2](#) for details).
 b: Expressed in mg/dL, and mmol/L in parentheses.
 SD = standard deviation.
 Atorvastatin = all doses of atorvastatin; EZ 10 mg + Atorvastatin = all doses of atorvastatin coadministered with ezetimibe 10 mg.

Source: Study Report P2154, Table 12, pg. 77.

In the atorvastatin monotherapy group, mean direct LDL-C was reduced from baseline to endpoint by approximately 35%. In comparison, on ezetimibe + atorvastatin co-administration mean direct LDL-C was reduced from baseline to endpoint by approximately 46%. These results are consistent with the parent study P692.

Study P079

The primary hypothesis for the study was addressed by the comparison between the addition of ezetimibe 10 mg to ongoing atorvastatin 20 mg therapy (atorvastatin 20 mg + EZ) and up-titrating to atorvastatin 40 mg (atorvastatin 40 mg) for the percent change from baseline in LDL-C. The following table summarizes the LDL-C results for this study.

Table 20: Mean Percent Change in LDL-C from Baseline to Endpoint- P079

Statistics	Atorva 20 mg + EZ (N=92)	Atorva 40 mg (N=92)
Baseline		
Mean	120.3	118.1
SD	19.7	17.2
Week 6		
Mean	82.1	105.4
SD	22.9	27.8
Percent Change from Baseline at Week 6		
LS Mean [†]	-30.8	-10.9
SE [†]	1.9	1.9
(95% CI [†])	(-34.5, -27.0)	(-14.7, -7.1)
Between-Treatment Difference: Atorva 20 mg + EZ minus Atorva 40 mg		
LS Mean [‡]	-19.9	
SE [‡]	2.7	
(95% CI [‡])	(-25.2, -14.5)	
p-Value [‡]	<0.001	
p-Value for Effects[†]		
Treatment	<0.001	
Baseline LDL-C	0.059	
N= Number of patients in full analysis set population.		
[†] LS Mean, SE, and 95% CI for within-treatment percent change from baseline and p-Value for effects based on an ANCOVA with terms for treatment and baseline LDL-C value.		
[‡] LS Mean of treatment difference, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.		

Source: Study Report P090. Table 11-1,pg. 80.

In P079 atorvastatin 40 mg decreased LDL-C by approximately 11% as compared to 31% for ezetimibe + atorvastatin 20 mg co-administration for a difference of approximately 20% favoring the co-administration of the two drugs (p<0.001).

Study P090

The primary hypothesis for the study was addressed by the comparison between the addition of ezetimibe 10 mg to ongoing atorvastatin 40 mg therapy and up-titrating to atorvastatin 80 mg for the percent change from baseline in LDL-C. The following table summarizes the LDL-C results for this study.

Table 21: Mean Percent Change in LDL-C from Baseline to Endpoint -P090

Statistics	Atorva 40 mg + EZ (N=277)	Atorva 80 mg (N=279)
Baseline		
Mean	88.6	89.7
SD	16.3	16.0
Week 6		
Mean	64.1	79.1
SD	19.9	19.9
Percent Change from Baseline at Week 6		
LS Mean [†]	-27.4	-11.0
SE [†]	1.1	1.1
(95% CI [†])	(-29.6, -25.1)	(-13.2, -8.8)
Between-Treatment Difference: Atorva 40 mg + EZ minus Atorva 80 mg		
LS Mean [‡]	-16.3	
SE [‡]	1.6	
(95% CI [‡])	(-19.4, -13.2)	
p-Value [‡]	<0.001	
p-Value for Effects[†]		
Treatment	<0.001	
Baseline LDL-C	<0.001	
N= Number of patients in full analysis set population.		
[†] LS Mean, SE, and 95% CI for within-treatment percent change from baseline and p-Value for effects based on an ANCOVA with terms for treatment and baseline LDL-C value.		
[‡] LS Mean of treatment difference, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.		

Source: Study Report P090, Table 11-1, pg. 88.

In P090 atorvastatin 80 mg decreased LDL-C by approximately 11% as compared to 27% for ezetimibe + atorvastatin 40 mg co-administration for a difference of approximately 16% favoring the co-administration of the two drugs (p<0.001).

Study P693

Results of the primary efficacy analysis demonstrated that the addition of ezetimibe 10 mg/day to a starting dose of atorvastatin 10 mg/day, followed by response-based titration up to atorvastatin 40 mg/day was significantly more effective in achieving target LDL-C goals of ≤ 100 mg/dL than response-based titration of atorvastatin alone up to 80 mg/day at Week 14.

For this primary analysis, data from the atorvastatin (20 mg, 40 mg, and 80 mg) monotherapy group were compared with data from the ezetimibe 10 mg plus

atorvastatin (10 mg, 20 mg, and 40 mg) treatment group. Overall, 22% of subjects on co-administration therapy achieved target plasma concentrations of LDL-C \leq 100 mg/dL at Week 14 compared with 7% of subjects on atorvastatin monotherapy. The 15% difference between co-administration therapy and atorvastatin monotherapy was statistically significant (P value <0.01).

The following table summarizes the LDL-C results for this study.

Table 22: Mean Percent Change in LDL-C from Baseline to Endpoint- P693

	Atorvastatin Monotherapy (N=316)	Ezetimibe 10 mg + Atorvastatin Coadministration (N=305)	P value ^a
Baseline	(n=316)	(n=305)	
Mean value in mg/dL [mmol/L]	187.25 [4.84]	186.22 [4.82]	0.78
Week 4	(n=298)	(n=292)	
Mean value in mg/dL [mmol/L]	169.62 [4.39]	144.29 [3.73]	<0.01
Mean percent change from baseline (standard error)	-8.55 (0.72)	-22.77 (0.73)	<0.01
Difference from Atorvastatin Monotherapy in mean percent change from baseline (95% confidence limits)	N/A	-14.22 (-16.24, -12.20)	N/A
a: Comparison between Atorvastatin (20 mg) Monotherapy and EZ 10 mg plus Atorvastatin (10 mg) Coadministration.			
Means and standard errors in this table are least-square means and standard errors and are based on the analysis of variance (ANOVA) model that extracts effects due to treatment (Atorvastatin Monotherapy and EZ 10 mg plus Atorvastatin Coadministration).			
EZ = ezetimibe; N/A = not applicable.			

Source: Study report P693, Table 15, pg. 110.

Comparison between atorvastatin 20 mg monotherapy and the co-administration of ezetimibe + atorvastatin 10 mg shows a difference of approximately 14% favoring the co-administration of the two drugs (see table above).

6.1.5 Analysis of Secondary Endpoints(s)

Primary Hyperlipidemia and Mixed Dyslipidemia- HDL-C

The HDL-C results are summarized by administered dose in the following table.

Table 23: Mean Percent change in HDL-C from Baseline to Endpoint- P692

	Placebo n = 60	EZ 10 n = 65	All Atorva n = 248	EZ 10+ All Atorva n = 255	Atorva 10 n = 60	EZ 10+ Atorva 10 n = 65	Atorva 20 n = 60	EZ 10+ Atorva 20 n = 62	Atorva 40 n = 66	EZ 10+ Atorva 40 n = 65	Atorva 80 n = 62	EZ 10+ Atorva 80 n = 63
Baseline	(n = 60)	(n = 65)	(n = 248)	(n = 255)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 66)	(n = 65)	(n = 62)	(n = 63)
Mean value in mg/dL [mmol/L]	50.38 [1.30]	50.61 [1.31]	53.70 [1.39]	50.79 [1.31]	53.69 [1.39]	51.86 [1.34]	55.48 [1.43]	49.34 [1.28]	52.97 [1.37]	51.10 [1.32]	52.65 [1.36]	50.86 [1.32]
Endpoint	(n = 60)	(n = 65)	(n = 246)	(n = 253)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 64)	(n = 64)	(n = 62)	(n = 62)
Mean value in mg/dL [mmol/L]	51.90 [1.34]	52.49 [1.36]	55.65 [1.44]	54.18 [1.40]	56.85 [1.47]	55.92 [1.45]	57.30 [1.48]	53.74 [1.39]	54.63 [1.41]	53.00 [1.37]	53.81 [1.39]	54.05 [1.40]
Mean percent change from baseline (SEM)	3.73 (1.49)	4.19 ^a (1.43)	4.25 (0.74)	7.34 (0.73)	6.46 (1.49)	9.01 (1.43)	3.96 (1.49)	9.21 (1.47)	3.76 (1.45)	4.58 (1.45)	2.81 (1.47)	6.55 (1.47)
Difference from same dose (or pool of doses) of atorvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	3.09** (1.06, 5.12) [versus All Atorva]	N/A	2.55 (-1.52, 6.61) [versus Atorva 10]	N/A	5.26** (1.14, 9.37) [versus Atorva 20]	N/A	0.82 (-3.19, 4.83) [versus Atorva 40]	N/A	3.74 (-0.34, 7.82) [versus Atorva 80]
Difference from next higher dose of atorvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	N/A	N/A	5.05** (0.99, 9.12) [versus Atorva 20]	N/A	5.45** (1.40, 9.50) [versus Atorva 40]	N/A	1.77 (-2.27, 5.82) [versus Atorva 80]	N/A	N/A

Source: Study Report P692, Table 22, pg. 134.

On placebo, HDL-C increased by approximately 3.7% as compared to ezetimibe monotherapy which increased HDL-C by 4.2% from baseline. Atorvastatin monotherapy at 10 mg, 20 mg, 40 mg, and 80 mg increased HDL-C by approximately 6.5%, 4.0%, 3.8%, and 2.8%, respectively.

The addition of ezetimibe to each dose of atorvastatin increased HDL-C further when compared to the corresponding dose of atorvastatin monotherapy. For example, the addition of ezetimibe to atorvastatin 10 mg further increased HDL-C by approximately 2.6%. At the atorvastatin 80 mg dose, the addition of ezetimibe further increased HDL-C by approximately 3.7%.

Study P2154 (extension of P692)

The following table summarizes the HDL-C results for P2154.

Table 24: Mean Percent Change in HDL-C from Baseline to Endpoint - P2154

	Atorvastatin ^a					EZ 10 mg + Atorvastatin				
	n	Actual ^b	Change ^b	% Change	SD of % Change	n	Actual ^b	Change ^b	% Change	SD of % Change
Baseline	45	51.50 (1.33)	--	--	--	201	52.36 (1.35)	--	--	--
Week 6	43	53.91 (1.39)	2.12 (0.05)	4.52	9.30	191	54.26 (1.40)	2.08 (0.05)	4.60	11.35
Month 3	40	53.80 (1.39)	1.57 (0.04)	3.56	9.71	189	55.02 (1.42)	2.23 (0.06)	5.15	14.26
Month 6	38	53.79 (1.39)	1.64 (0.04)	3.67	10.77	183	55.63 (1.44)	3.10 (0.08)	6.58	12.49
Month 9	39	53.79 (1.39)	1.89 (0.05)	3.95	11.65	173	56.57 (1.46)	3.26 (0.08)	6.93	13.19
Month 12	39	54.26 (1.40)	2.35 (0.06)	5.15	12.45	169	56.14 (1.45)	3.21 (0.08)	6.91	13.57
Endpoint	45	53.96 (1.40)	2.46 (0.06)	5.44	13.31	201	55.24 (1.43)	2.88 (0.07)	6.25	13.38

a: Subject 21/1308, who was randomized to coadministration therapy, initiated treatment in P02154 on atorvastatin monotherapy due to a dispensing error, and is reported in the monotherapy group (see [Section 10.2](#) for details).

b: Expressed in mg/dL, and mmol/L in parentheses.

SD = standard deviation.

Atorvastatin = all doses of atorvastatin; EZ 10 mg + Atorvastatin = all doses of atorvastatin coadministered with ezetimibe 10 mg.

Source: Study Report P2154, Table 13, pg. 80.

In P2154, on all doses of atorvastatin monotherapy (pooled) group, mean HDL-C was increased from baseline to endpoint by approximately 2.5%. In comparison, on ezetimibe + atorvastatin (all doses) co-administration mean HDL-C was increased from baseline to endpoint by approximately 2.9%. From these results it can be concluded that the addition of ezetimibe to atorvastatin results in only a slight increase in HDL-C over atorvastatin monotherapy.

Study P079

The efficacy results for HDL-C from study P079 are shown in the table below.

Table 25: Mean Percent Change in HDL-C from Baseline to Endpoint - P079

Statistics	Atorva 20 mg + EZ (N=92)	Atorva 40 mg (N=92)
Baseline		
Mean	50.9	52.1
SD	12.2	11.7
Week 6		
Mean	52.1	52.2
SD	12.5	12.1
Percent Change from Baseline at Week 6		
LS Mean [†]	3.2	0.8
SE [†]	1.5	1.5
(95% CI [†])	(0.2, 6.2)	(-2.2, 3.8)
Between-Treatment Difference: Atorva 20 mg + EZ minus Atorva 40 mg		
LS Mean [†]	2.4	
SE [‡]	2.1	
(95% CI [‡])	(-1.9, 6.6)	
p-Value [‡]	0.273	
p-Value for Effects[†]		
Treatment	0.273	
Baseline HDL-C	0.002	
N= Number of patients in full analysis set population.		
[†] LS Mean, SE, and 95% CI for within-treatment percent change from baseline and p-Value for effects based on an ANCOVA with terms for treatment and baseline HDL-C value.		
[‡] LS Mean of treatment difference, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.		

Source: Study Report P079, Table 11-3, pg. 82.

The efficacy results for HDL-C in study P079 were similar to results of previous studies; although a numerically greater increase in HDL-C was observed in the atorvastatin 20 mg + ezetimibe group compared with atorvastatin 40 mg as measured by percent change from baseline at Week 6, the difference between treatment groups was not statistically significant (3.2% vs. 0.8%, p=0.273).

Study P090

The efficacy results for HDL-C from study P090 are shown in the following table.

Table 26: Mean Percent Change in HDL-C from Baseline to Endpoint - P090

Statistics	Atorva 40 mg + EZ (N=277)	Atorva 80 mg (N=279)
Baseline		
Mean	47.7	46.9
SD	10.6	10.4
Week 6		
Mean	47.2	46.3
SD	10.6	10.7
Percent Change from Baseline at Week 6		
LS Mean [†]	-0.5	-1.0
SE [†]	0.6	0.6
(95% CI [†])	(-1.6, 0.7)	(-2.1, 0.2)
Between-Treatment Difference: Atorva 40 mg + EZ minus Atorva 80 mg		
LS Mean [‡]	0.5	
SE [‡]	0.8	
(95% CI [‡])	(-1.1, 2.1)	
p-Value [‡]	0.551	
p-Value for Effects[†]		
Treatment	0.551	
Baseline HDL-C	<0.001	
N= Number of patients in full analysis set population.		
[†] LS Mean, SE, and 95% CI for within-treatment percent change from baseline and p-Value for effects based on an ANCOVA with terms for treatment and baseline HDL-C value.		
[‡] LS Mean of treatment difference, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.		

Source: Study Report P090, Table 11-3, pg. 91.

As shown in the table above, small *reductions* in HDL-C were observed for both the atorvastatin 40 mg + ezetimibe group and the atorvastatin 80 mg group, as measured by percent change from baseline at Week 6. This unfavorable result occurred in both treatment arms and is inexplicable.

Study P693

In Study P693, for HDL-C parameters, mean percent change from baseline was not statistically significantly different between atorvastatin 20 mg monotherapy and the co-administration of atorvastatin 20 mg + ezetimibe (1.25% vs. 2.13%, p=0.28). The difference between atorvastatin monotherapy and ezetimibe + atorvastatin co-administration was 0.88 (-0.71, 2.46).

Table 27: Mean Percent Change in HDL-C from Baseline to Week 4- P693

	Atorvastatin Monotherapy (N=316)	Ezetimibe 10 mg + Atorvastatin Coadministration (N=305)	P value ^a
Baseline	(n=316)	(n=305)	
Mean value in mg/dL [mmol/L]	49.86 [1.29]	49.97 [1.29]	0.92
Week 4	(n=303)	(n=293)	
Mean value in mg/dL [mmol/L]	50.24 [1.30]	50.60 [1.31]	0.72
Mean percent change from baseline (standard error)	1.25 (0.57)	2.13 (0.58)	0.28
Difference from Atorvastatin Monotherapy in mean percent change from baseline (95% confidence limits)	N/A	0.88 (-0.71, 2.46)	N/A
a: Comparison between Atorvastatin (20 mg) Monotherapy and EZ 10 mg plus Atorvastatin (10 mg) Coadministration.			
Means and standard errors in this table are least-square means and standard errors and are based on the analysis of variance (ANOVA) model that extracts effects due to treatment (Atorvastatin Monotherapy and EZ 10 mg plus Atorvastatin Coadministration).			
EZ = ezetimibe; N/A = not applicable.			

Source: Study Report P693, Table 25, pg. 119.

Primary Hyperlipidemia and Mixed Dyslipidemia- TG

Study P692

The efficacy results for TG from study P693 are summarized below.

Table 28: Mean Percent Change in TG from Baseline to Study Endpoint- P692

	Placebo n = 60	EZ 10 n = 65	All Atorva n = 24 8	EZ 10+ All Atorva n = 255	Atorva 10 n = 60	EZ 10+ Atorva 10 n = 65	Atorva 20 n = 60	EZ 10+ Atorva 20 n = 62	Atorva 40 n = 66	EZ 10+ Atorva 40 n = 65	Atorva 80 n = 62	EZ 10+ Atorva 80 n = 63
Baseline	(n = 60)	(n = 65)	(n = 248)	(n = 255)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 66)	(n = 65)	(n = 62)	(n = 63)
Mean value in mg/dL [mmol/L]	156.79 [1.77]	159.07 [1.80]	167.63 [1.89]	174.58 [1.97]	162.57 [1.84]	170.72 [1.93]	170.78 [1.93]	181.65 [2.05]	169.47 [1.91]	183.44 [2.07]	167.70 [1.89]	162.53 [1.84]
Median value in mg/dL [mmol/L]	142.8 [1.6]	144.7 [1.6]	154.7 [1.7]	165.3 [1.9]	153 [1.7]	158 [1.8]	146.5 [1.7]	164.8 [1.9]	159 [1.8]	180 [2]	163 [1.8]	146 [1.6]
Endpoint	(n = 60)	(n = 65)	(n = 246)	(n = 253)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 64)	(n = 64)	(n = 62)	(n = 62)
Mean value in mg/dL [mmol/L]	155.17 [1.75]	150.71 [1.70]	127.93 [1.44]	118.48 [1.34]	134.02 [1.51]	122.38 [1.38]	132.42 [1.49]	126.58 [1.43]	132.05 [1.49]	125.02 [1.41]	113.26 [1.28]	99.94 [1.13]
Median value in mg/dL	140.50	128.00	118.50	108.00	121.50	103.00	126.50	122.50	128.00	112.50	104.50	92.00
Mean percent change from baseline (SEM)	4.43 (3.14)	-3.44 ^a (3.02)	-21.47 (1.55)	-29.47 (1.53)	-16.29 (3.14)	-25.75 (3.02)	-19.31 (3.14)	-26.99 (3.09)	-19.87 (3.04)	-30.02 (3.04)	-30.42 (3.09)	-35.14 (3.09)
Median percent change from baseline	-6.44	-5.14	-24.48	-32.77	-20.78	-31.07	-22.67	-30.02	-24.43	-33.78	-30.56	-39.89
Difference from same dose (or pool of doses) of atorvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-8.00** (-12.28, -3.73) [versus All Atorva]	N/A	-9.46* (-18.00, -0.91) [versus Atorva 10]	N/A	-7.68 (-16.33, 0.96) [versus Atorva 20]	N/A	-10.15* (-18.59, -1.71) [versus Atorva 40]	N/A	-4.72 (-13.29, 3.86) [versus Atorva 80]

*p≤0.05, ** p≤0.01

a: Pairwise comparison of ezetimibe 10 mg vs ezetimibe 10 mg plus all atorvastatin for mean percent change from baseline to endpoint was statistically significant, p<0.01.

Means and standard errors in this table are least-square means and standard errors and are based on the ANOVA model that extracts effects due to dose (atorvastatin: 0 mg, 10 mg, 20 mg, 40 mg, and 80 mg), treatment (ezetimibe 10 mg, ezetimibe placebo), and dose-by-treatment interaction.

EZ 10 = ezetimibe 10 mg; Atorva XX = dose of atorvastatin in milligrams; All Atorva = pool of all doses of atorvastatin; EZ 10+All Atorva = pool of all doses of

atorvastatin coadministered with ezetimibe 10 mg

Source: Study Report P692, Table 21, pg. 130.

On placebo, TG decreased by approximately 6.4% as compared to ezetimibe monotherapy which decreased TG by 5.1% from baseline. Atorvastatin monotherapy at 10 mg, 20 mg, 40 mg, and 80 mg decreased TG by approximately 21%, 23%, 24%, and 31%, respectively.

The addition of ezetimibe to each dose of atorvastatin decreased TG further when compared to the corresponding dose of atorvastatin monotherapy. For example, the addition of ezetimibe to atorvastatin 10 mg further decreased TG by approximately 9.5% (p ≤ 0.5). At the atorvastatin 80 mg dose, the addition of ezetimibe further decreased TG by approximately 4.7% (not a statistically significant difference).

Study P2154 (extension of P692)

The efficacy results for TG from P2154 are summarized in the table below.

Table 29: Mean Percent Change in TG from Baseline to Endpoint- P2154

	Atorvastatin ^a				EZ 10 mg + Atorvastatin			
	n	Actual ^b	Change ^b	% Change	n	Actual ^b	Change ^b	% Change
Baseline	45	162.33 (1.83)	--	--	201	162.33 (1.83)	--	--
Week 6	43	120.00 (1.35)	-30.33 (-0.34)	-21.05	191	115.00 (1.30)	-45.00 (-0.51)	-30.18
Month 3	40	129.00 (1.46)	-16.33 (-0.18)	-9.45	189	115.00 (1.30)	-42.33 (-0.48)	-29.02
Month 6	38	130.50 (1.47)	-23.67 (-0.27)	-17.17	183	108.00 (1.22)	-40.00 (-0.45)	-28.15
Month 9	39	113.00 (1.28)	-20.33 (-0.23)	-18.32	173	108.00 (1.22)	-47.00 (-0.53)	-30.68
Month 12	39	130.00 (1.47)	-31.33 (-0.35)	-18.35	169	114.00 (1.29)	-44.33 (-0.50)	-29.58
Endpoint	45	130.00 (1.47)	-30.33 (-0.34)	-16.89	201	115.00 (1.30)	-43.33 (-0.49)	-29.58

a: Subject 21/1308, who was randomized to coadministration therapy, initiated treatment in P02154 on atorvastatin monotherapy due to a dispensing error, and is reported in the monotherapy group (see [Section 10.2.](#) for details).

b: Expressed in mg/dL, and mmol/L in parentheses.

Atorvastatin = all doses of atorvastatin; EZ 10 mg + Atorvastatin = all doses of atorvastatin coadministered with ezetimibe 10 mg.

Source: Study Report P2154, Table 14, pg. 81.

In Study P2154, the addition of ezetimibe to the pooled doses of atorvastatin resulted in a mean decrease in TG from baseline to endpoint by 30% as compared to 17% on atorvastatin monotherapy (all doses).

Study P079

The efficacy results for TG from study P079 are summarized below.

Table 30: Nonparametric Analysis of Percent Change from Baseline to Endpoint inTG- P079

Statistics	Atorva 20 mg + EZ (N=92)	Atorva 40 mg (N=92)
Baseline		
Median	154.8	147.5
Robust SD [†]	71.9	77.4
Week 6		
Median	125.5	122.5
Robust SD [†]	61.9	73.0
Percent Change from Baseline at Week 6		
Median	-17.8	-5.5
Robust SD [†] (95% CI)	32.5 (-23.7, -11.4)	41.2 (-14.4, 0.0)
Between-Treatment Difference: Atorva 20 mg + EZ minus Atorva 40 mg		
Median [‡] (95% CI [§])	-8.9 (-17.7, -0.4)	
p-Value	0.159	
p-Value for Effects		
Treatment	0.159	
Baseline TG	<0.001	
N= Number of patients in full analysis set population. [†] Robust standard deviation was calculated as: interquartile range (IQR)/1.075, where IQR=3rd quartile-1st quartile. [‡] The between-treatment difference was based on the Hodges-Lehmann estimates of shift. [§] Distribution-free confidence interval was based on Wilcoxon's rank sum test statistic. The p-Value for the between-treatment comparison was based on Tukey normalized scores transformation of the percent change from baseline and was calculated using an ANCOVA model that included terms for treatment and baseline TG value (normalized scores).		

Source: Study Report, Table 11-6, pg. 85.

As shown in the table, although a numerically greater reduction in TG was observed in the atorvastatin 20 mg + ezetimibe group compared with atorvastatin 40 mg as measured by median percent change from baseline at Week 6, the difference between treatment groups was not statistically significant (-17.8% vs. -5.5%, p=0.159).

Study P090

The TG results for study P090 are summarized in the table below.

Table 31: Nonparametric Analysis of Percent Change from Baseline to Endpoint in TG- P090

Statistics	Atorva 40 mg + EZ (N=277)	Atorva 80 mg (N=279)
Baseline		
Median	131.0	135.5
Robust SD [†]	72.1	71.6
Week 6		
Median	117.0	124.0
Robust SD [†]	68.8	67.0
Percent Change from Baseline at Week 6		
Median	-12.3	-5.9
Robust SD [†]	27.1	33.3
(95% CI)	(-16.3, -8.2)	(-10.2, -0.7)
Between-Treatment Difference: Atorva 40 mg + EZ minus Atorva 80 mg		
Median [‡]	-7.3	
(95% CI [§])	(-11.5, -3.1)	
p-Value	<0.001	
p-Value for Effects		
Treatment	<0.001	
Baseline TG	<0.001	
N= Number of patients in full analysis set population. [†] Robust standard deviation was calculated as: interquartile range (IQR)/1.075, where IQR=3rd quartile-1st quartile. [‡] The between-treatment difference was based on the Hodges-Lehmann estimates of shift. [§] Distribution-free confidence interval was based on Wilcoxon's rank sum test statistic. The p-Value for the between-treatment comparison was based on Tukey normalized scores transformation of the percent change from baseline and was calculated using an ANCOVA model that included terms for treatment and baseline TG value (normalized scores).		

Source: Study Report, Table 11-6, pg. 94.

By the study endpoint at Week 6, there was a between treatment difference of -7.3%, favoring the co-administration of ezetimibe + atorvastatin 40 mg.

6.1.6 Other Endpoints

6.1.7 Subpopulations

Subgroup analysis was conducted on the largest efficacy study, P692. Mean percent change from Baseline to Endpoint in LDL-C was examined according to sex, age, and race.

Table 32: Subgroup Analysis of LDL-C by Sex- P692

Treatment	n		Mean ^a		SD		Median	
Sex								
	Male	Female	Male	Female	Male	Female	Male	Female
Placebo	29	31	3.2	8.4	9.7	14.9	3.8	6.1
EZ 10	29	36	-18.1	-18.7	11.8	14.3	-18.9	-18.1
All Atorva	93	152	-41.6	-43.1	15.1	16.3	-43.5	-46.6
EZ 10+ All Atorva	106	146	-52.4	-56.0	15.7	16.3	-55.7	-60.1
Atorva 10	19	40	-33.3	-36.4	16.2	16.0	-35.3	-38.2
EZ 10 + A 10	26	39	-47.2	-52.5	14.9	13.7	-50.2	-56.2
Atorva 20	23	37	-39.5	-39.9	11.4	14.9	-40.1	-42.1
EZ 10 + A 20	24	38	-49.1	-56.6	17.4	15.6	-50.5	-60.7
Atorva 40	27	37	-42.1	-43.7	13.4	17.7	-43.5	-49.8
EZ 10 + A 40	26	37	-52.4	-55.7	16.9	21.3	-57.6	-61.8
Atorva 80	24	38	-49.8	-52.4	15.8	12.0	-51.4	-52.4
EZ 10 + A 80	30	32	-59.7	-59.7	11.5	12.7	-62.2	-64.1

Source: Study Report P692, Table 16, pg. 117.

As summarized in the analysis of LDL-C by sex, pooled data of all atorvastatin monotherapy vs. ezetimibe + all atorvastatin co-administration showed similar results between men and women. (Table 29)

Table 33: Subgroup Analysis of LDL-C by Age- P692

Treatment	n		Mean ^a		SD		Median	
Age								
	<65 y	≥65 y	<65 y	≥65 y	<65 y	≥65 y	<65 y	≥65 y
Placebo	41	19	6.7	4.0	15	6.2	5.3	5.6
EZ 10	47	18	-17.7	-20.3	11.5	16.8	-18.2	-18.6
All Atorva	169	76	-42.7	-42.0	15.5	16.6	-45.1	-45.7
EZ 10+ All Atorva	173	79	-53.3	-57.0	17.1	13.5	-57.3	-59.9
Atorva 10	42	17	-35.4	-35.7	13.7	21.2	-34.9	-42.2
EZ 10 + A 10	49	16	-50.9	-48.8	13.7	16.3	-53.8	-51.8
Atorva 20	47	13	-39.5	-40.9	13.6	13.9	-40.4	-43.8
EZ 10 + A 20	40	22	-51.6	-57.5	17.7	14.0	-56.0	-59.4
Atorva 40	39	25	-45.1	-39.9	15.7	16.1	-48.4	-42.9
EZ 10 + A 40	42	21	-51.7	-59.5	21.7	13.0	-57.8	-61.8
Atorva 80	41	21	-51.8	-50.4	14.6	11.4	-53.8	-50.0
EZ 10 +A 80	42	20	-59.4	-60.4	13.5	8.3	-63.6	-62.2

Source: Study Report P692, Table 16, pg. 117.

Subgroup analysis of LDL-C by age also showed consistent results when categorized to < 65 years or ≥ 65 years.

Table 34: Subgroup Analysis of LDL-C by Race- P692

Treatment	n		Mean ^a		SD		Median	
Race								
	C	N-C	C	N-C	C	N-C	C	N-C
Placebo	49	11	6.4	3.3	13.4	10.2	6.0	3.1
EZ 10	57	8	-19.5	-10.7	13.1	11.4	-18.9	-7.8
All Atorva	204	41	-42.0	-44.9	16.0	14.9	-44.5	-48.8
EZ 10+								
All Atorva	220	32	-55.0	-50.6	15.0	22.3	-57.8	-57.7
Atorva 10	51	8	-35.6	-34.7	15.7	19.2	-37.2	-36.2
EZ 10 + A 10	56	9	-50.7	-48.6	13.7	18.5	-52.5	-54.7
Atorva 20	48	12	-39.7	-40.0	14.8	7.2	-42.7	-37.5
EZ 10 + A 20	55	7	-54.6	-46.6	13.4	33.3	-57.6	-63.8
Atorva 40	50	14	-40.5	-52.2	16.4	10.2	-42.7	-53.5
EZ 10 + A 40	55	8	-54.7	-52.0	20.0	16.0	-60.4	-51.4
Atorva 80	55	7	-51.5	-50.2	12.7	19.8	-51.8	-55.0
EZ 10 + A 80	54	8	-60.4	-55.1	9.5	23.5	-62.9	-66.6

a: Raw mean percent change from baseline.
EZ 10 = ezetimibe 10 mg; Atorva XX = dose of atorvastatin in milligrams; All Atorva = pool of all doses of atorvastatin; EZ 10+All Atorva = pool of all doses of atorvastatin coadministered with ezetimibe 10 mg
C = Caucasian; N-C = non-Caucasian

Source: Study Report P692, Table 16, pg. 117.

The analysis by race was confounded by the small sample size of non-Caucasians. Thus, although the results were consistent in both Caucasians and non-Caucasians, a robust interpretation cannot be made because of the small sample size.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study P2154 was a 12-month extension study of P692. Persistence of efficacy was demonstrated with this study. Please see the discussion above in Sections 6.1.4. and 6.1.5 for P2154.

6.1.10 Additional Efficacy Issues/Analyses

Study P1030 has been previously reviewed by the Agency and is currently described in the Zetia labeling. Study P1417 is an open-label study extension of P1030 that is reviewed in this document for safety (Section 7). The following is a brief summary of P1030 and P1417.

P1030 was a double-blind 12-week study in patients with a clinical and/or genotypic diagnosis of HoFH. Patients were randomized 2:1 to one of six treatment arms:

- atorvastatin 80 mg
- ezetimibe + atorvastatin 40 mg
- ezetimibe + atorvastatin 80 mg
- simvastatin 80 mg
- ezetimibe + simvastatin 40 mg
- ezetimibe + simvastatin 80 mg

Patients were allowed to continue their open-label statin 40 mg from the lead in period as part of their total dose. In all, 50 subjects were enrolled; 21 men and 29 women, aged 11 to 74 years.

The primary efficacy variable was percent change from baseline to endpoint in the plasma concentration of LDL-C. The primary efficacy analysis was the ezetimibe 10 mg + Statin (either 40mg or 80 mg) treatment group vs. the Statin 80 mg group.

For this NDA submission, 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. Please see the statistical reviewer's report for further analysis of this trial.

7 Review of Safety

Safety Summary

Both atorvastatin and ezetimibe are approved drugs currently available in the US. The safety profile of both drugs is known.

Atorvastatin safety concerns include musculoskeletal and hepatic events. Rhabdomyolysis is a statin-class effect and is included in the atorvastatin label. Uncomplicated myalgia has also been reported in atorvastatin treated patients.

In addition to muscle-related adverse events, statins are associated with liver enzyme elevations. Based on current prescribing information for atorvastatin, persistent elevations (>3X ULN occurring on two or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials; the incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

Similar to atorvastatin, ezetimibe safety concerns include musculoskeletal and hepatic events. According to the prescribing information for ezetimibe, the incidence of consecutive elevations (>3XULN) in liver enzymes was similar between ezetimibe (0.5%) and placebo (0.3%). In controlled clinical combination studies of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥ 3 XULN) in hepatic transaminase levels was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates.

In this NDA submission, ezetimibe + atorvastatin co-administration was evaluated for safety in over 2500 patients in clinical trials. Short-term trials ranged from 6 to 14 weeks while long-term trials evaluated safety up to 12 months. Up to 24 months of safety in a special population of patients with homozygous familial hypercholesterolemia was also evaluated.

The safety profile was consistent with that expected from the two active components of the combination used alone. In clinical trials, the incidence of CPK ≥ 10 XULN was 0% for ezetimibe + atorvastatin, 0% for placebo, 0% for ezetimibe monotherapy, and 0.1% for all atorvastatin monotherapy doses

One patient on ezetimibe + atorvastatin co-administration met the criteria for myopathy. The CPK ≥ 10 xULN result for this patient was measured at a local laboratory and consequently not included in the database, as pre-specified for the studies conducted by legacy Schering-Plough. The patient experienced moderate diffuse myalgia and moderate weakness. Treatment was discontinued and the symptoms resolved.

There was another case of a patient on atorvastatin monotherapy with CPK $\geq 10 \times \text{ULN}$ in conjunction with reported muscle pain which the investigator attributed to exercise. The elevation resolved despite continuation of atorvastatin monotherapy.

Except for these two patients, few patients had post-baseline CPK values $\geq 10 \times \text{ULN}$ and none of these met the criteria for myopathy (i.e., defined as the presence of muscle pain and/or weakness in association with CPK elevations to levels $\geq 10 \times \text{ULN}$, not explained by another etiology such as exercise or trauma). There were no statistically significant differences between atorvastatin monotherapy and ezetimibe + atorvastatin co-administration in the incidences of any of the categories of CPK $\geq 10 \times \text{ULN}$.

In the core safety pool, consecutive liver enzyme elevations $\geq 3 \times \text{ULN}$ were not observed with ezetimibe monotherapy, and only a small number of such events occurred with atorvastatin monotherapy (0.5%) and ezetimibe + atorvastatin co-administration (0.6%). There was one reported case of "hepatitis" in the ezetimibe + atorvastatin co-administration.

In addition, there were no clinically meaningful differences between treatment groups with respect to subgroups of age in the core safety pool.

7.1 Methods

All patients who took at least one dose of study medication were included in the safety analyses. For the purpose of the ISS, study medications consisted of placebo, atorvastatin (all doses), ezetimibe (all doses), ezetimibe and atorvastatin co-administration (all doses) arms of the individual studies.

In this submission, the applicant combined data from seven studies ranging from 6 to 14 weeks into a "core-safety pool" to evaluate short term safety of ezetimibe + atorvastatin co-administration. Long-term safety was evaluated in individual analyses of two 12 – month extension studies, one double-blinded and one open-label. Up to 24 months of safety in the HoFH was also evaluated.

According to the applicant, the analysis of safety results followed a tiered approach. The tiers differ with respect to the analyses that were performed. Safety parameters or adverse experiences of special interest identified a priori constituted "Tier 1" safety endpoints that were subjected to inferential testing for statistical significance with p-values and 95% confidence intervals provided for pooled atorvastatin versus pooled ezetimibe + atorvastatin between-group comparisons.

Other safety parameters were considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only descriptive statistics by treatment group were provided for Tier 3 safety parameters.

AEs and predefined limits of change in laboratory parameters that were not pre-specified as endpoints of special interest were classified as belonging to “Tier 2” or “Tier 3,” based on the number of events observed. Membership in Tier 2 required that at least 2% of patients in the atorvastatin or ezetimibe + atorvastatin treatment groups exhibit the event; all other adverse experiences and predefined limits of change belong to Tier 3.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 35: Clinical Trials Included in ISS

Protocol #	Design	Patient Population	Relevant treatments (Sample Size)
Short term studies – To be analyzed as a pool with stratification for study			
040	6-week, double-blind, randomized, placebo-controlled, ezetimibe or placebo, added to ongoing statin (n=3030)	Patients with hypercholesterolemia not at their LDL-C goal as defined by the NCEP ATP III guidelines	All Atorva (n = 401) EZ+All Atorva (n = 793)
2173	8-week, double-blind, randomized, placebo-controlled, ezetimibe or placebo, added to ongoing statin (n=769)	Patients with primary hypercholesterolemia	All Atorva (n = 162) EZ+All Atorva (n = 146)
079	6-week, double-blind, randomized, parallel group titration trial, titration of atorvastatin from 20 mg to 40 mg or addition of EZ 10 mg to Atorvastatin 20 mg (n=184)	Patients at moderate high risk for CHD who have not reached optional NCEP ATP III goal LDL-C level (<100 mg/dL) on atorvastatin 20 mg alone	All Atorva (n = 98) EZ+All Atorva (n = 96)
090	6-week, double-blind, randomized, parallel group titration trial, titration of atorvastatin from 40 to 80 mg or addition of EZ 10 mg to atorvastatin 40 mg (n=579)	Patients at high risk for Coronary Heart Disease (CHD) who have not reached optional NCEP ATP III goal LDL-C levels (<70 mg/dL) on atorvastatin 40 mg alone	All Atorva (n = 289) EZ+All Atorva (n = 286)
0692	12-week, double-blind, placebo-controlled, parallel-group, factorial study (n=628)	Patients with primary hypercholesterolemia, LDL-C \geq 145 mg/dL to \leq 250 mg/dL, and triglycerides $<$ 350 mg/dL	Placebo (n = 60) EZ (n = 65) All Atorva (n = 248) EZ+All Atorva (n = 255)
0693	14-week, double-blind, randomized, active-control, response-based atorvastatin dose titration vs EZ 10 mg plus atorvastatin 10 to 40 mg (n=1847)	Patients with HeFH or CHD or multiple cardiovascular risk factors (greater than or equal to two) and primary hypercholesterolemia	All Atorva (n = 316) EZ+All Atorva (n = 305)
112	12-week, double-blind, randomized, parallel arm, EZ 10 mg added to Atorvastatin 10 mg versus titration to Atorvastatin 20 mg and to 40 mg	Elderly patients with hypercholesterolemia at high risk for CHD	All Atorva (n = 525) EZ+All Atorva (n=526)
Long term studies – To be analyzed separately by study			
2154	12 month, double-blind extension study with ezetimibe 10 mg plus atorvastatin vs atorvastatin 10-80 mg (n=246)	Patients with primary hypercholesterolemia, LDL-C \geq 145 mg/dL to \leq 250 mg/dL, and triglycerides \leq 350 mg/dL	All Atorva (n = 45) EZ+All Atorva (n = 201)

Protocol #	Design	Patient Population	Relevant treatments (Sample Size)
1418	12 month, open-label, long-term extension study with EZ 10 mg plus 10-80 mg statin (n=621)	Patients with HeFH or subjects with CHD or multiple cardiovascular risk factors (greater than or equal to two), and primary hypercholesterolemia	All Atorva (n = 216) EZ+All Atorva (n = 216)
Special Population – To be analyzed separately by study			
1030	12-week, double-blind, randomized, parallel-group study, EZ 10 mg plus a statin vs statin monotherapy (n=50)	Patients with Homozygous Familial Hypercholesterolemia	All Atorva (n = 12) EZ+All Atorva (n = 24)
1417	24 month, open-label extension study, EZ 10 mg plus 40/80 mg statin (n=44)	Patients with Homozygous Familial Hypercholesterolemia	EZ+All Atorva (n = 35)

7.1.2 Categorization of Adverse Events

AEs were defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the applicant's product (active drug or placebo), whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that was temporally associated with the use of the applicant's product was also an AE.

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 11.0 terminology. Each literal term reported in a patient's CRF was linked to a preferred term that served to consolidate reports of a similar nature; these preferred terms were used for safety analyses. Preferred terms were then ordered within a Body System or System Organ Class to organize the AEs and to consolidate reports.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The applicant grouped eleven clinical studies into three data pools:

- core safety pool: 0692, 0693, 2173, 040, 079, 090 and 112
- long term studies: 2154 and 1418
- special population studies: 1030 and 1417

The seven clinical trials in the core safety pool were all of double-blind design, recruited similar patient populations and were between 6 and 14 weeks of duration.

The two long-term protocols P2154 (double-blind) and P1418 (open-label) were not pooled because of differences in study design, but were instead analyzed individually.

The special population protocols P1030 and P1417 were also reported as stand-alone studies. These two studies were of patients with homozygous familial hypercholesterolemia. P1030 was a 12 week, double-blind study and P1417 was a 24 month, open-label extension study in patients who had completed P1030.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Core Safety Pool

A total of 4569 patients participated in these studies, with 2041 patients randomized to atorvastatin monotherapy and 2403 randomized to ezetimibe 10 mg + atorvastatin, 65 on ezetimibe monotherapy and 60 patients on placebo. The remaining 125 patients were randomized to either placebo or ezetimibe. (Table 35)

Table 36: Core Safety Pool Exposure Data

	Placebo	EZ 10 mg Monotherapy	All Atorva Monotherapy	EZ 10mg + All Atorva
● Number of Studies	1	1	7	7
● Number of Patients	60	65	2041	2403
● Duration of Treatment:				
◇ Median Duration of Treatment (Weeks)	12	12	11	8
◇ Number of Patients:				
>3 weeks	59	64	1991	2345
>6 weeks	58	63	1560	1765
>12 weeks	22	22	623	621
Note: EZ 10 mg = Ezetimibe 10 mg; All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.				
Core safety pool studies (040, 079, 090, 112, 692, 693, and 2173)				

Source: Clinical Summary Table 2.7.4.:4; pg.30.

The mean treatment duration for the groups was as follows:

- Placebo: was 82 days (range: 10 to 95 days)
- Ezetimibe monotherapy: 82 days (range: 4 to 102 days) for
- Atorvastatin monotherapy: 67 days (range: 1 to 162 days) for and
- Ezetimibe + atorvastatin co-administration: 63 days (range: 1 to 136 days)

Table 37: Duration of Exposure- Core Safety Pool

Duration (Days)	Placebo (N= 60) n (%)	EZ 10 mg (N=65) n (%)	All Atorva (N=2041) n (%)	EZ 10 mg + All Atorva (N=2403) n (%)
1 to 7	0	1 (1.5)	18 (0.9)	19 (0.8)
8 to 21	1 (1.7)	0	30 (1.5)	35 (1.5)
22 to 42	1 (1.7)	1 (1.5)	431 (21.1)	579 (24.1)
43 to 78	3 (5.0)	5 (7.7)	540 (26.5)	770 (32.0)
79 to 115	55 (91.7)	58 (89.2)	1010 (49.5)	984 (40.9)
>115	0	0	10 (0.5)	11 (0.5)
Missing	0	0	2 (0.1)	5 (0.2)
Range (days)	10 to 95	4 to 102	1 to 162	1 to 136
Mean (days)	82	82	67	63
Median (days)	84	84	79	53

EZ = Ezetimibe, All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.

A patient may be counted under more than one dose or treatment if the patient was titrated to a higher dose or took another study treatment.

4 patients received both Atorva monotherapy and EZ 10 mg + Atorva and were counted under the specific doses of Atorva or EZ+ Atorva received: P00693 001076, P00693 001423, P00693 001557 and P00693 001558.

The following patients received the treatment in parentheses but treatment duration is unknown: P00692 000389 (Atorva 20 mg), P00692 001362 (Atorva 40 mg), P00692 000453, P00693 000641, P00693 001449,

P00693 001793 and P02173 000460 (EZ 10 mg + Atorva 20 mg).

Of these patients, P00693 001449, P00693 000641 and P00693 001793 were known to have received EZ+Atorva 10mg for 37, 39 and 42 days, respectively.

Source: Clinical Summary Table 2.7.4:8, pg. 37

Reviewer comment: The placebo and ezetimibe monotherapy groups had a mean duration that was approximately 19 days longer than the ezetimibe + atorvastatin co-administration group. However, mean duration of exposure was similar for the atorvastatin monotherapy as compared to ezetimibe + atorvastatin co-administration treatment group.

Long-term Trials (P2154, P1418)

In double-blind study 2154, the mean treatment duration was approximately 11 months on atorvastatin monotherapy as well as 11 months on ezetimibe + atorvastatin combination treatment. The total exposure to atorvastatin and to ezetimibe + atorvastatin for P2154 is presented below.

Table 38: Duration of Exposure- Protocol 2154

Duration (Months)	All Atorva (n=45) (%)	EZ 10 mg + All Atorva (n=201) (%)
<3	5(11.1)	14(7.0)
3 to <6	1(2.2)	7(3.5)
6 to <9	0(0.0)	10(5.0)
9 to <12	11(24.4)	45(22.4)
≥12	28(62.2)	125(62.2)
Missing	0(0.0)	0(0.0)
Range	0 to 13	0 to 13
Mean	11	11
EZ = Ezetimibe, All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.		

Source: Clinical Summary, Table 2.7.4:9, pg. 38.

Protocol 1418 was an open-label extension trial of P693. A total of 305 patients received ezetimibe + atorvastatin co-administration therapy in P693 with a mean duration of participation of 3 months or 95.8 days. With the addition of P1418, the extent of the co-administration experience increased to 521 patients with a mean duration of participation of 11.87 months.

Special Population Trials (P1030, P1417)

In P1030, the mean treatment duration was 82 days on atorvastatin monotherapy and 87 days on ezetimibe + atorvastatin co-administration.

Table 39: Duration of Exposure- Protocol 1030

Duration (Days)	All Atorva (n=12) (%)	EZ 10 mg + All Atorva (n=24) (%)
1 to 7	0(0.0)	0(0.0)
8 to 21	0(0.0)	0(0.0)
22 to 42	0(0.0)	0(0.0)
43 to 78	2(16.7)	1(4.2)
79 to 115	10(83.3)	23(95.8)
> 115	0(0.0)	0(0.0)
Missing	0(0.0)	0(0.0)
Range	58 to 98	66 to 98
Mean	82	87
EZ = Ezetimibe, All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.		

Source: Clinical Summary, Table 2.7.4:10, pg. 39.

Protocol 1417 was an open-label extension of P1030. A total of 24 patients received ezetimibe + atorvastatin co-administration therapy in the parent protocol P1030 with a mean duration of participation of 3 months (87 days). With the addition of the extension study under P1417, the extent of the co-administration experience increased to 36 patients with a mean duration of participation of 23.5 months.

7.2.2 Explorations for Dose Response

Review of dose response of the different strengths of Atozet is summarized in Section 6, under Analysis of Primary Endpoint.

7.2.3 Special Animal and/or In Vitro Testing

The applicant conducted a 3-month toxicity study in dogs with their amorphous atorvastatin plus a drug called MK-6213. This drug, MK-6213 is another investigational cholesterol absorption inhibitor and not ezetimibe. However, this study has a group of animals who received atorvastatin amorphous alone (at a dose of 10 mg/kg/day in dogs, study # TT #07-6039). They have also conducted genotoxicity studies (bacterial mutagenicity and chromosomal aberration assay) with their atorvastatin amorphous drug product to support impurity/degradant qualification found in their FDC product. Please see the pharmacology/toxicology review for analysis of this 3- month toxicity study.

All other studies with the combination have already been conducted under NDA 21-445, in which ezetimibe was approved for monotherapy and for co-administration therapy with statins (simvastatin, atorvastatin, pravastatin and lovastatin).

7.2.4 Routine Clinical Testing

The methods and frequency of monitoring laboratory parameters were, in general, adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant has adequately addressed enzymatic pathways responsible for clearance of ezetimibe and atorvastatin. See Section 8.2 for an overview of drug-drug interactions; please refer to previous clinical pharmacology reviews for the Zetia (NDA 21-445) for a more detailed analysis.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant has conducted appropriate evaluations to detect known class associations with myopathy/rhabdomyolysis and liver AT elevations.

7.3 Major Safety Results

7.3.1 Deaths

A total of five deaths were reported in the ezetimibe/atorvastatin development program. Four of these deaths were reported in Core Safety Pool studies and one death was reported in the Long Term Studies group.

Table 40: Deaths Core Safety Pool

Protocol Number	Patient ID	Gender	Race	Age	Relative Day on Onset	Causality of Death
Atorvastatin Monotherapy						
112	005071	Male	White	70	54	Brain stem hemorrhage
693	001073	Male	White	53	98	Myocardial Infarction
EZ 10 mg + All Atorvastatin						
112	006561	Female	White	70	3	Cerebrovascular accident
112	007093	Male	White	68	79	Unknown
1418	001043	Male	White	56	46	Complications of cardiopulmonary arrest

Brief case narratives of the deaths are described below:

Atorvastatin Monotherapy

Study P693, ID # 1073: (atorvastatin monotherapy), a 53-year-old Caucasian man, died due to a myocardial infarction. The subject had a clinical diagnosis of HeFH and a history of CABG, angina, stroke, and carotid bypass. On Days 65 and 67, the subject experienced 1-day events of mild thoracic pain, weakness, and anxiety that resolved without treatment. On Day 98, the subject was hospitalized with a myocardial infarction. This was reported as an SAE of life-threatening severity. Thrombolytic therapy was administered, but the subject died on Day 99. No autopsy was performed. The last dose of study medication was taken on Day 98. Per protocol, the subject's atorvastatin dose was increased to 40 mg daily on Day 36 and increased again to 80 mg on Day 71.

Study P112, ID # 5071: (atorvastatin 40 mg), a 70 year old white male with a history of obstructive sleep apnea, hemorrhagic brain infarction, lower backaches, depression, hyperlipidemia, atrial fibrillation, insomnia, prostatectomy, dilated cardiomyopathy, coronary artery disease, implantable cardioverter defibrillator insertion, atrial fibrillation, sick sinus syndrome, insomnia, and cardiac failure congestive (CHF) class 1 had a brain aneurysm which went into his brain stem. He was hospitalized and craniotomy was performed. The patient never regained consciousness and died due to brain stem hemorrhage. The reporting investigator did not feel this was related to study therapy.

Ezetimibe + Atorvastatin Co-administration

Study P112, ID #6561: (ezetimibe 10 mg + atorvastatin 10 mg), a 70-year old white female with a history of arterial hypertension, hyperlipidemia, chronic pyelonephritis and anemia died suddenly in her sleep. An autopsy was not performed. Based on the patient's medical history and mechanism of death, it was concluded the cause of death was stroke (cerebrovascular accident). The reporting investigator felt that stroke was not related to study therapy.

Study P112, ID # 7093: (ezetimibe 10 mg + atorvastatin 10 mg), a 68 year old white male with a history of myocardial infarction, ischemic stroke and duodenal ulcer disease died with unknown cause of death. No other information was able to be obtained as family refused communication with the site. The reporting investigator felt that death was not related to study therapy.

Long-term Studies; Ezetimibe + Atorvastatin Co-administration

Study P1418, ID #1043: (ezetimibe 10 mg + atorvastatin 10 mg), a 56-year-old Caucasian man, was randomized to receive atorvastatin 20 mg daily in the parent study, P693. The patient completed the parent study and continued into P1418 where he received ezetimibe 10 mg and atorvastatin 10 mg. He had a history of ischemic cardiomyopathy with angioplasty in 1995; there was no history of myocardial infarction or arrhythmia. The patient collapsed in cardiopulmonary arrest during public speaking 46 days after the start of co-administration therapy under Protocol P1418. He was resuscitated by an emergency mobile unit. Resuscitation included electrical cardioversion of ventricular fibrillation. Upon arrival at a hospital, the patient was comatose (Glasgow coma score of 3) and exhibited bilateral decerebrate movements and left flail chest. The patient was intubated; pneumonia was noted on the second hospital day. Three days after admission, the Glasgow score improved to 7, and the patient was extubated 8 days after admission. He was transferred to a long-term care facility 17 days after hospital admission. Within the next month, he was treated for a pulmonary infection and colitis. He remained in the long-term care facility with little improvement in neurologic status over the next year. He was unable to walk alone. He died 385 days after the initial hospitalization. His neurologic impairment was considered to be an encephalopathy related to anoxia suffered at the time of cardiopulmonary resuscitation. The investigator considered that death was related to complications of the cardiorespiratory arrest. The cardiorespiratory arrest was considered to be unlikely

related to study medication by the investigator. An autopsy was not performed. Study drug had been permanently discontinued at the time of initial hospitalization.

Reviewer Comment: Based on review of the case narratives, the reported causes of death appear accurate.

7.3.2 Nonfatal Serious Adverse Events

Core Safety Pool (0692, 0693, 2173, 040, 079, 090 and 112)

Overall, the incidence of nonfatal SAEs was 2.7% (65/2403) for the ezetimibe + atorvastatin group, 2.3% (46/2041) for the atorvastatin monotherapy group, 3.1% (2/65) for ezetimibe monotherapy group, and 3.3% (2/60) for placebo group.

The most commonly reported SAE in atorvastatin monotherapy or ezetimibe + atorvastatin co-administration groups were:

- myocardial infarction, reported by 5 (0.2%) atorvastatin monotherapy vs. 6 (0.2%) ezetimibe + atorvastatin co-administration group
- chest pain, reported by 3 (0.1%) in the atorvastatin monotherapy vs. 4(0.2%) in the ezetimibe + atorvastatin treatment group
- angina pectoris, reported by 3 (0.1%) in the atorvastatin monotherapy vs. 3 (0.1%) reported by ezetimibe + atorvastatin co-administration group

The following SAEs in the ezetimibe + atorvastatin co-administration group were reported for muscle-related issues:

Study P692-ID# 001311- 54 yo Hispanic man, on ezetimibe + atorvastatin co-administration, reported diffuse myalgias and weakness on Day 54. The myalgias were reported as an SAE. On the same day, the subject's CPK level was elevated to 403 mU/mL (normal range 0-120 mU/mL). This was reported as a severe serious adverse event, considered by the investigator to be of probable relationship to study medication. Per local laboratory results, the subject's CPK continued to rise and reached a high point of 5379 mU/mL on Day 56. The subject was discontinued from study. The myalgia and weakness resolved on Day 67, and the CPK elevation was considered to be resolved on Day 74, when the value had returned to normal range at 96 mU/mL.

- Study P693-ID# 001799- 40 yo Caucasian woman, on ezetimibe + atorvastatin co-administration, reported a SAE on Day 40 of myalgia.

The following SAEs in the ezetimibe + atorvastatin co-administration group were reported for hepatic-related issues:

- Study P693-ID#001793- 56 yo Caucasian woman on ezetimibe + atorvastatin co-administration, reported an SAE of hepatitis of unknown etiology associated with a hemolytic anemia on Day 38. Hepatitis was reported as an SAE of moderate severity, Day 38 ongoing, and was considered possibly related to study drug. The subject had taken a Voltaren suppository on Day 38 for epigastric pain and this was considered by the sponsor to be a second suspect in the increase of the subject's enzymes. Hepatitis serology was negative. The subject was also diagnosed with hemolytic anemia on the basis of a positive Coombs' test. This was reported as an SAE and was considered to be a possible autoimmune hemolytic anemia, although the possibility of a drug-induced hemolytic anemia could not be ruled out. The subject was discontinued from the study due to the hepatitis and hemolytic anemia; the last dose of study medications was on Day 41.
- Study P692-ID#000007-60 yo Caucasian woman on ezetimibe + atorvastatin co-administration, reportedly had elevated AST and ALT prior to receiving randomized study drug. This event was not treated and on Day 15, liver function tests were again abnormal (see table below). The levels further increased on Day 22, and the subject discontinued the study. Follow-up labs returned to normal.

Date	SGPT	SGOT	ALK-P	GGT
Normal Range	5-25 mU/mL	8-22 mU/mL	32-72 mU/mL	5-29 mU/mL
(b) (6)	21	15	58	88
	17	15	54	57
	64	34	83	187
	35	20	75	149
	56	38	102	184
	116	110	122	295
	239	143	232	473
	50	19	128	270
	25	19	81	153

- Study P692-ID#000199- 44 yo man on ezetimibe + atorvastatin co-administration, reported an SAE of hepatic enzymes elevated on Day 32 (see labs below). Although patient was asymptomatic, the patient was discontinued from the study. According to the applicant, the total bilirubin and CPK levels remained within normal ranges at all time points during the study.

Clinical Review
Iffat N. Chowdhury, MD
{NDA 200,153
{Atozet, ezetimibe/atorvastatin}

Date	SGPT	SGOT	GGT
Normal Range	5-25 mU/mL	8-22 mU/mL	5-29 mU/mL
(b) (6)	35	23	46
	27	15	48
	25	17	44
	38	21	51
	146	77	122
	78	32	79
	82	52	72
	40	20	64

Table 41: Number (%) of Patients with Serious Adverse Events by System/Organ/Class -Core Safety Pool

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
Number (%) of Patients:				
With no adverse experience	58(96.7)	63(96.9)	1995(97.7)	2338(97.3)
With one or more adverse experiences	2(3.3)	2(3.1)	46(2.3)	65(2.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Anaemia	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Haemolytic Anaemia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
CARDIAC DISORDERS	1(1.7)	0(0.0)	13(0.6)	17(0.7)
Acute Myocardial Infarction	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Angina Pectoris	0(0.0)	0(0.0)	3(0.1)	3(0.1)
Angina Unstable	0(0.0)	0(0.0)	2(0.1)	0(0.0)
Bradycardia	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Cardiac Failure	1(1.7)	0(0.0)	0(0.0)	0(0.0)
Cardiac Failure Congestive	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Coronary Artery Disease	0(0.0)	0(0.0)	3(0.1)	0(0.0)
Coronary Artery Occlusion	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Coronary Artery Stenosis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Myocardial Infarction	0(0.0)	0(0.0)	5(0.2)	6(0.2)
Myocardial Ischaemia	1(1.7)	0(0.0)	0(0.0)	1(0.0)
Supraventricular Tachycardia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Ventricular Tachycardia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
EAR AND LABYRINTH DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Vertigo	0(0.0)	0(0.0)	1(0.0)	0(0.0)
GASTROINTESTINAL DISORDERS	0(0.0)	0(0.0)	7(0.3)	8(0.3)
Abdominal Discomfort	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Abdominal Pain	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Abdominal Pain Lower	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Appendicitis Perforated	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Gastritis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Gastrointestinal Haemorrhage	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Gastrooesophageal Reflux Disease	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Haematemesis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Ileus	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Lower Gastrointestinal Haemorrhage	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Nausea	0(0.0)	0(0.0)	3(0.1)	0(0.0)
Reflux Oesophagitis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Small Intestinal Obstruction	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Vomiting	0(0.0)	0(0.0)	1(0.0)	0(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0(0.0)	1(1.5)	6(0.3)	9(0.4)
Asthenia	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Chest Discomfort	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Chest Pain	0(0.0)	1(1.5)	3(0.1)	4(0.2)
Death	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Fatigue	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hernia Obstructive	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Ischaemic Ulcer	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Non-Cardiac Chest Pain	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pyrexia	0(0.0)	0(0.0)	1(0.0)	0(0.0)
HEPATOBIILIARY DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Cholecystitis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hepatitis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
INFECTIONS AND INFESTATIONS	0(0.0)	0(0.0)	4(0.2)	9(0.4)
Abdominal Abscess	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Appendicitis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Cellulitis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Empyema	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Gastroenteritis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Liver Abscess	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Penile Infection	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Peridiverticular Abscess	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	3(0.1)
Pneumonia Bacterial	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pyelonephritis Chronic	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Salpingitis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0(0.0)	0(0.0)	4(0.2)	1(0.0)
Foreign Body Trauma	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Hip Fracture	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Overdose	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Procedural Pain	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Wrist Fracture	0(0.0)	0(0.0)	0(0.0)	1(0.0)
INVESTIGATIONS	0(0.0)	0(0.0)	1(0.0)	3(0.1)
Alanine Aminotransferase Increased	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Aspartate Aminotransferase Increased	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Blood Creatine Phosphokinase Increased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hepatic Enzyme Increased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Liver Function Test Abnormal	0(0.0)	0(0.0)	0(0.0)	1(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0(0.0)	0(0.0)	2(0.1)	5(0.2)
Costochondritis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Intervertebral Disc Protrusion	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Myalgia	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Neck Pain	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Spinal Column Stenosis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0(0.0)	2(3.1)	0(0.0)	6(0.2)
Basal Cell Carcinoma	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Bladder Cancer	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Breast Cancer	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Lung Adenocarcinoma	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Meningioma	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Metastases To Central Nervous System	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Rectal Cancer	0(0.0)	0(0.0)	0(0.0)	1(0.0)
NERVOUS SYSTEM DISORDERS	1(1.7)	0(0.0)	6(0.3)	6(0.2)
Brain Stem Haemorrhage	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Cerebrovascular Accident	1(1.7)	0(0.0)	0(0.0)	1(0.0)
Convulsion	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Dizziness	0(0.0)	0(0.0)	2(0.1)	1(0.0)
Dizziness Postural	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Headache	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Intracranial Aneurysm	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Presyncope	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Syncope	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Toxic Encephalopathy	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Transient Ischaemic Attack	0(0.0)	0(0.0)	1(0.0)	0(0.0)
PSYCHIATRIC DISORDERS	0(0.0)	0(0.0)	2(0.1)	0(0.0)
Anxiety	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Mental Status Changes	0(0.0)	0(0.0)	1(0.0)	0(0.0)
RENAL AND URINARY DISORDERS	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Hydronephrosis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Urinary Retention	0(0.0)	0(0.0)	0(0.0)	1(0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Benign Prostatic Hyperplasia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Cystocele	0(0.0)	0(0.0)	1(0.0)	0(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0(0.0)	1(1.5)	4(0.2)	5(0.2)
Acute Pulmonary Oedema	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Dyspnoea	0(0.0)	1(1.5)	2(0.1)	0(0.0)
Epistaxis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Haemoptysis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pleural Effusion	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Pleuritic Pain	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pneumothorax	0(0.0)	1(1.5)	0(0.0)	1(0.0)
Pulmonary Haemorrhage	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pulmonary Mass	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Respiratory Failure	0(0.0)	0(0.0)	0(0.0)	1(0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pruritus	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Rash Papular	0(0.0)	0(0.0)	1(0.0)	0(0.0)
SURGICAL AND MEDICAL PROCEDURES	0(0.0)	0(0.0)	0(0.0)	3(0.1)
Catheterisation Cardiac	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hysterectomy	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Mastectomy	0(0.0)	0(0.0)	0(0.0)	1(0.0)
VASCULAR DISORDERS	0(0.0)	0(0.0)	2(0.1)	3(0.1)
Arterial Occlusive Disease	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hypertensive Crisis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Intermittent Claudication	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Labile Hypertension	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Peripheral Vascular Disorder	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Vasculitis	0(0.0)	0(0.0)	1(0.0)	0(0.0)

EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses.
 Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

7.3.3 Dropouts and/or Discontinuations

Core Safety Pool

The applicant summarized adverse events leading to discontinuation and reported by \geq 2.0% of patients in the atorvastatin monotherapy or ezetimibe + atorvastatin treatment groups.

Overall, 125 (2.7%) of 4569 patients in the Core Safety Pool discontinued due to a clinical adverse experience; 3 (5.0%) of 60 in the placebo group, 3 (4.6%) of 65 in the ezetimibe monotherapy group, 56 (2.7%) of 2041 patients in the atorvastatin monotherapy treatment group and 63 (2.6%) of 2403 patients in the ezetimibe + atorvastatin treatment group.

Reviewer Comment: Discontinuations due to AEs were similar in ezetimibe + atorvastatin co-administration as compared to atorvastatin monotherapy.

Table 42: Number (%) of Patients with Adverse Events Leading to Discontinuation

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
Number (%) of Patients:				
With no adverse experience	57(95.0)	62(95.4)	1985(97.3)	2340(97.4)
With one or more adverse experiences	3(5.0)	3(4.6)	56(2.7)	63(2.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Haemolytic Anaemia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
CARDIAC DISORDERS	0(0.0)	0(0.0)	6(0.3)	6(0.2)
Acute Myocardial Infarction	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Angina Pectoris	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Arrhythmia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Coronary Artery Disease	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Myocardial Infarction	0(0.0)	0(0.0)	4(0.2)	1(0.0)
Myocardial Ischaemia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Ventricular Tachycardia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
EAR AND LABYRINTH DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Vertigo	0(0.0)	0(0.0)	1(0.0)	0(0.0)
EYE DISORDERS	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Eye Swelling	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Photophobia	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Vision Blurred	0(0.0)	0(0.0)	1(0.0)	0(0.0)
GASTROINTESTINAL DISORDERS	2(3.3)	0(0.0)	18(0.9)	15(0.6)
Abdominal Distension	1(1.7)	0(0.0)	1(0.0)	2(0.1)
Abdominal Pain	0(0.0)	0(0.0)	4(0.2)	2(0.1)
Abdominal Pain Upper	0(0.0)	0(0.0)	2(0.1)	1(0.0)
Constipation	0(0.0)	0(0.0)	2(0.1)	0(0.0)
Defaecation Urgency	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Diarrhoea	1(1.7)	0(0.0)	3(0.1)	4(0.2)
Dyspepsia	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Flatulence	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Frequent Bowel Movements	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Gastritis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Gastrointestinal Disorder	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Gastrooesophageal Reflux Disease	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Ileus	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Intestinal Mass	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Nausea	0(0.0)	0(0.0)	6(0.3)	3(0.1)
Proctalgia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Rectal Haemorrhage	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Small Intestinal Obstruction	0(0.0)	0(0.0)	0(0.0)	1(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
Stomach Discomfort	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Vomiting	0(0.0)	0(0.0)	1(0.0)	0(0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1(1.7)	0(0.0)	5(0.2)	6(0.2)
Asthenia	0(0.0)	0(0.0)	1(0.0)	2(0.1)
Chest Discomfort	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Fatigue	1(1.7)	0(0.0)	3(0.1)	4(0.2)
Generalised Oedema	1(1.7)	0(0.0)	0(0.0)	0(0.0)
Malaise	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Oedema Peripheral	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pain	0(0.0)	0(0.0)	0(0.0)	1(0.0)
HEPATOBIILIARY DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Cholecystitis Chronic	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hepatitis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
IMMUNE SYSTEM DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Seasonal Allergy	0(0.0)	0(0.0)	1(0.0)	0(0.0)
INFECTIONS AND INFESTATIONS	0(0.0)	0(0.0)	2(0.1)	8(0.3)
Bronchitis	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Diverticulitis	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Gastroenteritis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Helicobacter Infection	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Peridiverticular Abscess	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pyelonephritis Chronic	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Upper Respiratory Tract Infection	0(0.0)	0(0.0)	0(0.0)	1(0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0(0.0)	1(1.5)	1(0.0)	2(0.1)
Corneal Abrasion	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hip Fracture	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Muscle Strain	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Skin Laceration	0(0.0)	0(0.0)	0(0.0)	1(0.0)
INVESTIGATIONS	0(0.0)	0(0.0)	3(0.1)	6(0.2)
Alanine Aminotransferase Increased	0(0.0)	0(0.0)	1(0.0)	2(0.1)
Aspartate Aminotransferase Increased	0(0.0)	0(0.0)	2(0.1)	1(0.0)
Blood Creatine Phosphokinase Increased	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Gamma-Glutamyltransferase Increased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Haematocrit Decreased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Haemoglobin Decreased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Hepatic Enzyme Increased	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Liver Function Test Abnormal	0(0.0)	0(0.0)	0(0.0)	1(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0(0.0)	0(0.0)	12(0.6)	14(0.6)
Arthralgia	0(0.0)	0(0.0)	2(0.1)	1(0.0)
Arthritis	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Back Pain	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Muscle Spasms	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Muscular Weakness	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Musculoskeletal Pain	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Myalgia	0(0.0)	0(0.0)	7(0.3)	8(0.3)
Neck Pain	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Pain In Extremity	0(0.0)	0(0.0)	2(0.1)	2(0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0(0.0)	1(1.5)	0(0.0)	2(0.1)
Breast Cancer	0(0.0)	0(0.0)	0(0.0)	2(0.1)
Meningioma	0(0.0)	1(1.5)	0(0.0)	0(0.0)
NERVOUS SYSTEM DISORDERS	1(1.7)	1(1.5)	4(0.2)	6(0.2)
Amnesia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Cerebrovascular Accident	1(1.7)	0(0.0)	0(0.0)	0(0.0)
Convulsion	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Dizziness	0(0.0)	0(0.0)	0(0.0)	3(0.1)
Headache	0(0.0)	1(1.5)	2(0.1)	2(0.1)
Hemiparesis	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Lethargy	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Paraesthesia	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Syncope	0(0.0)	0(0.0)	1(0.0)	0(0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Pregnancy	0(0.0)	0(0.0)	0(0.0)	1(0.0)
PSYCHIATRIC DISORDERS	0(0.0)	0(0.0)	1(0.0)	2(0.1)
Depression	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Insomnia	0(0.0)	0(0.0)	0(0.0)	2(0.1)
RENAL AND URINARY DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Haematuria	0(0.0)	0(0.0)	1(0.0)	0(0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Menopausal Symptoms	0(0.0)	0(0.0)	1(0.0)	0(0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0(0.0)	1(1.5)	0(0.0)	2(0.1)
Dyspnoea	0(0.0)	1(1.5)	0(0.0)	0(0.0)

	Crude Event Rate			
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403
Pulmonary Haemorrhage	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Respiratory Failure	0(0.0)	0(0.0)	0(0.0)	1(0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0(0.0)	0(0.0)	3(0.1)	1(0.0)
Pruritus	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Rash	0(0.0)	0(0.0)	1(0.0)	1(0.0)
Rash Papular	0(0.0)	0(0.0)	1(0.0)	0(0.0)
Urticaria	0(0.0)	0(0.0)	1(0.0)	0(0.0)
SURGICAL AND MEDICAL PROCEDURES	0(0.0)	0(0.0)	0(0.0)	1(0.0)
Mastectomy	0(0.0)	0(0.0)	0(0.0)	1(0.0)
VASCULAR DISORDERS	0(0.0)	1(1.5)	1(0.0)	0(0.0)
Hypertension	0(0.0)	1(1.5)	0(0.0)	0(0.0)
Vasculitis	0(0.0)	0(0.0)	1(0.0)	0(0.0)
EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses. Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Source: Clinical Summary of Safety, Appendix 2.7.4:8, pg.217.

The major contributing SOC were Gastrointestinal Disorders and Musculoskeletal and Connective Tissue Disorders. A total of 35 (0.8%) of 4569 patients discontinued due to gastrointestinal adverse event; 2 (3.3%) of 60 patients in the placebo group, 0 of 65 patients in the ezetimibe monotherapy group, 18 (0.9%) of 2041 patients in the atorvastatin monotherapy group, and 15 (0.6%) of 2403 patients in the ezetimibe + atorvastatin co-administration group.

A total of 26 (0.6%) of 4569 patients discontinued due to musculoskeletal adverse experiences; 12 (0.6%) of 2041 patients on atorvastatin monotherapy and 14 (0.6%) of 2403 patients on ezetimibe + atorvastatin.

The most frequently reported AE causing discontinuation were nausea; 6 (0.3%) and 3 (0.1%) patients, respectively, and myalgia, 7 (0.3%) and 8 (0.3%) patients, respectively, in the atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups.

Long-Term Studies (P2154, P1418)

Protocol 2154

The applicant summarized a summary of specific adverse experiences causing discontinuation that occurred in 4 or more patients in one or more treatment groups. Of the 246 patients in P2154, 21 (8.5%) reported one or more adverse experiences causing discontinuation with 3 (6.7%) of 45 in the atorvastatin monotherapy group and 18 (9.0%) of 201 in the ezetimibe + atorvastatin co-administration group.

The major contributing SOC was Musculoskeletal and Connective Tissue Disorders. A total of 7 (2.8%) of 246 patients discontinued due to due to musculoskeletal adverse experiences; 2 (4.4%) of 45 patients in the atorvastatin monotherapy group and 5 (2.5%) of 201 patients in the ezetimibe + atorvastatin co-administration group.

The most frequently reported AE causing discontinuation was myalgia with two patients each in the atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups.

Table 43: Number (%) of Patients with AE Causing Discontinuations (Number \geq 4 in One or More Treatment Group) by System Organ Class- Protocol 2154

	Crude Event Rate		EZ/All Atorva minus All Atorva Difference(95% CI)†
	All Atorva N=45	EZ 10 mg + All Atorva N=201	
Number (%) of Patients:			
With no adverse experience	42(93.3)	183(91.0)	-2.3 (-9.0, 9.4)
With one or more adverse experiences	3(6.7)	18(9.0)	2.3 (-9.4, 9.0)
INVESTIGATIONS	0(0.0)	4(2.0)	2.0 (-5.9, 5.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2(4.4)	5(2.5)	-2.0 (-12.5, 2.6)
EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses.			
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.			
†Confidence Intervals are based on the Miettinen & Nurminen method.			

Source: Clinical Summary, Table 2.7.4:35, pg. 85.

Protocol 1418

Overall, 24 (5%) of the 521 patients discontinued due to adverse events during co-administration therapy in P693/P1418, with 12 of these discontinuations during P693 and 12 discontinuations during the P1418 extension. Each of the adverse experiences causing discontinuation was reported by less than 1% of patients.

The major contributing SOC was Musculoskeletal and Connective Tissue Disorders with 7 (<1%) of patients discontinuing due to events under this Body System. The adverse events in this system were myalgia (4), arthralgia (2), and musculoskeletal pain (1). One patient discontinued co-administration due to hemolytic anemia associated with hepatitis during the parent study. One patient discontinued due to elevated hepatic enzymes (ALT and AST).

Special Population Studies (P1030, P1417)

Protocol 1030

The applicant summarized specific AEs causing discontinuation that occurred in 4 or more patients in one or more treatment groups. Of the 36 patients in P1030, only one

patient (2.8%) reported adverse experiences (upper abdominal pain, chest pain, and chromaturia) causing discontinuation. This patient was in the ezetimibe + atorvastatin co-administration group.

Protocol 1417

Overall, 3 (8%) of the 36 patients discontinued due to adverse events during co-administration therapy in P1030/P1417 with one discontinuation during P1030 and two discontinuations during the P1417 extension.

7.3.4 Significant Adverse Events

See next section.

7.3.5 Submission Specific Primary Safety Concerns

Liver Related Events

Core Safety Pool (P040, P079, P090, P112, P692, P693, and P2173)

Of the patients with post baseline laboratory measurements, 11 (0.5%) of 2356 patients under ezetimibe + atorvastatin co-administration and 9 (0.4%) of 2006 patients under atorvastatin monotherapy had consecutive ALT elevations $\geq 3xULN$. There were no patients with consecutive ALT elevations $\geq 3xULN$ on ezetimibe monotherapy or placebo.

Table 44: Number (%) of Patients with ALT Greater Than the ULN- Core Safety Pool

ALT	Placebo N=60	EZ 10 mg N=65	All Atorvastatin Doses N= 2006	EZ 10 mg + All Atorvastatin Doses N=2356
$\geq 3XULN$, consecutive	0	0	9 (0.4)	11 (0.5)
$\geq 5XULN$, consecutive	0	0	5 (0.2)	4 (0.2)
$\geq 10 XULN$, consecutive	0	0	0	1 (0.0)

Source: Clinical Summary of Safety; Table 2.7.4:57, pg.111.

Reviewer’s Comment: Co-administration of ezetimibe + all doses of atorvastatin had a similar incidence of consecutive ALT > 3XULN as all doses of atorvastatin monotherapy.

Table 45: Number (%) of Patients with Post Baseline Values for ALT Greater Than Upper Limit of Normal by Dose- Core Safety Pool

ALT	EZ + Atorva 10mg m/n(%)	EZ + Atorva 20mg m/n(%)	EZ + Atorva 40mg m/n(%)	EZ + Atorva 80mg m/n(%)
≥ 3XULN, consecutive §	4/1189 (0.3)	3/680 (0.4)	5/724 (0.7)	0/204 (0)
≥ 5XULN, consecutive §	2/1189 (0.2)	1/680 (0.1)	1/724 (0,1)	0/204 (0)
≥ 10XULN, consecutive §	1/1189 (0.1)	0/680 (0)	0/724 (0)	0/204 (0)

%=m/n x 100 = (number of patients within the Tier 1 adverse event category / number of treated patients with one or more laboratory tests post baseline) x 100.

§This category includes those patients with (a) two consecutive measurements ≥3xULN, (b) a single, last measurement ≥3xULN, or (c) a measurement ≥3xULN followed by a measurement <3xULN that was taken more than 2 days after the last dose of study medication.

Note: This table includes 2 patients on atorvastatin 20 mg (P112/AN6543 and P693/AN1483) and one patient on ezetimibe 10 mg+ atorvastatin 20 mg (P693/AN1643) who had a normal range follow-up lab result, but this lab result was after the patient titrated to the next higher level dose of atorvastatin. These patients are not included in Table 30.

Source: Clinical Summary of Safety, Table 2.7.4:60, pg. 123.

Reviewer Comment: The consecutive elevations in ALT on ezetimibe + atorvastatin co-administration appear not to be dose related in the Core Safety Pool. This observation may be limited by small sample size.

In the Core Safety Pool, there was one reported case of “hepatitis” for a patient on ezetimibe + atorvastatin co-administration:

Study P0693-ID#-001793: A 56 yo Caucasian woman on ezetimibe+ atorvastatin co-administration was reported to have “hepatitis” on Day 38 of study drug. The patient had taken a Voltaren suppository for epigastric pain and this was considered by the sponsor to be a second suspect in the increase of the patient’s enzymes. Hepatitis serology was negative. The patient was also diagnosed with hemolytic anemia on the basis of a positive Coombs’ test. This was considered to be a possible autoimmune hemolytic anemia, although the possibility of a drug-induced hemolytic anemia could not be ruled out. The patient discontinued due to hemolytic anemia associated with the hepatitis.

Long Term Studies (P2154, P1418)
 Protocol 2154

None of the 245 patients (with post baseline laboratory measurements) under atorvastatin monotherapy or under ezetimibe + atorvastatin co-administration had *consecutive* ALT $\geq 3 \times \text{ULN}$. However, there were two patients (2/200; 1.0%) with isolated ALT elevations $\geq 3 \times \text{ULN}$.

Hepatitis-related AEs occurred in zero of the 45 patients that received atorvastatin monotherapy and in one (0.5%) of the 201 patients that received ezetimibe + atorvastatin co-administration. A brief case narrative of this patient follows:

ID#0527 Patient on co-administration therapy, with a history of cholecystectomy and alcohol intake, had a diagnosis of medication-induced “cholestatic hepatitis” with elevated ALT activity ($\geq 3 \times \text{ULN}$ to $< 5 \times \text{ULN}$) and elevated AST activity ($\geq 2 \times \text{ULN}$ to $< 3 \times \text{ULN}$), as determined by local laboratories. Total bilirubin reached a maximum of $3 \times \text{ULN}$, and alkaline phosphatase of $\geq 2 \times \text{ULN}$ to $< 3 \times \text{ULN}$. Abdominal ultrasound and abdominal MRI were normal, and hepatitis B surface antibody and hepatitis C antibody tests were negative. The cholestatic hepatitis was a serious adverse event (considered possibly related to treatment by the investigator) leading to study discontinuation. All liver function tests returned to normal after study drug (atorvastatin and ezetimibe) discontinuation.

Protocol 1418 was an open-labeled study and was not reviewed.

Special Population Studies (P1030, P1417)

Protocol 1030

One (4.2%) of the 24 patients in the ezetimibe + atorvastatin co-administration group and none in the atorvastatin monotherapy had consecutive ALT elevations $\geq 3 \times \text{ULN}$. Details of the narrative follow:

27 yo Caucasian man with a baseline ALT of 13 mIU/mL was hospitalized because of chest pain, epigastric pain and urine discoloration on Day 66. Study drug (ezetimibe + atorvastatin 40 mg) was discontinued. Patient had an ALT of 121 mIU/mL on Day 85. Evaluation revealed an 8X9 cm intra-hepatic echinoccal cyst judged unrelated to study medication. Follow-up lab values showed an ALT of 69 mIU/mL.

Protocol 1417

One patient on ezetimibe + atorvastatin co-administration had consecutive ALT elevations $\geq 3 \times \text{ULN}$ during the co-administration period P1030/ P1417, however this event occurred during the parent study P1030 and is discussed above. No cases of hepatitis, jaundice, or other clinical signs of liver dysfunction were reported. One patient (ID#0032) in the ezetimibe + atorvastatin co-administration group reported an adverse experience of fatty liver during P1418 open label extension.

Muscle Related Events Core Safety Population

Table 46: Number (%) of Patients with CPK Elevations-Core Safety Pool

CPK	Placebo N=60 (%)	EZ 10mg N=65 (%)	All Atorvastatin N=2006 (%)	EZ + All Atorvastatin N=2356 (%)
3XULN to <5XULN	0	1 (1.5)	13 (0.6)	11 (0.5)
5XULN to 10XULN	0	1 (1.5)	8 (0.4)	3 (0.1)
>10XULN	0	0	2 (0.1)	1*
>10XULN with muscle symptoms	0	0	1	1*

*Subject #AN1311, on ezetimibe 10 mg+ atorvastatin 40 mg fulfilled criteria for >10XULN, and >10XULN with muscle symptoms but was not included in the database because the samples were analyzed at a local laboratory in a legacy Schering-Plough study.

Source: Clinical Summary of Safety, Table 2.7.4:88, pg.158.

Reviewer's Comment: Co-administration of ezetimibe + all doses of atorvastatin and atorvastatin monotherapy had a similar incidence of CPK elevation >3XULN.

Table 47: Number (%) of Patients with CPK Elevations by Dose- Core Safety Pool

CPK	EZ + Atorvastatin 10mg m/n (%)	EZ + Atorvastatin 20mg m/n (%)	EZ + Atorvastatin 40mg m/n (%)	EZ + Atorvastatin 80mg m/n (%)
3XULN to <5XULN	5/1189 (0.4)	1/680 (0.1)	5/724 (0.7)	0/204 (0)
5XULN to 10XULN	1/1189 (0.1)	0/680 (0)	2/724 (0.3)	0/204 (0)
>10XULN	0/1189 (0)	0/680 (0)	1*/724	0/204 (0)
>10XULN with muscle symptoms	0/1189 (0)	0/680 (0)	1*/724	0/204 (0)

*Subject #AN1311, on ezetimibe 10 mg+ atorvastatin 40 mg fulfilled criteria for >10XULN, and >10XULN with muscle symptoms but was not included in the database because the samples were analyzed at a local laboratory in a legacy Schering-Plough study.

Source: Clinical Summary of Safety, Table 2.7.4:89, pg.159.

Reviewer’s Comment: Co-administration of ezetimibe + 40 mg atorvastatin had a higher incidence of CPK elevation > 3XULN than the co-administration of ezetimibe + 80 mg atorvastatin.

The following is a brief narrative of the patient on ezetimibe + atorvastatin 40 mg with CPK >10XULN and muscle symptoms. According to the sponsor, the results were from a local laboratory and thus were not in the central database. Since this was a legacy Schering-Plough study, the results could not be incorporated into the final analysis.

Study P0692-ID#1311: 54 year-old Hispanic man, was randomized to ezetimibe 10 mg + atorvastatin 40 mg co-administration. Patient reported moderate diffuse myalgias and moderate weakness beginning on Day 57, coincident with a CPK of 403 mU/mL. Follow-up at a local laboratory showed increasing CPK to 5,379 mU/mL (>10XULN) with ongoing symptoms. Treatment was discontinued and the symptoms resolved by Day 70 and CPK was 96 mU/mL on Day 76. The investigator considered this to be probably related to treatment.

Reviewer Comment: The Agency usually defines rhabdomyolysis as a CPK >10,000 IU/L (or >50XULN) with organ damage, usually renal compromise. Another definition of rhabdomyolysis is muscle symptoms with marked CPK elevation (typically greater than 10XULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)². With the history given by the applicant, this case would be categorized as myopathy.

Long Term Studies (P2154, P1418)
Protocol 2154

There were no adverse experience reports of either rhabdomyolysis or myopathy. Increased CPK was reported as an adverse experience in 3 (1.5%) of 201 patients on ezetimibe + atorvastatin co-administration therapy and none on atorvastatin monotherapy. There were no patients with CPK \geq 10XULN.

Table 48: Number (%) of Patients with CPK >ULN –Protocol 2154

CPK	All Atorvastatin m/n (%)	EZ + All Atorvastatin m/n (%)
3XULN to <5XULN	0/45	3/200 (1.5)
5XULN to <10XULN	0/45	1/200 (0.5)
\geq 10XULN	0/45	0/200
\geq 10XULN with muscle symptoms	0/45	0/200

² ACC/AHA/NHLBI (Pasternak, 2002).

CPK	All Atorvastatin m/n (%)	EZ + All Atorvastatin m/n (%)
EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses. %=m/n x 100 = (number of patients within the Tier 1 adverse event category / number of treated patients with one or more laboratory tests post baseline) x 100		

Source: Clinical Summary of Safety, Table 2.7.4:92, pg.161.

Protocol 1418

No adverse experiences of rhabdomyolysis or myopathy were reported during P693/ P1418 co-administration. One patient had an increase in CPK $\geq 10 \times \text{ULN}$ with associated muscle symptoms during the P1418 extension. The increase in CPK and mild myalgia both were reported to be attributed to exercise. The myalgia resolved on the same day that it began. Subsequent CPK levels returned to normal range without interruption of co-administration therapy and the patient completed the study.

Special Population Studies (P1030, P1417)

Protocol 1030

There were no adverse experience reports of either rhabdomyolysis or myopathy. There were also no patients with any post baseline value for creatine phosphokinase activity at least 10 times greater than or equal to the upper limit of the reference range. There were no reported adverse experiences of increased CPK.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 4569 patients, 1659 (36.3%) patients in the Core Safety Pool reported one or more adverse events. Adverse events were reported by 34 (56.7%) patients on placebo, 41 (63.1%) patients on ezetimibe monotherapy, 756 (37.0%) patients on atorvastatin monotherapy, and 828 (34.5%) patients on ezetimibe + atorvastatin combination.

Specific adverse experiences exceeding incidences of 2.0% among patients that received atorvastatin monotherapy or ezetimibe + atorvastatin co-administration were

- nasopharyngitis (placebo 8.3%; ezetimibe 6.2%; atorvastatin 1.9%; ezetimibe + atorvastatin 2.1%)
- myalgia (placebo 6.7%; ezetimibe 7.7%; atorvastatin 2.6%; ezetimibe + atorvastatin 2.5%)
- headache (placebo 8.3%; ezetimibe 7.7%; atorvastatin 2.4%; ezetimibe + atorvastatin 2.5%)

Table 49: Number (%) of Patients with AEs > 2% in All Atorva or EZ 10 mg + All Atorva Treatment Groups- Core Safety Pool

	Crude Event Rate				Exposure-adjusted Event Rate per 100 Patient-years§				EZ/All Atorva minus All Atorva Difference(95% CI)†
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403	
Number (%) of Patients: With no adverse experience	26(43.3)	24(36.9)	1285(63.0)	1575(65.5)					
With one or more adverse experiences	34(56.7)	41(63.1)	756(37.0)	828(34.5)	305.5	390.4	216.8	209.5	3.21(-18.03, 24.28)
CARDIAC DISORDERS	1(1.7)	2(3.1)	43(2.1)	41(1.7)	5.47	10.34	8.96	7.68	-0.88(-4.68, 2.74)
GASTROINTESTINAL DISORDERS	8(13.3)	14(21.5)	185(9.1)	207(8.6)	47.21	81.04	40.99	41.14	0.39(-7.92, 8.61)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8(13.3)	9(13.8)	86(4.2)	117(4.9)	47.12	49.08	18.33	22.61	4.89(-0.84, 10.65)
INFECTIONS AND INFESTATIONS	11(18.3)	12(18.5)	204(10.0)	213(8.9)	67.36	68.71	45.09	42.37	-0.97(-9.43, 7.40)
Nasopharyngitis	5(8.3)	4(6.2)	39(1.9)	50(2.1)	28.88	20.82	8.15	9.44	2.09(-1.68, 5.81)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(1.7)	5(7.7)	41(2.0)	57(2.4)	5.50	26.58	8.58	10.74	2.33(-1.61, 6.31)

	Crude Event Rate				Exposure-adjusted Event Rate per 100 Patient-years§				EZ/All Atorva minus All Atorva Difference(95% CI)†
	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403	Placebo N=60	EZ 10 mg N=65	All Atorva N=2041	EZ 10 mg + All Atorva N=2403	
INVESTIGATIONS	2(3.3)	4(6.2)	74(3.6)	108(4.5)	11.06	20.59	15.60	20.67	5.45(0.09, 10.81)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	13(21.7)	18(27.7)	193(9.5)	194(8.1)	82.81	113.5	42.98	38.52	-2.72(-10.97, 5.46)
Myalgia	4(6.7)	5(7.7)	54(2.6)	60(2.5)	22.89	26.96	11.37	11.39	0.52(-3.81, 4.78)
NERVOUS SYSTEM DISORDERS	6(10.0)	8(12.3)	110(5.4)	128(5.3)	34.00	43.99	23.68	24.74	2.05(-4.26, 8.31)
Headache	5(8.3)	5(7.7)	49(2.4)	59(2.5)	27.96	26.56	10.31	11.15	1.33(-2.91, 5.52)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3(5.0)	7(10.8)	77(3.8)	67(2.8)	16.69	37.68	16.29	12.69	-2.48(-7.47, 2.32)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1(1.7)	2(3.1)	41(2.0)	41(1.7)	5.49	10.11	8.58	7.71	-0.59(-4.30, 3.03)

EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses.

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

†Confidence Intervals are based on exposure-adjusted event rate using the Miettinen & Nurminen method with study as stratification factor.

§Exposure-adjusted event rate = 100 x weighted sum of [(number of patients with AE/sum of days at risk for AE) x 365.25days/year].

Source: Clinical Summary of Safety: Table 2.7.4:20, pg. 54.

7.4.2 Laboratory Findings

Hepatic Biochemistry

Liver-related laboratory results (ALT, AST, ALP, and TB) in the clinical trials are discussed in Section 7.3.5.

Muscle Biochemistry

Muscle-related laboratory results (CPK) in the clinical trials are discussed in Section 7.3.5.

Renal Biochemistry

Core Safety Pool

According to the applicant, the proportion of patients with values outside the predefined limits of change were small and similar between the atorvastatin and ezetimibe + atorvastatin treatment groups. The applicant also generated shift tables for BUN and serum creatinine for all patients who had at least one post-baseline value during treatment. Most patients remained in the same grade from baseline to maximum value. Thus, renal function as assessed by BUN and serum creatinine showed no clinically meaningful differences between the atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups.

The applicant analyzed the number of patients with values outside pre-specified limits of the reference ranges of urinalysis. The results are shown in the table below.

Long-term Studies

Protocol 2154

Renal function, as assessed by serum BUN and creatinine measurements, was unaffected by any treatment during the study. The proportions of patients with values outside pre-specified limits of the reference ranges for BUN were small and similar for the two treatment groups ([Table 2.7.4: 98]). No patient in either treatment group had post baseline values outside pre-specified limits of the reference ranges for creatinine (>2 mg/dL).

Protocol 1418

Renal function was assessed by serum BUN and creatinine measurements for the period P693/P1418. The proportion of patients with values outside pre-specified limits was small for BUN, and no subjects had serum creatinine values greater than 2 mg/dL at endpoint.

Special Population Studies

Protocol 1030

No patients exceeded the predefined limits for renal function, as assessed by serum BUN and creatinine measurements. Blood urea nitrogen (BUN) and serum creatinine values were examined for shifts in grade from baseline to maximum grade. Most patients remained in the same grade from baseline to maximum value.

Protocol 1417

Renal function was assessed by serum BUN and creatinine measurements for the period P1030/P1417. No patients had serum BUN values less than 5 mg/dL or greater than 30 mg/dL during co-administration, and no patients had serum creatinine values greater than 2 mg/dL during co-administration. Blood urea nitrogen (BUN) and serum creatinine values were examined for shifts in grade from baseline to maximum grade. Most patients remained in the same grade from baseline to maximum value.

7.4.3 Vital Signs

The applicant did not pool the data for vital sign parameters. Results for these parameters were reviewed in the individual study reports: P0692, P0693, P01030, P02154, P02173, P040, P079, P090, and P112. No effects on blood pressure or pulse parameters were observed.

7.4.4 Electrocardiograms (ECGs)

The applicant did not pool the data for ECG parameters. Results for these parameters were reviewed in the individual study reports: P0692, P0693, P01030, P02154, P02173, P040, P079, P090, and P112. No effects on EKG parameters were observed.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Although the applicant did not conduct specific immunotoxicity studies, repeat dose toxicity studies in animals did not indicate any effect of ezetimibe or atorvastatin on parameters associated with the immune response – white cell numbers, spleen or thymus – except at high doses in some studies. Further details are described in the pharmacology/toxicology review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the Core Safety Pool, the incidence rates of AEs across different doses of ezetimibe + atorvastatin did not quite follow a dose dependent relationship. For example, 37.5% of patients on ezetimibe + atorvastatin 80 mg reported an AE, which was greater than the 30.6% of patients on ezetimibe + atorvastatin 40; however, more patients reported an AE on ezetimibe+ atorvastatin 10 mg (33%) than ezetimibe + atorvastatin 20 mg (29.3%).

The AE dose dependency relationship could be characterized as similar for ezetimibe + atorvastatin for the first three doses (10/10mg, 10/20 mg, and 10/40 mg), but much greater for the highest dose of ezetimibe + atorvastatin 80 mg.

Table 50: Summary of Adverse Events by Dose- Core Safety Pool

Number (%) of Patients	EZ + Atorvastatin 10mg N=1207	EZ + Atorvastatin 20mg N=693	EZ + Atorvastatin 40mg N=741	EZ + Atorvastatin 80mg N=208
≥ 1 Adverse Event	398 (33.0)	203 (29.3)	227 (30.6)	78 (37.5)
Serious Adverse Event	29 (2.4)	13 (1.9)	18 (2.4)	5 (2.4)
Discontinued due to Adverse Event	33 (2.7)	9 (1.3)	14 (1.9)	7 (3.4)

Source: Clinical Summary of Safety, Appendix 2.7.4:1, pg. 192.

7.5.2 Time Dependency for Adverse Events

Refer to previous Agency reviews in the Zetia NDA for these analyses.

7.5.3 Drug-Demographic Interactions

The applicant conducted subgroup analysis of patients <65 years or ≥65 years on ezetimibe + atorvastatin (all doses) co-administration as compared to ezetimibe monotherapy and placebo.

Table 51: Summary of Adverse Events in Patients < 65 years old- Core Safety Pool

Number (%) of Patients	Placebo N=41	EZ 10 mg N=47	All Atorvastatin N=1020	EZ + All Atorvastatin N=1237
≥ 1 Adverse Event	24 (58.5)	32 (68.1)	427 (41.9)	482 (39.0)
Serious Adverse	1 (2.4)	1 (2.1)	16 (1.6)	34 (2.7)

Number (%) of Patients	Placebo N=41	EZ 10 mg N=47	All Atorvastatin N=1020	EZ + All Atorvastatin N=1237
Event				
Discontinued due to Adverse Event	3 (7.3)	1 (2.1)	31 (3.0)	32 (2.6)

Source: Clinical Summary of Safety, Appendix 2.7.4:19, pg. 240.

Table 52: Summary of Adverse Events in Patients \geq 65 years old- Core Safety Pool

Number (%) of Patients	Placebo N=41	EZ 10 mg N=47	All Atorvastatin N=1020	EZ + All Atorvastatin N=1237
\geq 1 Adverse Event	10 (52.6)	9 (50.0)	329 (32.2)	346 (29.7)
Serious Adverse Event	1 (5.3)	1 (5.6)	30 (2.9)	31 (2.7)
Discontinued due to Adverse Event	0	2 (11.1)	25 (2.4)	31 (2.7)

Source: Clinical Summary of Safety, Appendix 2.7.4:19, pg. 240

Reviewer Comment: For patients < 65 and those \geq 65 years, the AEs in the co-administration group (all doses) was similar to the all atorvastatin monotherapy group.

7.5.4 Drug-Disease Interactions

No analysis submitted.

7.5.5 Drug-Drug Interactions

Ezetimibe Drug-Drug interactions from Current Ezetimibe Labeling

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Co-administration of ezetimibe with fibrates other than fenofibrate is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. No clinical data are available.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Cyclosporine: Caution should be exercised when using ezetimibe and cyclosporine concomitantly due to the increase in exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ezetimibe and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 mL/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine.

Warfarin: If ezetimibe is added to warfarin, the International Normalized Ratio should be appropriately monitored.

Atorvastatin Drug-Drug Interactions from Current Atorvastatin Labeling

Inhibitors of cytochrome P450 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Clarithromycin: Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of CYP3A4.

Combination of Protease Inhibitors: Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC.

Itraconazole: Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5-3.3-fold increase in atorvastatin AUC.

Diltiazem hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin. Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin AUC. After initiation of diltiazem or following dosage adjustment, lipid levels should be monitored to ensure that the lowest dose necessary for atorvastatin is used.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Grapefruit juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATPIBI transporter. Inhibitors of the OATPIBI (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg.

Inducers of CYP3A4: Concomitant administration of atorvastatin with inducers of CYP3A4 (e.g. efavirenz, rifampin) can lead to reductions in plasma concentrations of atorvastatin that are variable. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacid: When atorvastatin and MaaloxB TCTM suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Amlodipine: In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please see the pharmacology/toxicology report by Dr. Karen Davis- Bruno for a complete review.

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and atorvastatin. The combination of ezetimibe with atorvastatin did not show evidence of mutagenicity in vitro in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed in vitro in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and atorvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 250 mg/kg with the combination of ezetimibe and atorvastatin (1:1) in the in vivo mouse micronucleus test.

7.6.2 Human Reproduction and Pregnancy Data

Atorvastatin and ezetimibe are contraindicated in women who are pregnant or breast feeding. There are no adequate and well-controlled studies of ATOZET use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased

risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

7.6.3 Pediatrics and Assessment of Effects on Growth

Both ezetimibe and atorvastatin are available as monotherapy and labeled for use in pediatric patients (10-17 years of age) for HeFH. In addition, both products have a statement about the lack of controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age in their respective US product circular.

With this NDA, the applicant submitted a waiver for pediatric patients 0-17 years of age. The Agency has granted the waiver based on the fact that the number of pediatric patients who would be appropriate for treatment with this FDC lipid-lowering agent is small. Therefore, the studies would be impossible or highly impractical to complete.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant submitted wording from approved circulars for Zetia and Lipitor addressing overdosage:

“No specific treatment of overdosage with ATOZET can be recommended. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

(b) (4)

Atorvastatin

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.”

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

The applicant summarized post-marketing data based on the listed adverse drug reactions in the following documents:

- Ezetimibe Company Core Data Sheet
- Lipitor United States Product Circular. (Atorvastatin is not a Merck product, thus the core label is not available. The safety profile of atorvastatin is based upon the currently approved Lipitor USPC and Sortis German SPC.)

Ezetimibe Co-administered with a Statin

According to the applicant, the Worldwide Adverse Experience System database was searched for all health care provider reports of ezetimibe use with concomitant statin from the date of market introduction of ezetimibe (17-Oct-2002) through 31-Dec-2010. A total of 5516 reports were identified for this time period. Of these reports, 1223 (22%) were serious reports and 4293 (78%) were non-serious reports. Age was reported in 3964 (72%) of the reports; 2204 (40% of patients in whom age was reported) were between 18 and 64 years of age, 1752 (32%) were ≥ 65 years of age, and 8 patients were < 18 years of age. Gender was noted in 3922 (71%) of the reports; of those patients in whom gender was noted, 2164 (55%) were male and 1758 (45%) were female.

The five most frequent AEs seen in patients on ezetimibe plus any statin were

- myalgia
- blood creatine phosphokinase increased
- diarrhea
- nausea
- alanine aminotransferase increased

All of these events are labeled events in the ezetimibe CCDS.

The five most frequent serious AEs reported were

- myalgia,
- rhabdomyolysis
- blood creatine phosphokinase increased
- alanine aminotransferase increased
- drug interaction

The first four of these events are also listed in the ezetimibe CCDS. The majority of drugs noted in the drug interaction reports are also noted in the CCDS.

Ezetimibe Co-administered with Atorvastatin

Within the reports described above, the search was refined to include HCP reports of ezetimibe use with concomitant atorvastatin use. A total of 2343 reports of ezetimibe as

primary therapy and atorvastatin as a concomitant or secondary suspect therapy were identified for this time period. Of these reports, 580 (25%) were serious reports and 1763 (75%) were non-serious reports. Age was reported in 1774 (76%) of the 2343 reports; 1020 (44% of patients in whom age was reported) were between 18 and 64 years of age, 750 (32%) were \geq 65 years of age, and 4 patients were $<$ 18 years of age. Gender was noted in 2193 (94%) of the reports; of those patients in whom gender was noted, 1208 (55%) were male and 985 (45%) were female.

To evaluate the safety profile of the combination of ezetimibe and atorvastatin, an analysis of AEs by SOC was conducted by the applicant.

The three most commonly affected SOCs during the period are:

- Investigations (31%),
- Musculoskeletal and connective tissue disorders (29%)
- Gastrointestinal disorders (22%)

Serious AEs occurred most frequently in these SOCs:

- Musculoskeletal and connective tissue disorders (33%)
- Investigations (30%)
- General disorders and administration site conditions (24%)
- Gastrointestinal disorders (20%)

The Investigations, Musculoskeletal and Connective Tissue disorders and Gastrointestinal disorders are described in more detail below.

The Investigations SOC contained the most frequent AEs reports: 720 (31%) and the second most frequent serious reports: 173 (30%). There were a total of 336 events contained in the 173 serious reports. The five most frequent serious AEs in the Investigations SOC were blood CPK increased (44/336), alanine aminotransferase increased (30/336), aspartate aminotransferase increased (29/336), blood cholesterol increased (21/336), blood triglycerides increased (16/336) and liver function test abnormal (16/336).

The Musculoskeletal and Connective Tissue disorders SOC contained the second most frequent AE reports: 682 (29%) and the most frequent serious reports: 193 (33%). The five most frequent serious AEs in the Musculoskeletal and Connective Tissue disorders SOC were myalgia (71/327), rhabdomyolysis (48/327), muscle spasms (29/327), muscular weakness (25/327), and pain in extremity (23/327).

The Gastrointestinal Disorders SOC contained the third most frequent ADR reports: 508 (22%), and the fourth most frequent serious reports: 116 (20%). There were a total of 173 serious events contained in the 116 serious reports. The five most frequent serious AEs in the Gastrointestinal Disorders SOC were abdominal pain (15/173), nausea

(14/173), pancreatitis (13/173), vomiting (13/173), and abdominal pain upper and vomiting (each 11/173).

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

This NDA submission is recommended for a Complete Response; therefore, no labeling recommendations were sent to the applicant.

9.3 Advisory Committee Meeting

As both ezetimibe and atorvastatin are approved drugs marketed in the US and there were no significant safety issues identified with the co-administration of ezetimibe and atorvastatin, an Advisory Committee meeting was not considered necessary.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IFFAT N CHOWDHURY
01/20/2012

ERIC C COLMAN
01/20/2012

CLINICAL FILING CHECKLIST/ MEMORANDUM FOR NDA 200,153 LIPAZET

NDA/BLA Number: 200,153 **Applicant: MSP Singapore** **Stamp Date: 4/26/2011**
(sponsor); Merck (agent)

Drug Name: Atozet **NDA/BLA Type: 505(b)(2)** **Standard Review**
(ezetimibe + atorvastatin)

Filing Meeting: June 27, 2011

Atozet (ezetimibe/atorvastatin; MK-0653C) Oral Capsules
10/10 mg, 10/20 mg, 10/40 mg, and 10/80 mg of ezetimibe/atorvastatin equivalent
MSP Singapore Co., LLC: Merck & Co., Inc. and Schering Corporation (505(b)2)

Clinical Reviewer: Iffat N. Chowdhury, MD

Introduction:

The sponsor, MSP Singapore, has re-submitted their 505(b)(2) application for Atozet (ezetimibe/atorvastatin) capsules for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia. Previously, the Agency issued a Refusal To File letter on 29 October 2009 due to CMC deficiencies in the initial NDA application for (b) (4) (submitted on 2 September 2009), now referred to as Atozet by the company.

Atozet is a fixed-dose combination formulation consisting of ezetimibe and atorvastatin calcium amorphous, two lipid-modulating drugs with two different mechanisms of action. Ezetimibe and atorvastatin calcium crystalline are active ingredients in the products Zetia® (Merck & Co., Inc.) and Lipitor® (Pfizer, Inc.), approved under NDA 21-445 and NDA 20-702, respectively.

NDA 21-445 for Zetia® included data for clinical efficacy and safety on the co-administration for ezetimibe + atorvastatin. Currently, the specific indication for their combined use is included in the product literature for Zetia®. According to the applicant, the ezetimibe/atorvastatin FDC tablet formulations are intended to provide a more convenient single tablet when a combination of the two drugs is prescribed.

List of related INDs/NDAs:

Application #	Drug
IND 101,953	MK-0653C (Lipazet)
IND 52,791	Ezetimibe (Zetia®)
NDA 21-445	Ezetimibe (Zetia®)
IND	Atorvastatin (Lipitor®)
NDA 20-702	Atorvastatin (Lipitor®)

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Efficacy Data:

This NDA application is an electronic submission containing 15 final clinical study reports for completed studies. There are four clinical pharmacology studies (P9396-001, 145, 146, and 183). The Phase 3 clinical trials that have been previously submitted to the Agency include Protocols 692, 693, 2173, 1030, 2154 (the 692 extension), 1418 (the 693 extension), 1417 (the 1030 extension). Protocols 40, 79, 90, and 112 are newly submitted clinical studies.

Clinical pharmacology studies:

- Pilot bio-comparison study – this pilot study was done to select an atorvastatin (b) (4) for use in the combination tablet (P9396-001)
- Descriptive food effect study of the combination tablet (Study 146)
- Two definitive bioequivalence studies – comparing the combination tablets to marketed agents dosed concomitantly (Studies 145 and 183)

Short-term Phase 3 Trials:

- Protocol 692- This was a randomized, double-blind, placebo-controlled, parallel-group study of 628 patients with primary hypercholesterolemia. Patients received treatment with placebo, ezetimibe 10 mg, atorvastatin (10, 20, 40, or 80 mg), or ezetimibe 10 mg co-administered with atorvastatin (10, 20, 40, or 80 mg) daily for 12 weeks. Patients were 18 to 86 years of age with LDL-C 145 mg/dL to 250 mg/dL and TG \leq 350 mg/dL at baseline.

According to the applicant, this study demonstrated that co-administration of ezetimibe 10 mg + atorvastatin (pooled across all doses) was more effective than atorvastatin alone (pooled across all doses) in reducing LDL-C from baseline to 12 weeks as evidenced by a mean percent change of -56.31% for co-administration versus -44.24% for atorvastatin alone ($p < 0.01$). Reductions in the plasma concentrations of Apo B, TC, and TG and increases in HDL-C were all significantly greater with the co-administration of ezetimibe 10 mg + atorvastatin compared to ezetimibe alone or atorvastatin alone.

Table 1: Mean Percent Change from Baseline to Endpoint in Lipid Levels (Study P0692)

Lipid Variable	Atorvastatin Alone (n = 248)	EZ 10 mg + Atorvastatin (n = 255)	EZ 10 mg Alone (n=65)	p-Value	
				EZ10 mg+Atorva vs Atorvastatin	EZ+Atorva vs Ezetimibe
LDL-C [†]	-44.24 (0.97)	-56.31 (0.95)	-19.95 (1.88)	p<0.01	p<0.01
TC	-32.06 (0.75)	-41.13 (0.74)	-13.52 (1.53)	p<0.01	p<0.01
TG	-21.47 (1.55)	-29.47 (1.53)	-3.44 (3.02)	p<0.01	p<0.01
HDL-C	4.25 (0.74)	7.34 (0.73)	4.19 (1.43)	p<0.01	p=0.05
Apo B	-36.07 (0.93)	-45.37 (0.92)	-15.40 (1.82)	p<0.01	p<0.01
Non-HDL-C	-41.05 (0.93)	-52.33 (0.91)	-17.68 (1.80)	p<0.01	p<0.01

Note: Not every subject had an endpoint measurement for every variable. The number of subjects ranged from 244 to 248 for the Atorvastatin Alone group, 249 to 255 for the Coadministration group, and 61 to 65 for the Ezetimibe Alone group.

[†] LDL-C: Calculated LDL-C was performed for the majority of studies and is presented here for consistency with other studies. Results for Direct and Calculated LDL-C were similar.

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- Protocol 693- This was a study conducted in patients with heterozygous familial hypercholesterolemia (HeFH) or in patients with CHD or multiple cardiovascular risk factors (≥ 2) adhering to an NCEP ATP Step I, or stricter diet, who were not controlled by a starting dose of atorvastatin 10 mg. This double-blind, randomized, active-controlled study in 621 patients, 18 to 82 years of age, with baseline LDL-C ≥ 130 mg/dL and TG ≤ 350 mg/dL on atorvastatin 10 mg, was designed to assess whether ezetimibe 10 mg co-administered with atorvastatin (titrated if necessary up to 40 mg) over 14 weeks, resulted in more patients meeting a target LDL-C level of ≤ 100 mg/dL than atorvastatin alone (titrated if necessary up to 80 mg).

According to the applicant, results of the primary efficacy analysis showed that a higher proportion of patients on co-administration of ezetimibe + atorvastatin (22%), than on atorvastatin alone (7%), achieved target LDL-C levels of ≤ 100 mg/dL at Week 14 (p-value < 0.01). Results of the secondary efficacy analysis demonstrated that addition of ezetimibe 10 mg to atorvastatin 10 mg was more efficacious than doubling the atorvastatin dose from 10 to 20 mg in reducing LDL-C from baseline to Week 4, as evidenced by a mean percent change of -22.8% for co-administration versus -8.6% for atorvastatin alone.

Protocol 0693 therefore demonstrated that the addition of ezetimibe 10 mg to a starting dose of atorvastatin 10 mg, followed by response-based titration up to a maximum of atorvastatin 40 mg/day, was significantly more effective in achieving the target LDL-C (≤ 100 mg/dL [2.59 mmol/L]) at Week 14 than was response-based titration of atorvastatin alone up to a maximum of 80 mg/day.

- Protocol 40- This was a double-blind, randomized, placebo-controlled study that evaluated the effect of ezetimibe 10 mg/day added to ongoing statin therapy vs. continued statin therapy alone (at unchanged dose) in 3030 patients with hypercholesterolemia who were not at their NCEP ATP III Target LDL-C level. The primary efficacy variable was change from baseline in plasma LDL-C after 6 weeks of treatment.

The findings in the subgroup of 1155 patients who were receiving atorvastatin were analyzed. The addition of ezetimibe to atorvastatin produced a reduction of 27.2% in LDL-C at Week 6 (relative to the on-statin baseline) compared to 4.2% for placebo, a difference of 23.0%. The mean dose of co-administered atorvastatin in this subgroup was 30 mg (range 5-80 mg).

Protocols 079, 090, and 112 were designed to compare the addition of add-on ezetimibe to established atorvastatin therapy vs. up titration of atorvastatin in various patient groups and at various baseline atorvastatin doses.

- Protocol 79- was a multi-center, double-blind, randomized study to evaluate the percent change from baseline in LDL-C after 6 weeks of atorvastatin 20 mg plus

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ezetimibe compared to doubling the dose of atorvastatin from 20 to 40 mg in 196 patients at moderately high risk of CHD who had not reached optional NCEP ATP III goal LDL-C level on atorvastatin 20 mg alone.

Results of protocol 79 showed a significantly greater reduction in LDL-C in the ezetimibe add-on treatment group compared to the atorvastatin up-titration group over 6 weeks of treatment (-30.8% vs. -10.9%; $p < 0.001$). Significantly more patients in the ezetimibe add-on treatment group reached a LDL-C level < 100 mg/dL than in the atorvastatin up-titration group after 6 weeks of treatment (83.7% vs. 48.9%, $p < 0.001$). There was no statistically significant difference between treatment groups with respect to HDL-C, TG, Apo A-1 and CRP over 6 weeks of treatment.

- Protocol 90- This was a double-blind, randomized, parallel group study with a primary objective to determine the LDL-C lowering efficacy of atorvastatin 40 mg plus ezetimibe 10 mg compared to doubling the dose of atorvastatin from 40 to 80 mg in 579 patients at high risk for CHD who had not reached optional NCEP ATP III goal LDL-C levels of < 70 mg/dL on atorvastatin 40 mg alone.

The addition of ezetimibe 10 mg to ongoing atorvastatin 40 mg therapy resulted in a significantly greater reduction from baseline in LDL-C levels compared to up-titration to atorvastatin 80 mg after 6 weeks of treatment (-27.4% vs. -11.0%, $p < 0.001$). The addition of ezetimibe 10 mg to ongoing atorvastatin 40 mg therapy also resulted in a significantly greater percentage of patients reaching LDL-C levels < 70 mg/dL (1.81 mmol/L) compared to up-titration to atorvastatin 80 mg after 6 weeks of treatment (73.6% vs. 31.5%, $p < 0.001$).

- Protocol 112- was designed as a multicenter, randomized, double-blind, parallel arm, 12-week study to evaluate the lipid altering efficacy and safety of the addition of ezetimibe 10 mg to atorvastatin 10 mg as compared to doubling the dose of atorvastatin from 10 mg to 20 mg and followed by further up-titration from atorvastatin 20 to 40 mg in 1053 patients 65 years of age and older at high risk for CHD with or without diagnosed atherosclerotic vascular disease (AVD) who had not reached an LDL-C level of < 70 mg/dL or < 100 mg/dL, respectively, on atorvastatin 10 mg/day.

Ezetimibe 10 mg added to atorvastatin 10 mg significantly reduced LDL-C from baseline after 6 weeks of treatment compared with doubling the dose of atorvastatin from 10 to 20 mg. Greater efficacy was also observed when comparing patients randomized to ezetimibe 10 mg added to atorvastatin 10 mg for 12 weeks of treatment, versus atorvastatin titrated from 10 mg to 20 mg for 6 weeks followed by titration to 40 mg for an additional 6 weeks.

Safety Data:

According to the applicant, the safety of ezetimibe + atorvastatin has been evaluated in over 2500 patients who received co-administration of ezetimibe + atorvastatin in clinical

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trials summarized in the current application. To evaluate short-term safety, data from seven studies ranging from 6 to 14 weeks were combined into a 'core safety pool'. To evaluate long-term safety, individual analyses of two 12-month extension studies, one double-blinded and one open-label, were performed. Up to 24 months of safety in a special population of patients with homozygous familial hypercholesterolemia was also evaluated. In brief, the safety profile was consistent with that expected from the two active components of the combination used alone.

In the trials reported in this application, there was no evidence for any clinical or laboratory adverse effect not expected on the basis of the safety profile of the components of the combination. In the core safety pool, consecutive liver enzyme increases $\geq 3xULN$ as well as hepatitis-related and gallbladder-related adverse experiences were not observed with ezetimibe monotherapy, and only a small number of such events occurred with atorvastatin and ezetimibe + atorvastatin. In general, increases in liver function enzymes were limited and resolved without sequelae either spontaneously or after therapy was discontinued. However, in some cases, liver abnormalities did require discontinuation of therapy. No clinically meaningful differences between treatment groups with respect to subgroups of age, gender or race were observed in the core safety pool though these observations are limited by the small number of events overall and in the subgroups

In particular, there were no reports of rhabdomyolysis with ezetimibe monotherapy or with ezetimibe + atorvastatin, and only a small number (0.1%) of elevations in CK $\geq 10xULN$ with atorvastatin. One patient on ezetimibe + atorvastatin co-administration met the criteria for myopathy. The CPK $\geq 10xULN$ result for this patient was measured at a local laboratory and consequently not included in the database, as pre-specified for the studies conducted by legacy Schering-Plough. The patient experienced moderate diffuse myalgia and moderate weakness. Treatment was discontinued and the symptoms resolved.

There was another case of a patient on atorvastatin monotherapy with CPK $\geq 10xULN$ in conjunction with reported muscle pain which the investigator attributed to exercise. The elevation resolved despite continuation of the study drug. Except for these previously mentioned patients, few patients had post-baseline CPK values $\geq 10xULN$ and none of these met the criteria for myopathy (i.e., defined as the presence of muscle pain and/or weakness in association with CPK elevations to levels $\geq 10xULN$, not explained by another etiology such as exercise or trauma). There were no statistically significant differences between atorvastatin monotherapy and ezetimibe + atorvastatin co-administration in the incidences of any of the categories of CPK $\geq 10xULN$.

Labeling: The applicant submitted both clean and annotated draft Package Insert and draft Patient Package Insert labeling for ATOZET with clean Word and pdf versions.

Pediatric waiver: The applicant requests a waiver of the requirements of 21 CFR 314.55(a) for pediatric studies based on the initial approval of Zetia. The FDA granted a waiver of pediatric studies in children < 10 years of age (October 25, 2002) consistent

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with the current American Heart Association and American Academy of Pediatrics guidelines for drug-based treatment of high risk lipid abnormalities for Zetia®. In addition the FDA agreed on June 28, 2003 that a study evaluating ezetimibe and simvastatin in pediatric patients ≥ 10 years of age would suffice to demonstrate safety and efficacy of ezetimibe co-administered with all approved statins and that individual studies evaluating ezetimibe co-administered with each statin were not required.

Financial Disclosure: The applicant identified the clinical investigators who met the disclosure criteria regarding financial interests and arrangements as defined in 21 CFR 54.2(a,b,c,f).

DSI Inspection Sites: “Subject accountability by investigator” tables for Protocols 079, 090, 112, and 145 were provided by the applicant. There were no investigators identified for site investigations by this clinical reviewer using the usual tools for such identifications.

CHECKLIST

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?				
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) RLD: Zetia/ezetimibe and Lipitor/atorvastatin

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	Content Parameter	Yes	No	NA	Comment
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)? (<i>See clinical trials descriptions in memorandum</i>)	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? (<i>See clinical trials descriptions in memorandum</i>)	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST/ MEMORANDDUM FOR NDA 200,153 LIPAZET

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric Waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

**CLINICAL FILING CHECKLIST/ MEMORANDDUM FOR
NDA 200,153 LIPAZET**

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____ YES _____

If the Application is not fileable from the clinical 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.

Not applicable for clinical issues.

Iffat N. Chowdhury, MD 6/22/2011

 Reviewing Medical Officer Date

Eric Colman, MD 6/22/2011

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IFFAT N CHOWDHURY
06/27/2011

ERIC C COLMAN
06/27/2011

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

NDA Number: 200,153

**Applicant: MSP Singapore
(sponsor); Merck (agent)**

Stamp Date: 02 Sept 2009

IND Number: 101,953

**Drug Name: (b) (4)
(Ezetimibe + Atorvastatin)**

NDA/BLA Type: 505 (b) 2

Priority or Standard: Standard

Filing Meeting: October 7, 2009

(b) (4) (ezetimibe/atorvastatin; MK-0653C) (b) (4)

10/10 mg, 10/20 mg, 10/40 mg, and 10/80 mg of ezetimibe/atorvastatin equivalent
MSP Singapore Co., LLC: Merck & Co., Inc. and Schering Corporation (505(b)2)

Submission Date: 02 Sept 09

Filing Date: 01 Nov 2009

Mid-cycle Review Meeting: 14 Jan 2010

Reviews sign-off in DARRTS: end of June 2010

PDUFA Date: 01 July 2010

Clinical Reviewer: Katrina Rhodes, MD, MS

Introduction

The sponsor, MSP Singapore, submits under the provisions of Section 505 (b) 2 of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, a New Drug Application (NDA) for (b) (4) (ezetimibe/atorvastatin) (b) (4) as a 505(b)(2) application. MSP Singapore, a Joint Venture between Merck & Co., Inc. and Schering Plough Corporation, has developed (b) (4) as a fixed-dose combination (FDC) formulation consisting of ezetimibe and atorvastatin calcium amorphous, two lipid-modulating drugs with two different mechanisms of action. Ezetimibe and Atorvastatin calcium crystalline are active ingredients in the products Zetia® (Merck & Co., Inc.) and Lipitor® (Pfizer, Inc.), approved under NDA 21-445 and NDA 20-702, respectively.

Regulatory Background

The ezetimibe/atorvastatin combination product contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and amorphous atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Atorvastatin crystalline was first approved in the USA in 1998 for Pfizer, Inc. Ezetimibe was first approved in the USA in 2002 for Merck Inc.

In November 7, 2005, Pfizer, Inc. filed a Citizen's Petition regarding the approval of any ANDA containing amorphous atorvastatin in the USA. Pfizer Inc. was concerned that applicants would seek approval of polymorphs of atorvastatin that are different from, and may be inferior in quality to, Lipitor. These physical forms of atorvastatin may be susceptible to higher levels of impurities and may degrade more quickly and have inferior stability compared to Lipitor. As there weren't any active ANDA applications, the Citizen's Petition was put on hold. Excerpts from the Citizen's Petition follow below.

Clinical Filing Checklist for NDA 200,153 (b) (4)

Crystalline forms in general, and the crystalline forms of atorvastatin, are more chemically stable than amorphous forms. Pfizer found during its own developmental work on atorvastatin that the bulk amorphous drug substance degraded quickly during accelerated stability studies at 40 °C/75% RH and 80 °C. By comparison, Pfizer's crystalline atorvastatin showed no significant increase in degradation impurities during the accelerated stability studies.

Crystallization is usually utilized to achieve the desired chemical purity during the production of active ingredients. The amorphous form has a higher specific surface area, a greater tendency to absorb solvents, and a higher reactivity than the more ordered crystalline form. Therefore, production of an amorphous form increases the likelihood that increased impurities will be incorporated in the active ingredient during production. In addition to the chemical impurities, higher amounts of solvents may also be incorporated into the amorphous form.

Drug Substance

The ezetimibe/atorvastatin FDC tablet is a (b) (4) oral tablet containing ezetimibe drug substance manufactured by Schering-Plough Corporation (NDA 21-445 for Zetia) and atorvastatin calcium (amorphous) drug substance manufactured by Dr. Reddy's Laboratories Ltd., (Type II DMF 18468). The dosage of the ezetimibe component is fixed at 10 mg, the same dose as for monotherapy. The dosage of the atorvastatin component is 10, 20, 40, or 80 mg. Therefore, 4 tablet strengths of the combination product are available and presented in this application: ezetimibe/atorvastatin 10/10, 10/20, 10/40, and 10/80 mg. The ezetimibe/atorvastatin combination is being developed for adjunctive therapy to diet for the reduction of elevated TC, LDL-C, Apo B, TG, and non-HDL cholesterol and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia, or mixed hyperlipidemia. In addition, the ezetimibe/atorvastatin combination would be indicated for the reduction of elevated TC and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Clinical Development Program

The goal of the ezetimibe/atorvastatin clinical development program is to demonstrate bioequivalence of the ezetimibe/atorvastatin fixed dose combination (FDC) tablets (10/10 mg, 10/20 mg, 10/80 mg) to the corresponding coadministered ezetimibe + atorvastatin tablets to support bridging of the ezetimibe/atorvastatin FDC tablet to the ezetimibe + atorvastatin coadministration clinical efficacy and safety data in the original NDA 21-445 as well as to additional coadministration studies completed since marketing approval.

All clinical efficacy and safety studies were conducted with ezetimibe + atorvastatin coadministered as separate entities. (b) (4)

(b) (4) a "bracketing strategy" similar to that used for the Vytorin NDA, was proposed as the primary approach to demonstrate bioequivalence for this range of FDC dosage strengths. Therefore, the effects of the components of the combination administered as separate entities will be comparable to those of ezetimibe and atorvastatin administered together in the ezetimibe/ atorvastatin combination tablet

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

proposed for marketing,

Submitted Protocols in Tabular Form

Protocols

Protocol	Title	Dataset	Financial
Biopharmaceutical Studies			
145	A Study to Evaluate the Definitive Bioequivalence of MK-0653C with Marketed Products	√	√
146	An Open-Label, Randomized, 2-Period Crossover Study to Compare the Effects of Food on MK-0653C in Healthy Adult Subjects	√	Non-covered
001	An Open-Label, Randomized, Single-Dose, 3-Period, Balanced Crossover Study to Compare the Pharmacokinetic Profiles of 3 Formulations of Atorvastatin in Healthy Young Adult Subjects	√	Non-covered
186 (O460)	Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers	Missing; not used in E/S eval.	Non-covered
Newly Submitted Clinical Studies			
079	A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate and Compare the Efficacy and Safety of Ezetimibe added on to Atorvastatin 20 mg Versus Up Titration to Atorvastatin 40 mg in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart Disease Not Adequately Controlled on Atorvastatin 20 mg	√	√
090	A Multicenter, Randomized, Double-Blind, Titration Study to Evaluate and Compare the Efficacy and Safety of Ezetimibe Added On to Atorvastatin 40 mg Versus Up Titration to Atorvastatin 80 mg in Hypercholesterolemic Patients at High Risk for Coronary Heart Disease Not Adequately Controlled on Atorvastatin 40 mg	√	√
112	A Multicenter, Randomized, Double-Blind, Parallel Arm, 12-Week Study to Evaluate the Efficacy and Safety of Ezetimibe 10 mg When Added to Atorvastatin 10 mg Versus Titration to Atorvastatin 20 mg and to 40 mg in Elderly Patients With hypercholesterolemia at High Risk for CHD	√	√
Previously Submitted Clinical Studies			
00692 (013)	A Phase 3, Double-Blind Efficacy and Safety Study of Ezetimibe 10 mg in Addition to Atorvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia	√	Prior
00693 (030)	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe 10 mg in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Cardiovascular Risk Factors with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin	PDF file	Prior
01030 (018)	A Phase III Efficacy and Safety Study of Ezetimibe 10 mg in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia	√	Prior
02154 (x692; 017)	Long-Term, Safety and Tolerability Study of Ezetimibe or Placebo in Addition to Atorvastatin in Subjects with Primary Hypercholesterolemia	Missing	Prior
01418 (x693; 032)	Long Term, Open-Label, Safety and Tolerability Study of Ezetimibe in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Risk Factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin	Missing	Prior
O1417 (x1030; 019)	Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia	Missing	Non-covered
02173/02246 (001, 002)	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 (Ezetimibe 10 mg) When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease or Multiple Cardiovascular Risk Factors	√	Prior
02173R/02246 (Reversa)	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 (Ezetimibe 10 mg) When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary	Missing	Missing (? Prior)

(b) (4)

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

Protocol	Title	Dataset	Financial
bility Period 02173) 040	Hypercholesterolemia, Known Coronary Heart Disease or Multiple Cardiovascular Risk Factors A Multi-center, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, 6-Week Study to Evaluate the Efficacy and Safety of Ezetimibe 10 mg/day When Added to Ongoing Therapy with a Statin Versus Statin Therapy Alone, in Patients with Hypercholesterolemia Who Have Not Reached National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Target LDL-Cholesterol Level	√	Prior
051	A multicenter, randomized, double-blind, 8 arm parallel group 6-week study. Following a 4-week placebo run-in period, patients were randomized to 1 of 8 treatment groups: the ezetimibe/simvastatin combination tablet at doses of 10/10, 10/20, 10/40, or 10/80 mg/mg, or atorvastatin alone at doses of 10, 20, 40, or 80 mg for 6 weeks.	Missing	√

Biopharmaceutical

The formulation development process was directed to support the bioequivalence-based bridging strategy. (b) (4)

(b) (4)

(b) (4)

(b) (4)

a “bracketing strategy” was justified as the primary approach to demonstration of bioequivalence for this range of FDC dosage strengths. This strategy includes the following: Demonstration of in vivo bioequivalence between the FDC tablet at the ezetimibe/atorvastatin 10/20 mg and the 10/80 mg dosage strengths and the corresponding ezetimibe + atorvastatin tablets coadministered; and Demonstration of similar in vitro dissolution profiles for ezetimibe + atorvastatin among the 3 combination tablet dosage strengths.

In the bioequivalence study, AUC and Cmax parameters were matched for 10/10 mg and 10/80 mg. Only AUC was met for 10/20 mg (Cmax parameter was not met; (b) (4)). The 10/40 mg dose bioequivalence was determined by a bracketing strategy between the 10/20 and 10/80 mg doses.

The study drugs were developed at a research and development site. The commercial manufacturer sites will not all be available for inspection until December, 2009. A

bioequivalence bridge is also needed between the research and development clinical site study drug and the manufacturing commercial site product.

Biopharmaceutical studies in healthy subjects

Pilot biocomparison study Supported formulation development of atorvastatin (b) (4) component	P001
Definitive bioequivalence study Bracketing strategy comparing combination tablets to marketed agents dosed concomitantly	P145
Descriptive food effect study Used the highest FDC dosage strength of the combination tablet	P146

Efficacy

This filing consists of data from seven placebo- or active-controlled short-term (6- to 14-week) studies that evaluated the safety and efficacy of ezetimibe + atorvastatin in 6,876 patients with primary hypercholesterolemia. Data are also presented for 503 patients with mixed hyperlipidemia (defined as hypercholesterolemia with TG concentrations >200 mg/dL [2.27 mmol/L]) based on a subgroup analysis. Long-term data are reported from one controlled, blinded 52-week extension study conducted in 246 hypercholesterolemic patients, and, from one open-label 12 month, uncontrolled study in 432 hypercholesterolemic patients. Data from a small population of 36 patients with Homozygous Familial Hypercholesterolemia (HoFH) who were evaluated for up to two years are also included.

Seven placebo- or active-controlled short-term (6- to 14-week) studies (P692, P693, P2173, P040, P079, P090, P112) evaluated the efficacy of ezetimibe + atorvastatin in patients with primary hypercholesterolemia. These multicenter studies involved a total of 6,876 patients. Of these, 231 received ezetimibe + atorvastatin for a minimum of 10 weeks in P692, 288 received ezetimibe + atorvastatin for a minimum of 11 weeks in P693, 288 received ezetimibe + atorvastatin for a minimum of 11 weeks in 2173, 249 received ezetimibe + atorvastatin for a minimum of 7 weeks in P040, 377 received ezetimibe + atorvastatin for a minimum of 2 weeks (128 of these for a minimum of 6 weeks) in P079 and P090, and 509 received ezetimibe + atorvastatin for a minimum of 8 weeks (241 of these for a minimum of 12 weeks) in P112.

One controlled, blinded 52-week extension study (P2154) was conducted in 246 hypercholesterolemic patients who successfully completed the respective base study P692. One open-label, uncontrolled study, the 52-week Open Label Extension Study (P1418) included 432 hypercholesterolemic patients. Between these Long-Term Studies, 678 patients received ezetimibe + atorvastatin therapy, with mean exposure of 10.93 months for P2154 and 11.24 months for P1418.

The efficacy of ezetimibe + atorvastatin in HoFH patients was evaluated in P1030 and P1417, the 2-year extension study for P1030. In the base study, 12 patients were treated with atorvastatin monotherapy (80 mg) and 12 were treated with ezetimibe + atorvastatin

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

40 mg or 80 mg for 12 weeks. In the extension study P1417, 35 patients were initially treated with ezetimibe + atorvastatin 40 mg and allowed to up-titrate to 80 mg as needed to achieve LDL-C goal for 2 years.

Results also are presented for 503 patients with mixed hyperlipidemia (defined as hypercholesterolemia with TG concentrations >200 mg/dL [2.27 mmol/L]) based on a subanalysis of data from P692. Among these patients, 248 were treated with atorvastatin monotherapy and 255 were treated with ezetimibe + atorvastatin for approximately 12 weeks.

Efficacy

Short-Term Studies (6 to 14 weeks) - Factorial Study - Add-On Studies - Add-On Titration Studies	P692 - Atorvastatin Factorial P2173 - EZ Add-On for statins P040 - EASE P079 - TEMPO P090 - EZ-PATH P112 - Zetia in the Elderly P693 - Add-On and Titration
Long-Term Studies (52 weeks) - Blinded Comparator Extension - Open-label Extension	P2154 (extension for P692) P1418 (extension for P693)
Special Population Studies - Homozygous Familial Hypercholesterolemia (HoFH) - HoFH open-label extension - Mixed Hyperlipidemia	P1030 P1417 (extension for P1030) P692

Safety

The Ezetimibe/Atorvastatin Integrated Summary of Safety summarizes the safety profiles of the coadministration of ezetimibe and atorvastatin in previous Phase III and Phase IV trials. These Ezetimibe/Atorvastatin co-administration studies include (1) Short term studies (protocols P00692, P00693, P02173, 040, 079, 090 and 112); (2) Long term extension study (protocol P02154) where Ezetimibe/Atorvastatin was co-administered for 12 months; and (3) Special population study (protocol P01030) consisting of patients with homozygous familial hypercholesterolemia.

Safety

(1) Short term studies: post-approval NDA 21-445 Zetia (not yet reviewed): pre-approval/application NDA 21-445 Zetia (previously reviewed): supplement application NDA 21-445 Zetia (S-12) (previously reviewed):	79, 90, 112 692, 693, 2173 40
(2) Long term extension study – 12 months (pre-approval/application NDA Zetia)	2154 (x 692), 1418 (x693)

(b) (4)

(3) Special population study – HoFH (pre-approval/application NDA Zetia)	1030, 1417 (x 1030)
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Proposed Indications

In Module 1, the sponsor submitted a draft Package Insert as a pdf version (proposed-pi-original-sep2009.pdf), as an annotated version (annotated-pi-original-sep2009.pdf), and as a Word document (proposed-pi-original-sep2009.doc) in Physician Labeling Rule (PLR) format. A draft Patient Information was also submitted as a pdf version (proposed-pi-original-sep2009.pdf) and a Word document (proposed-pi-original-sep2009.doc).

Indications for Use of (b) (4)

<p>1.1 Primary Hyperlipidemia (b) (4) is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.</p> <p>1.2 Homozygous Familial Hypercholesterolemia (HoFH) (b) (4) is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.</p> <p>1.3 Limitations of Use No incremental benefit of (b) (4) on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. (b) (4) has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.</p>
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The following sections are not included in the labeling for (b) (4) because there are no data that meet the criteria for these sections as specified in 21 CFR §201.57:

<p>Highlights Controlled substance symbol Initial US approval date Boxed warning Recent major changes Use in specific populations Revision date</p>	<p>Full Prescribing Information Boxed warning Labor and delivery Drug abuse and dependence References</p>
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Publications Based on the Study

None identified in submission.

Pediatric Waiver

MSP Singapore Company, LLC proposes to request a waiver of the requirements of 21 CFR 314.55(a) for pediatric studies based on the initial approval of Zetia. The FDA granted a waiver of pediatric studies in children < 10 years of age (October 25, 2002) consistent with the current American Heart Association and American Academy of Pediatrics guidelines for drug-based treatment of high risk lipid abnormalities. In addition the FDA agreed on June 28, 2003 that a study evaluating ezetimibe and simvastatin in pediatric patients ≥ 10 years of age would suffice to demonstrate safety and efficacy of ezetimibe coadministered with all approved statins and that individual studies evaluating ezetimibe coadministered with each statin were not required.

Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Categorical Exclusion

Merck Research Laboratories, a division of Merck & Co., Inc., is filing an NDA for ezetimibe/atorvastatin combination tablets. Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b) for ezetimibe. The patient use of ezetimibe meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of this active drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). Atorvastatin is an approved agent that is widely used in the treatment of high cholesterol and will be generic at the time of product launch. To the best of Merck’s knowledge, no extraordinary circumstances exist in regards to this action.

Financial Disclosures:

Previously Filed Protocols (not re-submitting financial disclosures.)

'ZETIA' NDA 21-445 Filing Date: 27-December-2001	001 (Schering-Plough PO2173) 002 (Schering-Plough PO2246) 013 (Schering-Plough PO0692) 017 (Schering-Plough PO2154) 018 (Schering-Plough PO1030)
Vytorin NDA 21-687 Filing Date 24-sept-2003	001 (Schering-Plough PO2173) 002 (Schering-Plough PO2246)
'ZET IA' sNDA 21-445/S-012 29-March-2005	040
'ZETIA' sNDA 21-445/S-013 Filing Date: 26-July-2005	030 (Schering-Plough PO0693) 032 (Schering-Plough PO1418)

Merck & Co., Inc.

Summary of Covered Clinical Studies	079, 090, 112, 145
Summary of Non-Covered Clinical Studies	019 (P01417), 186 (P0460), 146, 001
Schering-Plough	
Summary of Covered Clinical Studies	
Summary of Non-Covered Clinical Studies	019 (P0417), 186 (P0460), 146, 001

All Clinical Investigators/Subinvestigators Not Certified

Product/Protocol/Site	Investigator/ Subinvestigator	Reason
	(b) (6)	Did not return form with requested information. Forms sent on 03-14-2006; 02-13-2007; 08-21-2007; 03-18-2008; 04-29-2008; 03-25-2009; 06-25-2009

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

(b) (6)	Did not return form with requested information. Forms sent on 04-17-2006; 02-19-2007; 08-20-2007; 01-29-2008; 03-18-2008; 05-14-2009
	Investigator Left Site. Forms sent on 04-24-2007; 07-03-2007; 08-20-2007; 02-04-2009; 04-22-2009
	Investigator Deceased. Forms sent on 02-10-2009

Source: (Merck & Co., Inc., Table C-2)

All Clinical Investigators/Subinvestigators Who Hold Financial Interests or Arrangements Requiring Disclosure

Product/Protocol/Site	Investigator/ Subinvestigator	Financial Interests or Arrangements
(b) (6)	(b) (6)	<p>Significant Payments of Other Sorts: Amount: \$35,000.00 (Approximately \$35,000.00 in speaker fees as reported by investigator on 03-02-2009.)</p> <p>Significant Payments of Other Sorts: Amount: \$36,000.00 (Approximately \$36,000.00 in speaker honorarium as reported by investigator on 03-21-2007.)</p> <p>Significant Payments of Other Sorts: Amount: \$33,000.00 (Approximately \$33,000.00 in speaker honorarium as reported by investigator on 04-15-2009.)</p> <p>Significant Payments of Other Sorts: Amount: \$50,000.00 (Approximately \$50,000.00 in speaker honorarium as reported by investigator on 05-19-2006.)</p> <p>Significant Payments of Other Sorts: Amount: \$41,004.00 (Merck payments in the amount of \$29,504.00 and Schering-Plough payments in the amount of \$11,500.00 for educational programs and advisory/consultant meetings as reported by investigator on 03-17-2009.)</p> <p>Significant Payments of Other Sorts: Amount: \$39,398.00 (Merck payments in the amount of \$28,398.00 and Schering-Plough payments in the amount of \$11,000.00 for educational programs and advisory/consultant meetings as reported by investigator on 11-19-2008.)</p> <p>Significant Payments of Other Sorts: Amount: \$38,900.00 (Merck: \$11,700.00 for out of town and \$9,000.00 for local educational programs and advisory/consultant meetings. Schering Plough: \$14,600.00 for out of town and \$3,600.00 for local educational programs and advisory/consultant meetings per 2006 tax records as reported by investigator on 02-02-2007.)</p> <p>Significant Payments of Other Sorts: Amount: \$38,900.00 (Merck: \$11,700.00 for out of town and \$9,000.00 for local educational programs and advisory/consultant meetings. Schering Plough: \$14,600.00 for out of town and \$3,600.00 for local educational programs and advisory/consultant meetings per 2006 tax records as reported by investigator on 03-16-2007.)</p>

(b) (4)

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

Product/Protocol/Site	Investigator/ Subinvestigator	Financial Interests or Arrangements
(b) (6)		Significant Payments of Other Sorts: Amount: \$244,081.00 (Payments in the amount of \$104,074.00 in 2007 and \$140,007.00 in 2008 for speaking and consulting honorarium as reported by investigator on 06-22-2009.)
		Significant Payments of Other Sorts: Amount: \$208,000.00 (Payments in the amount of \$105,000.00 in 2007 and \$103,000.00 in 2008 for speaking and consulting honorarium as reported by investigator on 02-27-2009.)
		Significant Payments of Other Sorts: Amount: \$100,000.00 (Approximately \$100,000.00 in 2005 for honorarium and consulting fees as reported by investigator on 08-04-2006.)
		Significant Payments of Other Sorts: Amount: \$86,296.00 (Payments in the amount of \$30,420.00 in 2007 and \$55,876.00 in 2008 for speaking honoraria as reported by investigator on 07-13-2009.)
		Significant Payments of Other Sorts: Amount: \$57,425.00 (Payments in the amount of \$21,178.00 in 2006 and \$36,247.00 in 2007 for speaking honoraria as reported by investigator on 10-13-2008.)
		Significant Payments of Other Sorts: Amount: \$30,000.00 (Payments from Merck and Schering-Plough for consulting and speaking estimated at \$30,000.00 as reported by investigator on 04-24-2009.)
		Significant Payments of Other Sorts: Amount: \$27,000.00 (Approximately \$27,000.00 in speaker and consultant honoraria as reported by investigator on 02-12-2008.)

Source: (Merck & Co., Inc., Table D-1)

Site Inspection:

This will be determined with DSI investigator pending receipt of additional information on subject accountability per individual investigators from MSP.

Since Protocol 145 is the pivotal bioequivalence study, Clinical Pharmacology has recommended this site for inspection.

Patent Certification:

MSP has submitted certification of six patents to Pfizer, Inc. for reference drug atorvastatin calcium (see below). Three patents are Paragraph III Certification (4,681,893; 5,273,995; and RE40,667), and three patents are Paragraph IV Certification (5,686,104; 5,969,156; 6,126,971).

(b) (4)

NDA Applicant: MSP Singapore LLC
Page 1 of 2

PATENT CERTIFICATION
EZETIMIBE-ATORVASTATIN TABLETS

Paragraph III Certification

The undersigned hereby certifies that, to the best of MSP Singapore Company, LLC's knowledge and in its opinion, there are six patents listed in the Food and Drug Administration publication, Approved Drug Products with Therapeutic Equivalence Evaluations, that claim the reference drug atorvastatin calcium.

U.S. Patent No.	Expiration Date	Pediatric Exclusivity Expiration Date
4,681,893	September 24, 2009	March 24, 2010
5,273,995	December 28, 2010	June 28, 2011
5,686,104	November 11, 2014	May 11, 2015
5,969,156	July 8, 2016	January 8, 2017
6,126,971	January 19, 2013	July 19, 2013
RE40,667	December, 28, 2010	June 28, 2011

The undersigned hereby certifies pursuant to Section 505(b)(2)(A)(iii) of the Federal Food, Drug, and Cosmetic Act that, to the best of MSP Singapore Company, LLC's knowledge and in its opinion, U.S. Patents Nos. 4,681,893; 5,273,995; and RE40,667; and their respective extensions for pediatric exclusivity, will expire on the dates noted above. MSP Singapore Company, LLC, will not engage in the commercial distribution of the ezetimibe-atorvastatin tablets for which this application is submitted before the expiration of U.S. Patents Nos. 4,681,893; 5,273,995; and RE40,667; and their respective extensions for pediatric exclusivities.

18 August 2009
Date

S. Mackenzie
Sandra Mackenzie B.Sc.
Director, Regulatory Affairs
Agent for the MSP Singapore Company, LLC

NDA Applicant: MSP Singapore LLC
Page 2 of 2

PATENT CERTIFICATION

EZETIMIBE-ATORVASTATIN TABLETS

Paragraph IV Certification

The undersigned hereby certifies that, to the best of MSP Singapore Company, LLC's knowledge and in its opinion, there are six patents listed in the Food and Drug Administration publication, Approved Drug Products with Therapeutic Equivalence Evaluations, that claim the reference drug atorvastatin calcium.

U.S. Patent No.	Expiration Date	Pediatric Exclusivity Expiration Date
4,681,893	September 24, 2009	March 24, 2010
5,273,995	December 28, 2010	June 28, 2011
5,686,104	November 11, 2014	May 11, 2015
5,969,156	July 8, 2016	January 8, 2017
6,126,971	January 19, 2013	July 19, 2013
RE40,667	December, 28, 2010	June 28, 2011

The applicant, MSP Singapore Company, LLC, certifies that U.S. Patents Nos. 5,686,104; 5,969,156; and 6,126,971; are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the ezetimibe-atorvastatin tablets for which this application is submitted. MSP Singapore Company, LLC, will comply with the requirements of 21 C.F.R. § 314.52(a) and (c) with respect to providing notice and the content of that notice to the assignee of U.S. Patents Nos. 5,686,104; 5,969,156; and 6,126,971; and to Pfizer Inc. as the holder of the approved New Drug Application for the drug product or a use thereof which is claimed by U.S. Patents Nos. 5,686,104; 5,969,156; and 6,126,971.

18 August 2009
Date

S. Mackenzie
Sandra Mackenzie B.Sc.
Director, Regulatory Affairs
Agent for the MSP Singapore Company, LLC

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

	Content Parameter	Yes	No	NA	Comment
15.	Do all new/pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Clinical studies include US subjects.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			However no integration of vital signs, physical findings, or ECG parameters.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			The sponsor presents safety concerns for Statin Drug Class and EZ/Atorva as co-administered.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		Could not identify, or find location in submission, coding dictionary for mapping terms (i.e.: MedDRA version).
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric Waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			However P051 missing
34.	Are all datasets to support the critical safety analyses available and complete?	X			Could use: unique subject identifier; additional MedDRA hierarchy terms LLT, HLT, and HLGT; concomitant meds; Creatinine; and vitals.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		X		Could use: subject accountability by individual investigators in tabular format for all randomized subjects in newly submitted studies.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

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

1. Please provide, or indicate location in the submission, subject accountability by individual investigators for all randomized subjects in tabular format for the following protocols: 079, 090, 112,145, and 051.

(b) (4) /MK-0653C: Subject Accountability by Selected Investigators (All Randomized Subjects Per Individual Protocol)

Investigator (Site #) Treatment	# Subjects Randomized	# Subjects Treated	# Subjects Discontinued	% of Randomized Subjects that Discontinued
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Per Protocol

- EZ/Atorva 10/10 mg
- EZ/Atorva 10/20 mg
- EZ/Atorva 10/40 mg
- EZ/Atorva 10/80 mg
- Atorvastatin
- Ezetimibe
- Total

Per Investigator

- EZ/Atorva 10/10 mg
- EZ/Atorva 10/20 mg
- EZ/Atorva 10/40 mg
- EZ/Atorva 10/80 mg
- Atorvastatin
- Ezetimibe
- Total

2. Regarding Protocol P051, please provide, or indicate location in submission, financial disclosure information and an explanation of why this study is not included in the safety or efficacy analysis.

3. Regarding individual study AE datasets and ISS AE dataset, please identify, or provide location in submission, coding dictionary for mapping terms (i.e.: MedDRA Version used).

4. Please provide, or indicate location in the submission, datasets (as SAS transport files) for the following protocol(s):

Protocol	Title
051	A multicenter, randomized, double-blind, 8 arm parallel group 6-week study. Following a 4-week placebo run-in period, patients were randomized to 1 of 8 treatment groups: the ezetimibe/simvastatin combination tablet at doses of 10/10, 10/20, 10/40, or 10/80 mg/mg, or atorvastatin alone at doses of 10, 20, 40, or 80 mg for 6 weeks.
01418 (x693; 032)	Long Term, Open-Label, Safety and Tolerability Study of Ezetimibe in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Risk Factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin

(b) (4)

CLINICAL FILING CHECKLIST FOR NDA 200,153

(b) (4)

O1417 (x1030; 019) 02173R/ 02246 (Reversability Period 02173)	Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 (Ezetimibe 10 mg) When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease or Multiple Cardiovascular Risk Factors
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5. Please add the following variables to ISS datasets (ADSL/AE/LB): 1) unique subject identifier (in the same format as individual studies' variable 'USUBJID' (Char40)) (ADSL/AE/LB); 2) MedDRA hierarchy terms for LLT, HLT, and HLG (AE); 3) concomitant medications (ADSL/AE); 4) vitals (LB); and 5) Creatinine (LB).

6. Please provide, or identify location in submission, any publications based on newly submitted clinical studies post-approval of Zetia (NDA 21,445).

Reviewing Medical Officer

Date

Clinical Team Leader

Date

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATRINA RHODES
10/09/2009

ERIC C COLMAN
10/09/2009