Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ezetimibe and Atorvastatin

Proprietary Product Name: Ezetrol Plus Atorva / Zetia Plus Atorva

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

First round report: 23 July 2012

Second round report: 18 October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ALT	Alanine aminotransferase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATP	Adult treatment panel
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CHD	Coronary Heart Disease
CI	Confidence interval
CK	Creatine phosphokinase
CRF	Case Report Form
Cmax	Maximum concentration
CSR	Clinical study report
CV	Coefficient of variation
DDI	Drug drug interaction
ECG	Electrocardiogram
FDC	Fixed dose combination
FMI	Final marketing image
FSG	Fasting serum glucose

Abbreviation	Meaning
GI	Gastrointestinal
GMR	Geometric mean ratio
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
HR	Heart rate
IV	Intravenous
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein cholesterol
LS mean	Least-squares mean
MS	Metabolic Syndrome
MSD	Merck Sharp & Dohme
NCEP	National Cholesterol Education Program
NDA	New drug application
NMSC	Non-melanoma skin cancer
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QD	once daily
RBC	Red blood (cell) count
SD	Standard deviation
SEM	Standard error of the mean
SOC	System Organ Class
SPC	Summary of product characteristics
TC	Total cholesterol
TG	Triglycerides

Abbreviation	Meaning
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood (cell) count

1. Clinical rationale

Ezetimibe inhibits cholesterol absorption and is indicated in the treatment of primary hypercholesterolaemia, or HoFH, and phytosterolaemia, as monotherapy or in conjunction with a statin. Atorvastatin is a well-known statin indicated for the treatment of primary hypercholesterolaemia and in hypertensive patients with CHD risk factors to reduce the risk of myocardial infarction or stroke. These two medications have complementary mechanisms of action and co-administration is approved.

The rationale for the composite pack provided by the sponsor is that "*having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed. In addition, a composite pack would reduce the cost to patients, as patients will only pay for one PBS co-payment instead of two*."

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The dossier contained Modules 1 and 2. There was no Module 5 and a justification for this was included in the Clinical Overview. There was an additional section in the dossier labelled "Part IV". The sponsor stated the co-administration of the two products is based on the data package which was used to support the registration of ezetimibe (Ezetrol).

The submission contained the following clinical information:

- Module 1. Application letter, application form, draft Australian PI and CMI and pre-submission meeting correspondence.
- Module 2. Clinical Overview, information relating to the original ezetimibe evaluation including ADEC meeting and responses, product information for ezetimibe and atorvastatin SZ and PBS data estimated numbers of patients prescribed ezetimibe and a statin.
- Part IV. This included clinical study data from the ezetimibe submission dated January 2002.

Subsequent to the s31 questions after the first round of evaluation the Sponsor submitted data from the submission [information redacted]. The response included the following clinical information:

- Module 2. Clinical Overview, Summary of clinical efficacy, Summary of clinical safety and synopses of individual studies.
- Module 5. Ten controlled clinical studies (P040, P079, P090, P112, P0692, P0693, P1030, P2154, P2173 and P2173R), two uncontrolled clinical studies (P1417 and P1418), a statistical analysis plan for the integrated summary of safety, and a summary of post-marketing data of ezetimibe with atorvastatin.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The studies contained in the submissions for ezetimibe and for the [information redacted] ezetimibe and atorvastatin were stated to have been conducted in accordance with GCP standards and relevant ethical and regulatory approval.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

No new pharmacokinetic data were submitted.

3.2. Summary of pharmacokinetics

As the products in the composite packs are the same as the registered products, no biopharmaceutic or pharmacokinetic data were submitted. The following is a summary of data taken from the relevant product information and the clinical evaluation reports for ezetimibe and the [information redacted].

3.3. Pharmacokinetics in healthy subjects

3.3.1. Absorption

3.3.1.1. Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10 mg dose of ezetimibe in fasting adults, mean ezetimibe peak plasma concentrations (Cmax) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (Tmax). Ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours (Tmax). There was no substantial deviation from dose proportionality between 5 and 20 mg.

3.3.1.2. Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose.

3.3.2. Bioavailability

3.3.2.1. Ezetimibe

The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

3.3.2.2. Atorvastatin

The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

3.3.2.2.1. Influence of food

3.3.2.2.1.1. Ezetimibe

Concomitant administration of food (high fat or non-fat meals) was not shown to effect the oral bioavailability of ezetimibe 10 mg tablets.

3.3.2.2.1.2. Atorvastatin

Food decreases the rate (Cmax) and extent (AUC) of absorption by 25% and 9%, respectively, however the LDL-C reduction is similar. In addition, there is an approximate 30% reduction in Cmax and AUC with evening administration compared to morning administration although the LDL-C reduction is similar.

3.3.3. Distribution

Mean volume of distribution of atorvastatin is approximately 381 litres. Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. Atorvastatin is ≥98% bound to plasma proteins.

A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

3.3.4. Metabolism

3.3.4.1. Atorvastatin

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation. In conclusion, during the bioequivalence studies and the food effect study, parent as well as ortho- and parahydroxylated derivatives were measured in order to characterise the atorvastatin exposure fully in humans.

3.3.4.2. Ezetimibe

Ezetimibe is primarily metabolised in the small intestine and liver via glucuronide conjugation (a Phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a Phase I reaction) has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolised to ezetimibe-glucuronide.

Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide.

Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

3.3.4.2.1. Metabolites identified in humans

Both ezetimibe and its metabolite ezetimibe-glucuronide are pharmacologically active, with ezetimibe-glucuronide inhibiting cholesterol absorption to at least as great an extent

as the unconjugated parent. Thus, total ezetimibe (unconjugated ezetimibe + ezetimibe-glucuronide) represents the sum of both active ezetimibe-derived substances in plasma following an oral dose.

Two active atorvastatin metabolites (ortho-hydroxyatorvastatin and para-hydroxy-atorvastatin) have been identified in human plasma. *In vitro* inhibition of HMG-CoA reductase by the ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin and approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to the active metabolites.

3.3.5. Excretion

3.3.5.1. Ezetimibe

Following oral administration of 14C-ezetimibe (20 mg) to human subjects, approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in faeces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

3.3.5.2. Atorvastatin

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

3.4. Pharmacokinetics in the target population

Not applicable.

3.5. Pharmacokinetics in other special populations

3.5.1. Pharmacokinetics in subjects with impaired hepatic function

3.5.1.1. Ezetimibe

After a single 10mg dose of ezetimibe, AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3-4 fold and 5-6 fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe is not recommended in these patients.

3.5.1.2. Atorvastatin

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

3.5.2. Pharmacokinetics in subjects with impaired renal function

3.5.2.1. Ezetimibe

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

3.5.2.2. Atorvastatin

Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary. While clinical pharmacology studies have not been conducted in patients with end-stage renal disease, haemodialysis is not expected to enhance the clearance of atorvastatin significantly since the drug is extensively bound to plasma proteins.

3.5.3. Pharmacokinetics according to age

3.5.3.1. Paediatric patients

3.5.3.1.1. Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe (ezetimibe + ezetimibe-glucuronide), there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population <10 years of age are not available.

3.5.3.1.2. Atorvastatin

Pharmacokinetic data in the paediatric population are not available.

3.5.3.2. Geriatric patients

3.5.3.2.1. Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

3.5.3.2.2. Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

3.5.4. Pharmacokinetics related to genetic factors

3.5.4.1. Gender

3.5.4.1.1. Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

3.5.4.1.2. Atorvastatin

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

3.5.4.2. Race

3.5.4.2.1. Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in Caucasian subjects.

3.6. Pharmacokinetic interactions

3.6.1. Ezetimibe

Adverse drug-drug interactions are known to occur between ezetimibe and the following drugs: cholestyramine; fenofibrate; gemfibrozil; cyclosporine; and warfarin. The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied and therefore is not recommended.

From the Clinical Evaluation Report of ezetimibe, seven studies assessed the potential interaction of ezetimibe with HMG CoA reductase inhibitors in healthy volunteers with hypercholesterolaemia (LDL-C ≥130 mg/dL). The studies assessed simvastatin (10 and 20 mg), lovastatin (20 and 40 mg), pravastatin (10 mg), atorvastatin 10 mg), cerivastatin (0.3 mg) and fluvastatin (20 mg). There was no significant effect on the PK of ezetimibe reported. The PI of ezetimibe states "*No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin."*

3.6.2. Atorvastatin

Adverse drug-drug interactions (DDIs) are known to occur between atorvastatin and the following drugs: inhibitors of cytochrome P450 3A4, clarithromycin, erythromycin, combination of protease inhibitors, itraconazole, diltiazem hydrochloride, grapefruit juice, cyclosporine, inducers of CYP3A4, antacid, colestipol, digoxin and oral contraceptives. No DDIs have been identified between atorvastatin and cimetidine, azithromycin or warfarin.

3.7. Evaluator's overall conclusions on pharmacokinetics

There was no clinically significant drug interaction reported between ezetimibe 10 mg and atorvastatin 10 mg.

It is noted that LIPITOR (from the US) was the atorvastatin used in the clinical trials assessing the combination of ezetimibe and atorvastatin evaluated in the [information redacted] dossier. No data has been provided to the evaluator on the bioequivalance of ATORVASTATIN SZ and the LIPITOR (from US).

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

No new pharmacodynamic data were submitted.

4.2. Evaluator's overall conclusions on pharmacodynamics

There were seven studies assessing the PK and PD of ezetimibe with statin co-administration in the ezetimibe clinical evaluation report. These found that the

combination was generally more effective in lowering lipids (LDL-C and total cholesterol) than either agent alone and significantly more effective than placebo.

5. Dosage selection for the pivotal studies

The proposed dosage is the same as the currently registered products (ezetimibe 10 mg and atorvastatin 10, 20, 40 and 80 mg) in the combinations of 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg.

6. Clinical efficacy

No new clinical efficacy studies were submitted in the original dossier. Data have been extracted from the evaluations of Ezetrol (ezetimibe) and from the clinical study reports in the [information redacted] (ezetimibe + atorvastatin [information redacted]) submission, the latter having been provided by the Sponsor in response to the s31 questions. The evaluator has summarised the relevant available data in two sections: efficacy with statins and efficacy with atorvastatin.

6.1. Hypercholesterolaemia and HoFH

6.1.1. Efficacy of ezetimibe with statins

6.1.1.1. Co-administration with statin

The ezetimibe submission contained four multicentre, phase III, randomised, placebo-controlled, 12 week factorial studies of ezetimibe co-administered with statins in 1861 patients with primary hypercholesterolaemia (**P0679, P0680, P0691, P0692**). The four statins studied were lovastatin, simvastatin, pravastatin, and atorvastatin. Study P0692 is discussed in more detail under *Efficacy of ezetimibe and atorvastatin* below. Efficacy of ezetimibe with co-administered statin was compared to the statin monotherapy. Inclusion required mean plasma LDL-C (from 2 pre-randomisation visits) of 145-250 mg/dL and mean TG ≤350 mg/dL.

The mean percentage change from baseline in direct LDL-C was -39.0%, -49.9%, -37.7% and -54.5% for the co-administration of ezetimibe with pooled doses of lovastatin, simvastatin, pravastatin and atorvastatin, respectively. This compared to -24.7%, -36.1%, -24.3% and -42.4% for the pooled statin monotherapy doses, respectively. The difference of approximately -13.8% was consistent across statins and statistically significant ($p \leq 0.01$). The effect was seen from week 2 and sustained to week 12.

A statistically significant reduction in LDL-C was noted for each dose of ezetimibe + statin compared to the corresponding dose of statin monotherapy (Table 1). The co-administration of ezetimibe and statin resulted in significantly greater reduction in LDL-C compared to the next higher dose of statin monotherapy. The evaluation also reported favourable results for the co-administration on the mean percentage change from baseline in TC, TG, HDL-C and Apo-B (Table 2).

Table 1. Mean absolute and percent change from baseline in plasma concentration of calculated LDL-C for Ezetrol administered with statins, as presented in Ezetrol PI

	Atorvastatin Study Abs[a] (Pct[b])	Simvastatin Study Abs[a] (Pct[b])	Pravastatin Study Abs[a] (Pct[b])	Lovastatin Study Abs[a] (Pct[b])
Placebo	0.20 (+4%)	-0.08 (-1%)	-0.03 (-1%)	0.00 (0%)
Ezetrol®	-0.92 (-20%)	-0.92 (-19%)	-0.91 (-20%)	-0.86 (-19%)
10mg statin	-1.76 (-37%)	-1.25 (-27%)	-0.96 (-21%)	-0.94 (-20%)
Ezetrol® + 10mg statin	-2.46 (-53%)	-2.10 (-46%)	-1.55 (-34%)	-1.56 (-34%)
20mg statin	-1.91 (-42%)	-1.74 (-36%)	-1.10 (-23%)	-1.18 (-26%)
Ezetrol® + 20mg statin	-2.59 (-54%)	-2.16 (-46%)	-1.82 (-40%)	-1.87 (-41%)
40mg statin	-2.09 (-45%)	-1.75 (-38%)	-1.43 (-31%)	-1.44 (-30%)
Ezetrol® + 40mg statin	-2.69 (-56%)	-2.55 (-56%)	-1.97 (-42%)	-2.15 (-46%)
80mg statin	-2.57 (-54%)	-2.11 (-45%)	-	-
Ezetrol® + 80mg statin	-2.93 (-61%)	-2.64 (-58%)	-	-
Pooled data: All statin doses	-2.08 (-44%)	-1.71 (-36%)	-1.16 (-25%)	-1.19 (-25%)
Pooled data: All Ezetrol® + statin doses	-2.67 (-56%)	-2.36 (-51%)	-1.78 (-39%)	-1.86 (-40%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline

Table 2. Pooled analysis of absolute and percent change from baseline in total-C, ApoB, TG, and HDL-C as presented in Ezetrol PI

	Total-C Abs[a] (Pct[b])	Apolipoprotein B Abs[c] (Pct[b])	Triglycerides Abs[d] (Pct[e])	HDL-C Abs[a] (Pct[b])
Ezetrol® + Atorvastatin	-2.86 (-41%)	-0.78 (-45%)	-0.55 (-33%)	0.09 (+7%)
Atorvastatin alone	-2.24 (-32%)	-0.61 (-36%)	-0.40 (-24%)	0.05 (+4%)
Ezetrol® + Simvastatin	-2.49 (-37%)	-0.69 (-41%)	-0.53 (-29%)	0.11 (+9%)
Simvastatin alone	-1.78 (-26%)	-0.51 (-30%)	-0.32 (-20%)	0.09 (+7%)
Ezetrol® + Pravastatin	-1.86 (-27%)	-0.51 (-30%)	-0.36 (-21%)	0.10 (+8%)
Pravastatin alone	-1.17 (-17%)	-0.35 (-20%)	-0.26 (-14%)	0.08 (+7%)
Ezetrol® + Lovastatin	-1.96 (-29%)	-0.57 (-33%)	-0.44 (-25%)	0.10 (+9%)
Lovastatin alone	-1.25 (-18%)	-0.36 (-21%)	-0.21 (-12%)	0.04 (+4%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline
[c] Mean absolute change from baseline, expressed as g/L
[d] Median absolute change from baseline, expressed as mmol/L
[e] Median percent change from baseline

6.1.1.2. Add-on to ongoing statin

The study **P2173** (also referred to as P2173/2246) was evaluated part of the ezetimibe submission. It was an 8 week randomised, double-blind, placebo-controlled multicentre study which assessed the effect of adding ezetimibe 10 mg to statin therapy in 769 patients with primary hypercholesterolaemia with CHD or cardiovascular risk factors who had not met NCEP ATP II LDL-C target levels. Following the 8 week treatment phase, there was a 6 week cholesterol reversibility phase (**P2173R**). [information redacted] The main statins used during these studies were atorvastatin (31.3%), simvastatin (31.3%) and pravastatin (14.3%).

In P2173, the LS mean percentage change from baseline in LDL-C was -25.1% in the ezetimibe + statin group compared with -3.7% in the placebo + statin group, and the difference (-21.5%) was statistically significant ($p<0.001$). In addition, 75.5% of patients in the ezetimibe + statin group reached LDL-C target levels compared to 27.3% of those on a statin + placebo. Excluding those who were already at the target level at baseline, target attainment was still greater with the addition of ezetimibe (71.5% versus 18.9%). Efficacy was seen across statin subgroups, including atorvastatin.

Study P040 was a large phase IV multicentre, double-blind, randomised, placebo-controlled, parallel group study to evaluate the efficacy and safety of ezetimibe 10 mg per day when added to ongoing therapy with a statin compared to statin therapy alone in

3030 patients with hypercholesterolaemia who had not reached NCEP ATP III target LDL-C levels. [information redacted] The statin treatment at baseline was predominantly atorvastatin (40%), simvastatin (29%) and pravastatin (21-22%).

The LS mean percentage change from baseline in LDL-C was -25.8 and -2.7 in the ezetimibe and placebo groups, respectively, giving a statistically significant (p<0.001) difference of -23.1% (95% CI: -24.4, -21.7) (Table 3). For the analysis of the primary endpoint by NCEP ATP III risk category, a significantly greater reduction in LDL-C was seen with ezetimibe than placebo across the three subgroups (Table 4). Target LDL-C level attainment was significantly greater in the ezetimibe group (74.9% versus 28.3%) with an adjusted OR of 9.81 (95% CI: 8.08, 11.90, p<0.001). This was also the case across the three NCEP ATP III risk groups.

This study demonstrated, in patients not attaining their target LDL-C level despite statin therapy, that the addition of ezetimibe 10 mg per day resulted in a significantly greater reduction in LDL-C levels than placebo, with consistent results across CHD risk categories.

Table 3. Study 040 Analysis of percent change from baseline in LDL-C (mg/dL). Modified Intent-to-Treat Population.

Statistic	Placebo (N=968)	Ezetimibe 10 mg (N=1940)
Baseline		
Mean (mg/dL)	129.4	128.9
SD	32.2	28.8
Postbaseline		
Mean (mg/dL)	124.8	95.4
SD	32.7	26.7
Percent Change From Baseline[†]		
LS Mean	-2.7	-25.8
SE	0.8	0.6
(95% CI)	(-4.2, -1.2)	(-27.0, -24.5)
p-Value[‡]	<0.001	<0.001
Difference: Ezetimibe 10 mg - Placebo[†]		
LS Mean	-	-23.1
SE	-	0.7
(95% CI)	-	(-24.4, -21.7)
p-Value[§]	-	<0.001

[†] Based on ANOVA model with terms for treatment and strata: NCEP ATP III risk category (using lipid values from Screening, Visit 1) and percentage above LDL-C goal at Visit 1(<8%, ≥8% to <18%, ≥18% to <30%, or ≥30%).

[‡] P-value is from paired t-test on within-treatment change from baseline based on ANOVA model above.

[§] P-Value for comparison between Ezetimibe 10 mg and Placebo groups.

- Not applicable.

Table 4. Study P040. Study 040 Analysis of percent change from baseline in LDL-C (mg/dL) by NCEP ATP III Risk Categories. Modified Intent-to-Treat Population.

	NCEP ATP III Category					
	CHD or CHD Risk Equivalent†		Multiple (≥2) Risk Factors		<2 Risk Factors	
Statistic	Placebo (N=763)	Ezetimibe 10 mg (N=1496)	Placebo (N=164)	Ezetimibe 10 mg (N=354)	Placebo (N=41)	Ezetimibe 10 mg (N=90)
Baseline						
Mean (mg/dL)	123.5	122.7	147.6	147.1	166.6	161.7
SD	28.7	25.6	29.7	27.3	49.2	31.5
Postbaseline						
Mean (mg/dL)	120.1	90.3	139.7	111.2	152.2	118.4
SD	30.6	23.3	31.0	29.8	45.8	30.2
Percent Change From Baseline‡						
LS Mean	-1.1	-25.1	-4.1	-23.8	-5.8	-25.7
SE	0.7	0.5	1.4	1.0	2.8	1.9
(95% CI)	(-2.4, 0.2)	(-26.0, -24.2)	(-6.8, -1.4)	(-25.7, -21.9)	(-11.2, -0.3)	(-29.4, -22.0)
Difference: Ezetimibe 10 mg-Placebo‡						
LS Mean	-	-24.0	-	-19.7	-	-20.0
SE	-	0.8	-	1.7	-	3.4
(95% CI)	-	(-25.5, -22.4)	-	(-23.0, -16.4)	-	(-26.6, -13.4)
p-Value	-	<0.001	-	<0.001	-	<0.001
p-Value for Effects‡:	Treatment:	<0.001				
	Percentage above LDL-C target:	<0.001				
	NCEP ATP III risk category:	0.248				
	Treatment*risk category interaction:	0.046				

† Includes patients with ≥ 2 risk factors with a >20% 10-year risk of CHD by Framingham risk scoring.
‡ Based on analysis of variance model with terms for treatment, percentage above LDL-C target at Visit 1 (<8%, ≥8% to <18%, ≥18% to <30%, or ≥30%), NCEP ATP III risk category, and treatment by NCEP ATP III risk category interaction.
- Not applicable.

6.1.1.3. Co-administration versus statin up-titration

Two multicentre, double blind, randomised, 14 week studies evaluated the efficacy of ezetimibe co-administration with a statin compared to statin dose titration in patients not reaching LDL-C targets (NCEP ATP II) despite statin therapy. **P0700** was with simvastatin and **P0693** with atorvastatin (discussed below). In the 100 patients in P0700, after 4 weeks of treatment, the mean percentage reduction in LDL-C was -24.5% for those treated with ezetimibe and simvastatin 20 mg compared to -11.1% for those treated with up-titrated simvastatin 40 mg ($p<0.01$).

6.1.2. Efficacy of ezetimibe with atorvastatin

Studies P0692, P0693, P2173 and P1030 were evaluated in the ezetimibe submission and the remaining studies discussed in this section (P2154, P1418, P1417, P079, P090, P112) were evaluated in the [information redacted] submission.

6.1.2.1. Co-administration with atorvastatin

6.1.2.1.1. Study P0692 and extension P2154

P0692 was a phase III, randomised, double-blind, placebo-controlled, parallel-group study in 628 subjects with primary hypercholesterolaemia (LDL-C ≥145 mg/dL and ≤250 mg/dL after drug wash-out). After a 4 week single-blind placebo run-in period, subjects were randomised to one of 10 treatment groups: ezetimibe 10 mg, atorvastatin (10, 20, 40, or 80 mg), ezetimibe 10 mg plus atorvastatin (10, 20, 40, or 80 mg), or placebo. Treatment was taken once daily in the morning for 12 weeks.

There were 628 patients randomised and 576 (92%) completed the study. For the primary analysis, data were pooled in the four atorvastatin monotherapy groups and the four atorvastatin plus ezetimibe groups. The addition of ezetimibe to atorvastatin was more effective than atorvastatin alone ($p<0.01$) or ezetimibe alone ($p<0.01$) in reducing LDL-C levels after the 12 weeks of treatment (Table 5). It was also found that the addition of ezetimibe to atorvastatin 10 mg or 20 mg resulted in a significantly greater mean percentage reduction in LDL-C than the next higher dose of the atorvastatin monotherapy (20 mg and 40 mg, respectively).

Table 5. Study P0692 Least square changes from baseline to end-point in plasma concentration of various lipid-related variables in the intent-to-treat data set.

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	0<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

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 253 for the Coadministration group, and 61 to 65 for the Ezetimibe Alone group.

P02154 was a randomised, placebo-controlled, double-blind (to ezetimibe) 12 month extension study. Patients who completed from P0692 were eligible and were randomised in a 4:1 ratio to receive daily ezetimibe 10 mg or matching placebo on top of open-label atorvastatin 10 mg per day. Titration of atorvastatin (to 20, 40 then 80 mg) occurred at 6 weekly intervals if the patient's NCEP ATP II target LDL-C level had not been attained. Down titration was allowed if LDL-C was <50 mg/dL. The investigator was blinded to LDL-C results and was only provided with information on whether the patient needed to have the atorvastatin dose titrated. Other lipid lowering medications were prohibited.

Of the 576 patients completing P0692, 246 (39%) entered the extension study, 45 in the atorvastatin group and 201 in the atorvastatin + ezetimibe group. There were 41 (17%) who discontinued, 6/45 (13%) in the atorvastatin group and 35/201 (17%) in the atorvastatin + ezetimibe group. The discontinuation rate due to AEs was 7% and 9%, respectively. The mean duration of exposure was similar at 10.6 months and 10.7 months, respectively. The groups were well balanced on baseline characteristics except gender with fewer females in the atorvastatin than the atorvastatin + ezetimibe group (49% versus 61%). The mean baseline LDL-C was 185.6 mg/dL and 181.1 mg/dL, respectively.

The reduction in LDL-C was evident at 6 weeks and maintained over the year, with a greater response in the atorvastatin + ezetimibe group (-48.4% versus -38.6% at study end) (Table 6). Only small numbers had their atorvastatin dose titrated: 22% (10/45) of the atorvastatin group and 9% (19/201) of the atorvastatin + ezetimibe group. For those who did not have a dose titration (i.e. remained on atorvastatin 10 mg) the maintenance of response over the 12 months is seen in Figure 1. The changes in HDL-C, TC and TG were seen by week 6 and maintained over the study duration (Tables 7 and 8).

Comment: The maintenance of response in those who did not have the atorvastatin dose up-titrated may be a biased finding as the group would consist of treatment responders.

Table 6. Study P02154 Mean values and percent change from baseline in calculated and direct low-density-lipoprotein cholesterol over time.

	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

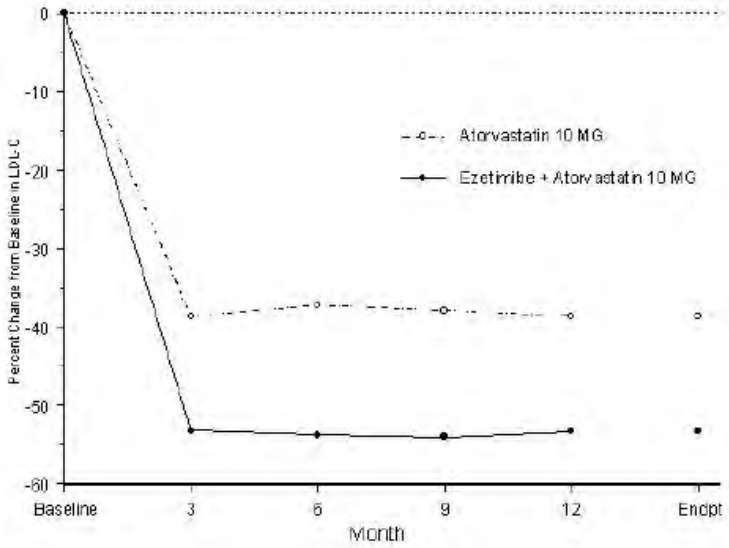
a: Subject 21/1308, who was randomized to coadministration therapy, initiated treatment in P02154 on atorvastatin monotherapy due to a dispensing error, and is reported in the monotherapy group (see **Section 10.2.** for details).

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.

Figure 1. Study P02154. Mean percent change from baseline in calculated LDL-C for subjects who completed P02154 and remained on atorvastatin 10 mg or ezetimibe 10 mg plus atorvastatin 10 mg throughout the study.



Mean Percent Change From Baseline in Calculated LDL-C for Subjects Who Completed P02154 and Remained on Atorvastatin 10 mg or Ezetimibe 10 mg Plus Atorvastatin 10 mg Throughout the Study
(n = 28 to 29 subjects on atorvastatin 10 mg and 145 to 151 subjects on ezetimibe 10 mg + atorvastatin 10 mg at each timepoint)

Table 7 Study P02154 Mean values and percent change from baseline in high-density-lipoprotein cholesterol and total cholesterol over time.

Protocol No. P02154

	Atorvastatin[a]					EZ 10 mg + Atorvastatin				
	n	Actual[b]	Change[b]	% Change	SD of % Change	n	Actual[b]	Change[b]	% Change	SD of % Change
Total Cholesterol (TC)										
Baseline	45	269.79 (6.98)	--	--	--	201	267.89 (6.92)	--	--	--
Week 6	43	199.63 (5.16)	-70.71 (-1.83)	-25.97	10.12	191	163.43 (4.23)	-104.26 (-2.70)	-38.84	10.30
Month 3	40	197.25 (5.10)	-71.76 (-1.86)	-26.38	8.02	189	165.92 (4.29)	-102.42 (-2.65)	-38.02	9.61
Month 6	38	196.74 (5.09)	-70.97 (-1.84)	-26.23	8.10	183	167.72 (4.34)	-100.19 (-2.59)	-37.25	10.00
Month 9	39	194.10 (5.02)	-73.85 (-1.91)	-27.27	10.14	173	170.19 (4.40)	-98.80 (-2.55)	-36.73	12.42
Month 12	39	191.90 (4.96)	-76.05 (-1.97)	-28.10	7.89	169	165.57 (4.28)	-102.24 (-2.64)	-38.08	10.40
Endpoint	45	194.82 (5.04)	-74.96 (-1.94)	-27.46	10.38	201	172.91 (4.47)	-94.78 (-2.45)	-35.39	14.03
HDL-C										
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.

Table 8. Study P02154 Median values and percent change from baseline in triglycerides over time.

	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.

6.1.3. Co-administration versus atorvastatin up-titration

6.1.3.1. Study P0693 and extension P1418

P0693 was a phase III, randomised, double-blind, double-dummy, dose titration study of ezetimibe in addition to atorvastatin in 621 subjects with heterozygous familial hypercholesterolaemia (HeFH) or CHD or multiple cardiovascular risk factors and with primary hypercholesterolemia inadequately controlled after 4 weeks on open label atorvastatin 10 mg (LDL-C ≥130 mg/dL). It was conducted between 2000 and 2001 in 141 centres worldwide. Subjects were randomised in a 1:1 ratio to receive 14 weeks of ezetimibe 10 mg or atorvastatin 10 mg. In addition, all subjects received background open label atorvastatin 10 mg. If the NCEP ATP II target LDL-C level was not met, atorvastatin dose was up-titrated at 4 weekly intervals to a maximum total of 80 mg in the atorvastatin monotherapy group and 40 mg in atorvastatin + ezetimibe group.

For the primary endpoint at week 14, there were more subjects in the atorvastatin + ezetimibe group than the atorvastatin monotherapy group who met the target LDL-C level of ≤100 mg/dL (22% versus 7%, p<0.01). At the end of the study, 85% of the atorvastatin monotherapy group were on the maximal dose of 80 mg while 60% of the atorvastatin +

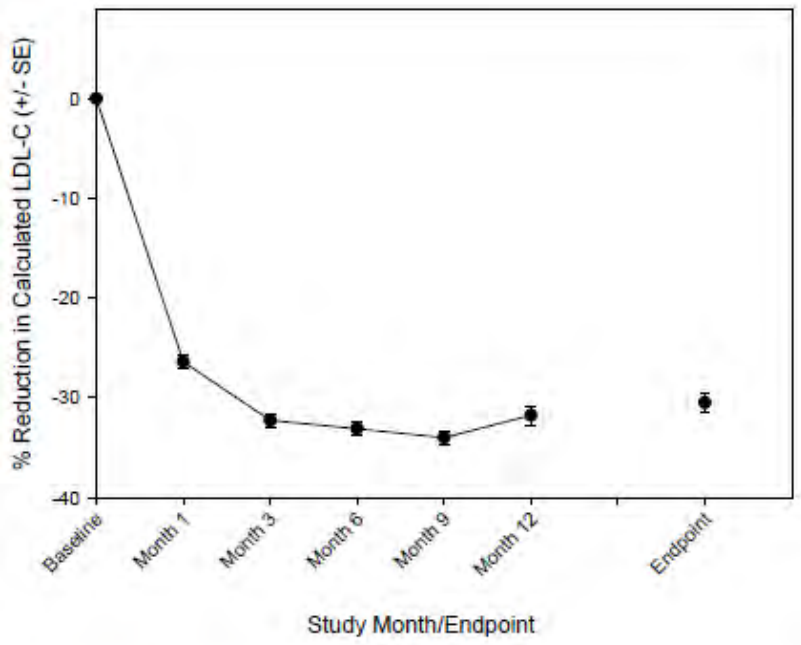
ezetimibe group were on the maximal atorvastatin dose of 40 mg. Target attainment for the subgroup with HeFH was also greater with atorvastatin + ezetimibe (17% versus 4%, p<0.01). At week 4, the mean percentage reduction in LDL-C, TG and TC was significantly greater with atorvastatin 10 mg + ezetimibe than with atorvastatin 20 mg, although there was no difference in HDL-C levels.

P01418 was a 12 month, open label extension study of P0693. All subjects who completed the 14 weeks treatment in P0693 were eligible. Treatment was with once daily ezetimibe 10 mg and atorvastatin 10 mg. After 4 weeks of therapy at the same dose, atorvastatin dose could be up-titrated, at the investigator's discretion, to a maximal dose of 80 mg to achieve NCEP APT II LDL-C target of ≤100 mg/dL.

There were 432 subjects enrolled (70% of the cohort randomised in P0693) and 34 (8%) discontinued with 12 (3%) due to adverse events. The subjects in the extension study had a mean age of 52.2 years, 56% were male, 92% Caucasian and the mean baseline direct LDL-C was 186.6 mg/dL. Cardiovascular risk factors were present in 89% of subjects.

LDL-C reduction was maintained for the 12 months of the study and with a mean reduction of 28% (direct measurement) at the study endpoint (last non-missing value) (Figure 2). Changes in HDL-C, TC and TG were also maintained over the 12 months (Table 9). Target LDL-C of ≤100 mg/dL was attained by 24% of subjects at study endpoint. At this time 63% of subjects were receiving ezetimibe with the lower doses of 10 mg or 20 mg of atorvastatin.

Figure 2. Study P1418 Percent reduction in calculated LDL-C (±SE) from parent study baseline during the extension study.



Percent Reduction in Calculated LDL-C (± SE) From Parent Study Baseline During the Extension Study

n=432 (Baseline), n=416 (Month 1), n=402 (Month 3), n=414 (Month 6), n=399 (Month 9), n=403 (Month 12), and n=430 (Endpoint). Note: Endpoint is defined as the last available non-missing value for each subject. Source Data: Section 14.2.1.1.

Table 9. Study P1418 Changes in HDL-C, TC and TG

	Baseline [a] (n=432)	Month 1 (n=416)[b]	Month 3 (n=402)	Month 6 (n=414)	Month 9 (n=399)[c]	Month 12 (n=403)[d]	Endpoint (n=430)[e]
Direct LDL-C							
Actual	186.57 (4.82)	--	--	--	--	129.02 (3.34)	131.40 (3.40)
Change	--	--	--	--	--	-57.08 (-1.48)	-55.13 (-1.43)
% Change	--	--	--	--	--	-29.39	-28.38
SD of % Chg	--	--	--	--	--	17.44	18.79
Calculated LDL-C							
Actual	186.03 (4.82)	136.90 (3.55)	124.99 (3.24)	123.50 (3.20)	121.73 (3.15)	124.43 (3.22)	127.44 (3.30)
Change	--	-49.37 (-1.28)	-61.01 (-1.58)	-63.07 (-1.63)	-64.75 (-1.68)	-61.35 (-1.59)	-58.73 (-1.52)
% Change	--	-26.40	-32.28	-33.10	-34.00	-31.78	-30.50
SD of % Chg	--	13.36	13.85	15.15	13.11	18.62	20.07
HDL-C							
Actual	49.85 (1.29)	51.50 (1.33)	51.82 (1.34)	51.79 (1.34)	51.68 (1.34)	51.48 (1.33)	51.23 (1.32)
Change	--	1.61 (0.04)	2.01 (0.05)	1.93 (0.05)	1.62 (0.04)	1.47 (0.04)	1.30 (0.03)
% Change	--	3.72	4.20	4.11	3.57	3.30	2.94
SD of % Chg	--	12.09	y12.34	12.51	12.59	12.84	12.97
Total Cholesterol (TC)							
Actual	262.51 (6.79)	211.41 (5.47)	199.40 (5.16)	197.51 (5.11)	195.36 (5.05)	198.24 (5.13)	201.22 (5.20)
Change	--	-51.38 (-1.33)	-63.21 (-1.63)	-65.51 (-1.69)	-67.63 (-1.75)	-64.03 (-1.66)	-61.43 (-1.59)
% Change	--	-19.24	-23.46	-24.14	-25.01	-23.38	-22.44
SD of % Chg	--	10.61	10.95	12.41	10.96	14.73	15.78
Triglyceride (TG)[f]							
Actual	117.00 (1.32)	101.00 (1.14)	99.00 (1.12)	97.00 (1.10)	98.00 (1.11)	100.00 (1.13)	100.00 (1.13)
Change	--	-17.83 (-0.20)	-17.00 (-0.19)	-19.00 (-0.21)	-19.33 (-0.22)	-15.33 (-0.17)	-15.33 (-0.17)
% Change	--	-15.53	-16.77	-17.43	-17.67	-14.29	-14.29

a: Refers to the baseline of Protocol P00693; baseline means (and median for TG) presented are for the Intent-to-Treat Population (n=432).

b: n=414 for calculated LDL-C

c: n=398 for calculated LDL-C

d: n=398 for direct LDL-C

e: n=423 for direct LDL-C

f: Median values are presented for triglycerides.

6.1.3.2. Study P079

Study **P079** was a phase III, multicentre, randomised, double-blind, titration study to evaluate the efficacy and safety of ezetimibe added to atorvastatin 20 mg compared to up titration to atorvastatin 40 mg in hypercholesterolaemic patients with a moderately high risk for CHD. A 4 week (or 5 week for naïve or switching patients) single-blind run-in period on atorvastatin 20 mg was followed by a 6 week treatment period.

This study found that patients with moderately high risk of CHD showed a greater reduction in LDL-C with addition of ezetimibe 10 mg to atorvastatin 20 mg (-30.8%) compared to up-titration of atorvastatin to 40 mg (-10.9%). The between group treatment difference of -19.9% (95% CI: -25.2, -14.5) was statistically significant (p<0.001).

6.1.3.3. Study P090

Study **P090** was a phase III, multicentre, randomised, double-blind, titration study to evaluate the efficacy and safety of ezetimibe added on to atorvastatin 40 mg compared to

up titration to atorvastatin 80 mg in hypercholesterolaemic patients with a high risk for CHD. The study had the same design and methodology as study P079. There was a 4-5 week single blind period and 6 week double blind treatment period.

For patients at high CHD risk not adequately controlled on atorvastatin 40mg, the addition of ezetimibe 10 mg, compared to up-titration of atorvastatin to 80 mg, resulted in a greater reduction in LDL-C after 6 weeks of treatment (-27.4% versus -11.0%) and a greater proportion of patients reaching a target LDL-C of <70 mg/dL (73.6% versus 31.5%).

6.1.3.4. Study P112

Study **P112** was a multicentre, randomised, 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 of CHD. The design was essentially the same as P079 and P090 except there was a forced titration after 6 weeks of treatment in the atorvastatin 20 mg group to 40 mg and a further 6 weeks of treatment. The atorvastatin 10 mg + ezetimibe 10 mg group remained on this regimen for the 12 weeks of treatment.

In high CHD risk elderly (≥65 years) patients with hypercholesterolaemia not adequately controlled with atorvastatin 10 mg, the addition of ezetimibe 10 mg resulted in a significantly greater reduction in LDL-C after 6 weeks of treatment compared to up-titration to atorvastatin 20 mg (Table 10). The combination treatment also resulted in greater LDL-C reduction compared to a further 6 weeks treatment with atorvastatin 40 mg (Table 11). Target LDL-C attainment (<70 mg/dL for those with atherosclerosis and <100 mg/dL for those without) was also greater with the combination compared to up-titration of atorvastatin.

Table 10. Study P112 Analysis of percent change from baseline in LDL=C (mg/dL) at Week 6 (Full Analysis Set Population).

Statistics	Atorva 10 mg + EZ (N=515)	Atorva 20 mg (N=515)
Baseline		
Mean	102.9	101.4
SD	27.8	20.5
Week 6		
Mean	75.2	88.7
SD	25.1	22.7
Percent Change From Baseline at Week 6 †		
LS Mean	-26.7	-12.8
SE	1.0	1.0
(95% CI)	(-28.6, -24.7)	(-14.8, -10.9)
Between-Treatment Difference: Atorva 10 mg + EZ minus Atorva 20 mg ‡		
LS Mean	-13.8	
SE	1.1	
(95% CI)	(-16.0, -11.7)	
p-Value	<0.001	
p -Value for Effects †		
Treatment	<0.001	
Baseline LDL-C	<0.001	
AVD status	0.388	

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, baseline LDL-C and AVD status.

‡ LS Mean of treatment difference, SE, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.

Table 11. Study P112 Analysis of percent change from baseline in LDL=C (mg/dL) at Week 12 (Full Analysis Set Population).

Statistics	Atorva 10 mg + EZ (N=516)	Atorva 20 mg/Atorva 40 mg (N=509)
Baseline		
Mean	102.9	101.7
SD	27.8	20.6
Week 12		
Mean	79.1	83.1
SD	31.6	24.8
Percent Change From Baseline at Week 12 †		
LS Mean	-22.5	-17.9
SE	1.3	1.3
(95% CI)	(-25.0, -19.9)	(-20.5, -15.4)
Between-Treatment Difference: Atorva 10 mg + EZ minus Atorva 20 mg/Atorva 40 mg ‡		
LS Mean	-4.6	
SE	1.4	
(95% CI)	(-7.4, -1.8)	
p-Value	0.001	
p -Value for Effects †		
Treatment	0.001	
Baseline LDL-C	0.008	
AVD status	0.999	

Atorva 20 mg/Atorva 40 mg = Atorva 20 mg for 6 weeks followed by titration to Atorva 40 mg for an additional 6 weeks.

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, baseline LDL-C and AVD status.

‡ LS Mean of treatment difference, SE, p-Value, and 95% confidence interval on LS Mean between treatments based on the ANCOVA above.

6.2. Homozygous familial hypercholesterolaemia

P1030 was a 12 week, randomised, double-blind, parallel-group, phase III study in 50 subjects with HoFH with LDL-C ≥100 mg/dL while receiving atorvastatin 40 mg or simvastatin 40 mg. Subjects were randomised to either ezetimibe 10 mg + statin (40 mg or 80 mg of atorvastatin or simavastatin) or statin alone (atorvastatin or simvastatin 80 mg). Regular LDL apheresis or stable resin therapy continued during the study.

Of the 50 randomised subjects, 17 received statin alone and 33 received ezetimibe + statin (with 24 receiving ezetimibe + atorvastatin). At baseline there was a greater proportion of the ezetimibe + statin group, than the statin alone group, who were receiving concomitant LDL apheresis (58% versus 47%). Baseline LDL-C was also slightly lower in this group (321 versus 345.9 mg/dL). The co-administration of ezetimibe + statin (40 mg or 80 mg) resulted in a significantly greater reduction of direct LDL-C compared to a statin alone (80 mg) (-20.7% versus -6.7%) with a difference of -14.1% (95% CI: -24.1,-4.01, p=0.007). Ezetimibe + statin 80 mg also produced a significant difference compared to statin 80 mg of -20.5% (p=0.001).

P1417 was a 24 month, open label, multicentre extension study of P1030. Eligible subjects needed to have completed the 12 week double-blind period of study P1030. Treatment was with ezetimibe 10 mg and atorvastatin 40 mg or simvastatin 40 mg. The same statin as used in P1030 was continued. After 4 weeks of treatment, the statin dose could be up-titrated to 80 mg to achieve NCEP ATP II LDL-C target of ≤100 mg/dL. As with P1030, regular LDL apheresis or stable resin therapy could be continued during the study.

Of the 50 subjects randomised in P1030, 48 completed the study and 44 of these (88%) enrolled in the extension study with 36 treated with atorvastatin. The mean LDL-C reduction from baseline to study endpoint was 13.8% by direct measurement and 15.3%

by calculated measurement. Over this time, the reduction in TG was -15.1% and TC was -12.3% and there was an 8.6% increase in HDL-C (Table 12). Efficacy appeared consistent between males and females while the numbers of non-Caucasians and those aged <18 years were too small to draw conclusions. Only one subject reached the LDL-C target of 100 mg/dL. Of the 36 who received ezetimibe + atorvastatin, 34 (94%) had the atorvastatin dose titrated and the mean LDL-C reduction from baseline to study endpoint was -14.9%.

Table 12. Study P1417 Mean or median values and percent change from baseline for lipid parameters in mg/dL (SD) over time.

	Baseline[a] (n = 44)	Month 6[b] (n = 43)	Month 12 (n = 34)	Month 18 (n = 36)	Month 24 (n = 34)	Endpoint (n = 44)
Calculated LDL-C (mg/dL)						
Actual	337.21 (120.77)	249.58 (103.97)	258.15 (100.3)	260.83 (105.98)	278.03 (125.49)	282.95 (119.35)
Change		-92.77 (81.89)	-88.10 (93.99)	-83.88 (79.12)	-66.52 (80.97)	-54.26 (81.55)
% Change		-25.90 (19.84)	-23.30 (21.42)	-22.66 (18.57)	-18.32 (20.82)	-15.30 (22.29)
Triglyceride[c] (mg/dL)						
Actual	88.67	78.00	78.50	69.50	84.50	80.00
Change		-7.67	-12.00	-15.17	-14.17	-13.83
% Change		-9.67	-11.65	-17.84	-16.38	-15.10
HDL-C (mg/dL)						
Actual	40.08 (10.69)	41.81 (12.12)	43.24 (12.08)	42.92 (12.07)	44.12 (13.26)	43.39 (12.51)
Change		1.49 (6.45)	2.05 (5.61)	2.50 (6.74)	3.68 (7.03)	3.31 (6.54)
% Change		4.36 (14.83)	5.79 (12.57)	7.23 (16.95)	9.43 (17.32)	8.57 (16.31)
Total Cholesterol (mg/dL)						
Actual	398.51 (123.75)	308.33 (104.82)	319.74 (100.45)	322.44 108.76)	341.21 (128.46)	344.89 (121.19)
Change		-95.03 (85.10)	-89.86 (93.65)	-84.46 (81.46)	-65.75 (84.74)	-53.63 (85.31)
% Change		-22.19 (17.83)	-19.79 (18.52)	-19.01 (16.46)	-14.83 (18.53)	-12.33 (19.81)

SD=Standard Deviation

a: Baseline means (and median for TG) presented are for the intent-to-Treat Population.

b: Time points are defined in Section 9.9.1, Table 8. Data was collected for the time points at Baseline, Month 1, Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, and Endpoint. The time points at the end of 6 month periods are displayed here to facilitate comparisons.

c: Median values are presented for TG.

6.3. Mixed hyperlipidaemia

The [information redacted] submission contained a post-hoc subgroup analysis from the factorial study P0692. In this study there were 139 patients who received atorvastatin and had baseline TG ≥200 mg/dL. In this group, 66 received atorvastatin (doses pooled) and 73 atorvastatin + ezetimibe. The mean TG levels were 252.6 and 260.1 mg/dL, respectively. The mean percentage reduction from baseline in LDL-C was -56.5% in the ezetimibe + all atorvastatin group compared to -45.5% in the all atorvastatin group, with a difference of -11% (95% CI: -15.8, -6.2). This result was similar to those with TG <200 mg/dL. The reduction in TG in those with a baseline ≥200 mg/dL was -38.5% versus -30.6% with atorvastatin monotherapy with a difference of -7.9% (95% CI: -15.4,-0.49). There was also a positive result on other lipid variables (TC, HDL-C, non-HDL-C and Apo B) that was greater with the combination than with atorvastatin monotherapy and similar to that seen in patients with TG <200 mg/dL (Tables 13A-D).

Table 13A. Mean percent changes in total cholesterol (TC) from baseline at study endpoint in patients with baseline TG <200 mg/dL and ≥200 mg/dL Modified Intent-to-Treat Approach. P692

	Baseline TG <200 mg/dL		Baseline TG ≥200 mg/dL	
	All Atorva	EZ 10 mg + All Atorva	All Atorva	EZ 10 mg + All Atorva
Baseline				
N	182	182	66	73
Mean (mg/dL)	264.7	262.0	279.0	280.2
SD	24.9	26.7	25.9	25.7
Study Endpoint				
N	180	180	66	73
Mean (mg/dL)	181.82	155.44	182.95	160.89
SE	2.8	2.7	4.2	4.3
Percent Change From Baseline at Study Endpoint				
LS Mean	-31.37	-40.54	-34.24	-42.48
Difference From All Atorva				
LS Mean (95% CI)	-	-9.17 (-11.90,-6.44)	-	-8.24 (-12.22,-4.25)
EZ = ezetimibe. All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.				

Table 13 B. Mean percent changes in HDL-C from baseline at study endpoint in patients with baseline TG <200 mg/dL and ≥200 mg/dL Modified Intent-to-Treat Approach. P692

	Baseline TG <200 mg/dL		Baseline TG ≥200 mg/dL	
	All Atorva	EZ 10 mg + All Atorva	All Atorva	EZ 10 mg + All Atorva
Baseline				
N	182	182	66	73
Mean (mg/dL)	56.2	53.5	46.6	44.2
SD	12.4	13.1	9.3	8.4
Study Endpoint				
N	180	180	66	73
Mean (mg/dL)	57.82	56.23	49.59	49.16
SE	1.0	1.0	1.2	1.2
Percent Change From Baseline at Study Endpoint				
LS Mean	3.18	5.49	7.07	11.89
Difference From All Atorva				
LS Mean (95% CI)	-	2.30 (-0.04,4.64)	-	4.82 (0.68,8.97)
EZ = ezetimibe. All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.				

Table 13C. Mean percent changes in total cholesterol non-HDL-C from baseline at study endpoint in patients with baseline TG <200 mg/dL and ≥200 mg/dL Modified Intent-to-Treat Approach. P692

	Baseline TG <200 mg/dL		Baseline TG ≥200 mg/dL	
	All Atorva	EZ 10 mg + All Atorva	All Atorva	EZ 10 mg + All Atorva
Baseline				
N	182	182	66	73
Mean (mg/dL)	208.5	208.6	232.4	236.1
SD	23.3	23.8	24.8	25.0
Study Endpoint				
N	180	180	66	73
Mean (mg/dL)	123.99	99.22	133.36	111.73
SE	2.7	2.6	4.1	4.3
Percent Change From Baseline at Study Endpoint				
LS Mean	-40.7	-52.2	-42.4	-52.5
Difference From All Atorva				
LS Mean (95% CI)	-	-11.5 (-14.88,-8.15)	-	-10.1 (-15.02,-5.30)
EZ = ezetimibe. All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.				

Table 13D. Mean percent changes in Apolipoprotein B (ApoB) from baseline at study endpoint in patients with baseline TG <200 mg/dL and ≥200 mg/dL Modified Intent-to-Treat Approach. P692

	Baseline TG <200 mg/dL		Baseline TG ≥200 mg/dL	
	All Atorva	EZ 10 mg + All Atorva	All Atorva	EZ 10 mg + All Atorva
Baseline				
N	182	182	66	73
Mean (mg/dL)	164.2	164.6	177.3	184.6
SD	20.7	24.1	22.8	25.9
Study Endpoint				
N	177	176	64	72
Mean (mg/dL)	103.96	89.59	113.13	99.08
SE	2.0	2.0	3.1	3.1
Percent Change From Baseline at Study Endpoint				
LS Mean	-36.5	-45.1	-35.3	-45.9
Difference From All Atorva				
LS Mean (95% CI)	-	-8.6 (-11.85,-5.36)	-	-10.6 (-15.72,-5.45)

EZ = ezetimibe.
All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.

Further to clinical questions in the [information redacted] submission the sponsor provided subgroup analyses for subjects with baseline triglycerides ≥150 or <150 mg/dL from the 3 studies P079, P090 and P112. In P079, which assessed atorvastatin 20 mg + ezetimibe, the LS mean percentage change from baseline in LDL-C at week 6 was -33.5% (95% CI: -38.7,-28.3) for those with baseline TG level of ≥150 mg/dL (n=49). This compared favourably with the reduction in those with baseline TG <150 mg/dL (n=43)(-27.7%, 95% CI: -33.2, 22.2).

In P090 (atorvastatin 40 mg + ezetimibe), the LS mean LDL-C percentage change from baseline at week 6 in subjects with baseline TG ≥150 mg/dL was -30.1% (95% CI: -33.7, -26.5) (n=104) compared to -25.7% (95% CI: -28.5, -22.9) in those with baseline TG <150 mg/dL (n=173). In P112 (atorvastatin 10 mg + ezetimibe in elderly patients), the LS mean reduction in LDL-C at week 12 was -25.3% (95% CI: -28.5,-22.1) for those with baseline TG ≥150 mg/dL (n=127) compared to -27.2% (95% CI: -29.3, -25.0) in those with baseline TG <150 mg/dL (n=388).

These three studies provided data on an additional 280 patients with elevated triglycerides with results indicating a consistent effect on lowering LDL-C in this subgroup. The magnitude of LDL-C reduction was in line with that seen in patients with baseline triglyceride levels <150 mg/dL.

6.4. Analyses performed across trials (pooled analyses and meta-analyses)

No data submitted.

6.5. Evaluator's conclusions on clinical efficacy

The clinical efficacy data were derived from studies submitted as part of the Ezetrol (ezetimibe, 99/3917/3). The evaluator also considered the evidence submitted as part of the [information redacted] (ezetimibe + atorvastatin [information redacted]) submission because it is intended that a composite pack will be used clinically in the same manner as a fixed dose combination product. Therefore, the efficacy and safety data from the [information redacted] submission are relevant to this submission. The clinical study data from the [information redacted] submission were subsequently provided in response to s31 questions.

All studies were in patients with primary hypercholesterolaemia apart from P1030 and its extension in HoFH. The evaluator had access to the clinical evaluation reports relating to these submissions as well as all clinical study data from the ezetimibe submission.

Data on ezetimibe efficacy with statins were primarily located in the original ezetimibe submission. Co-administration of ezetimibe with a statin was derived from four factorial studies (P0679, P0680, P0691 and P0692) which assessed lovastatin, simvastatin, pravastatin, and atorvastatin, respectively. Data on ezetimibe therapy added to ongoing statin therapy comes from two placebo-controlled studies, P2173 and P040[information redacted] Co-administration of ezetimibe with a statin compared to up-titration of the statin dose was assessed in two studies, P0700 (simvastatin) and P0693 (atorvastatin).

Data on the use of ezetimibe in combination with atorvastatin specifically come from five short term studies (6 to 14 weeks) in patients with primary hypercholesterolaemia (P079, P090, P112, P0692 and P0693) [information redacted]**.** One study (P692) had a factorial design. The other four (P079, P090, P112 and P693) were add-on studies which compared the addition of ezetimibe to up-titration of the atorvastatin dose. All had 6 weeks treatment duration except P693 which had 14 weeks.

Study P693 was in patients with CHD or multiple risk factors and compared ezetimibe + atorvastatin 10 mg to atorvastatin 20 mg with possible up-titration of atorvastatin in either group. In study P079 in patients with moderate and high risk of CHD, treatment compared ezetimibe + atorvastatin 20 mg to atorvastatin 40 mg, while P090 in the same population compared ezetimibe + atorvastatin 40 mg to atorvastatin 80 mg. Study P112 was in the elderly and compared ezetimibe + atorvastatin 10 mg to atorvastatin 20 mg and 40 mg.

Long term data of ezetimibe with atorvastatin in primary hypercholesterolaemia came from two 52 week studies, one controlled (P2154 the extension of P692) which included 246 patients and one open label and uncontrolled (P1418 the extension of P693) which included 432 patients. [information redacted]

Data in the special population with HoFH came from the 50 patients (12 on atorvastatin 80 mg and 24 on ezetimibe + atorvastatin 40 mg or 80 mg) treated for 12 weeks in study P1030. There was also a two year open label extension (P1417) which included 44 patients of whom 36 received ezetimibe + atorvastatin 40 mg or 80 mg.

Data on the population with mixed hyperlipidaemia were derived from a subgroup of 139 patients in P0692 who had hypercholesterolaemia with TG ≥200mg/dL. In this group, 66 received atorvastatin and 73 ezetimibe + atorvastatin for 12 weeks. Following questions in the [information redacted] evaluation, further post-hoc analysis data from studies P079, P090 and P112 were provided including an additional 280 patients with TG ≥150mg/dL.

The main clinical efficacy endpoint was mean percentage change from baseline in LDL-C. In general, LDL-C level was calculated using the Friedewald equation. Studies excluded patients with TG >350 mg/dL. The proportion of patients attaining LDL-C targets was the main secondary efficacy variable (primary in P693). Safety was the primary objective in the long term studies with efficacy a secondary objective. Lipid assessment was centralised for all studies.

The four factorial studies (P0679, P0680, P0691, P0692) demonstrated an increased mean percentage LDL-C reduction with ezetimibe plus the stain compared to monotherapy (difference of approximately -14%). The effect was consistent across the four statins (lovastatin, simvastatin, pravastatin, and atorvastatin).

When ezetimibe was added to ongoing statin therapy (P2173 and P040) there was a significantly greater reduction in LDL-C levels than placebo (difference of -23.1% in P040 and -21.5% in P2173), with consistent results across CHD risk categories. When the

subgroup of patients taking atorvastatin was assessed, efficacy was comparable to the overall statin group (Table 14).

Table 14. Mean percent changes in LDL-C from baseline at study endpoint Modified Intent-to-Treat Approach. P2173, P040, P079 and P090

	P2173		P040		P079		P090	
	Placebo + Atorva	EZ 10 mg + All Atorva	Placebo + All Atorva	EZ 10 mg + All Atorva	Atorva 40 mg	EZ 10 mg + Atorva 20 mg	Atorva 80 mg	EZ 10 mg + Atorva 40 mg
Baseline								
N	162	146	386	769	92	92	279	277
Mean (mg/dL)	133.75	104.81	130.7	129.2	118.1	120.3	89.7	88.6
SD	-	-	34.4	30.6	17.2	19.7	16.0	16.3
Percent Change From Baseline at Study Endpoint								
LS Mean	-4.01	-24.98	-4.2	-27.2	-10.9	-30.8	-11.0	-27.4
Difference From All Atorva								
LS Mean (95% CI)	-	-21.0** (-24.2, -17.8)	-	-23.0*** (-25.2, -20.8)	-	-19.9*** (-25.2, -14.5)	-	-16.3*** (-19.4, -13.2)
p-Value†		p<0.01		p<0.001		p<0.001		p<0.001

*p<0.05; **p<0.01;***p<0.001.
EZ = ezetimibe.
All Atorva = atorvastatin (10, 20, 40, and 80 mg) pooled across doses.
† p-Value for the primary comparison (EZ 10 mg + All Atorva versus All Atorva).
- = Not Available

The addition of ezetimibe to atorvastatin resulted in a significantly greater LDL-C reduction than up-titrating to the next atorvastatin dose (P079, P090, P112 and P693)(Tables 14-16). Target LDL-C level attainment was greater with ezetimibe compared to placebo added to atorvastatin and also greater when ezetimibe was added to atorvastatin compared to up-titrating the atorvastatin dose.

Table 15. Mean percent changes in LDL-C from baseline at 6 and 12 Weeks. Full Analysis Set Population. P112

	Week 6		Week 12	
	Ezetimibe 10 mg + Atorvastatin 10 mg	Atorvastatin 20 mg + Placebo	Ezetimibe 10 mg + Atorvastatin 10 mg	Atorvastatin 20/40 mg + Placebo
Baseline				
N	515	515	516	509
Mean (mg/dL)	102.9	101.4	102.9	101.7
SD	27.8	20.5	27.8	20.6
Endpoint (Week 6 or 12)				
Mean (mg/dL)	75.2	88.7	79.1	83.1
SD	25.1	22.7	31.6	24.8
Percent Change From Baseline at Study Endpoint				
LS Mean	-26.7	-12.8	-22.5	-17.9
Between-Treatment Difference				
LS Mean (95% CI)	-13.8*** (-16.0, -11.7)	-	-4.6*** (-7.4,-1.8)	-
*p<0.05; **p<0.01;***p<0.001.				

Table16. Mean percent changes in LDL-C from baseline at 4 weeks. Modified Intent-to-Treat Approach. P693

	Atorva 20 mg	EZ 10 mg + Atorva 10 mg
Baseline		
N	316	305
LS Mean (mg/dL)	186.84	185.93
SE	2.62	2.66
Percent Change From Baseline at Study Endpoint (4 wks)		
LS Mean	-8.99	-23.84
Difference From All Atorva		
LS Mean (95% CI)	-	-14.85** (-16.87, -12.83)
*p<0.05; **p<0.01. EZ = ezetimibe. Atorva = atorvastatin.		

There was very limited long term efficacy data with ezetimibe and atorvastatin co-administration in the initial ezetimibe submission. The two long term studies in the [information redacted] submission filled this gap. After 52 weeks of treatment in these two studies, there was maintenance of LDL-C reduction and the proportion attaining LDL-C target levels that were achieved in the short term studies.

On cessation of ezetimibe (P2173R) lipid levels returned to baseline levels with no evidence of a rebound increase.

The effect on the reduction of other lipids (TG, TC, Apo B and non-HDL-C) were also more favourable with the combination treatment. There was less of an effect on increasing HDL-C.

Efficacy was seen in the small group of patients with HoFH and maintained for 2 years of treatment. Efficacy was also consistent across subgroups of age and gender. In post-hoc analyses, which included 419 patients with mixed hyperlipidaemia (TG ≥150 mg/dL in P079, P090 and P112 and TG ≥200 mg/dL in P0692), results indicated a consistent effect on lowering LDL-C in this subgroup. The magnitude of LDL-C reduction was in line with that seen in patients with baseline triglyceride levels <150 mg/dL.

7. Clinical safety

7.1. Studies providing evaluable safety data

The most relevant source of safety data for the composite pack comes from the [information redacted] submission, the data for which was provided in the response to the s31 questions. The safety data from that clinical evaluation report have been reproduced here. In that submission there were 11 studies which provided evaluable safety data and they were grouped into three data pools for the safety analyses:

- Core Safety pool consisted of the seven controlled short term (6 to 14 weeks) studies P040, P079, P090, P112, P692, P693 and P2173. These studies included 4569 patients with 2041 and 2403 randomised to atorvastatin monotherapy and ezetimibe 10 mg + atorvastatin (all doses), respectively. There were also 60 and 65 patients who were randomised to placebo or ezetimibe monotherapy, respectively.
- Long Term (12 month) studies P2154 and P1418. These studies included 246 and 432 patients, respectively. These studies were analysed individually as P2154 was randomised (ezetimibe + atorvastatin versus atorvastatin) and blinded, while P1418 was open label (ezetimibe + atorvastatin).
- Special Population studies consisted of P1030 and P1417 in HoFH. There were 36 patients in P1030 (24 receiving ezetimibe + atorvastatin) and 35 (who received ezetimibe + atorvastatin) in the extension P1417.

In the efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by questioning at each study visit.
- AEs of particular interest included allergic reaction/rash AEs, gallbladder related AEs, gastrointestinal related AEs, liver effects (hepatitis, ALT and AST elevation, potential Hy's Law cases[1]), and creatinine phosphokinase (CK) and muscle-related symptoms.

[1] A potential Hy's Law case was defined as ALT or AST ≥3x ULN with ALP ≤2x ULN and total BR >2x ULN.

- Laboratory tests, including blood chemistry (including AST, ALT, and CK), haematology and urinalysis were performed at baseline and study endpoint as well as at specified intervals. Thyroid function was assessed in P693, P1030 and P1417.
- ECGs were conducted in P692, P693, P2173, P1030 and P1418.
- Physical examination and vital signs.

Safety was based on analysis of all randomised patients who took at least one dose of study medication.

In addition to this main safety analysis, the safety data from the Ezetrol submission has been summarised under *Ezetrol Safety data* below.

7.2. Pivotal studies that assessed safety as a primary outcome

In the two long term extension studies (P2154 and P1418) safety was the primary objective. The data from these studies are discussed below.

7.3. Patient exposure

In the core safety pool, the mean treatment duration was 82 days for placebo and ezetimibe monotherapy, 67 days for atorvastatin monotherapy and 63 days for ezetimibe + atorvastatin (all doses) (Table 17). Details by dose are in Table 18.

Table 17. Scope of the core safety pool and patient population treated with placebo, ezetimibe monotherapy, atorvastatin monotherapy and ezetimibe +atorvastatin

	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)				

Table 18. Treatment by dose. Core safety pool.

Duration (Days)	Atorva 10 mg (N= 223) n(%)	Atorva 20 mg (N=1069) n(%)	Atorva 40 mg (N=1116) n(%)	Atorva 80 mg (N= 714) n(%)	EZ 10 mg + Atorva 10 mg (N=1207) n(%)	EZ 10 mg + Atorva 20 mg (N= 693) n(%)	EZ 10 mg + Atorva 40 mg (N= 741) n(%)	EZ 10 mg + Atorva 80 mg (N= 208) n(%)	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	5(2.2)	4(0.4)	8(0.7)	5(0.7)	6(0.5)	10(1.4)	2(0.3)	3(1.4)	0(0.0)	1(1.5)	18(0.9)	19(0.8)
8 to 21	2(0.9)	19(1.8)	12(1.1)	25(3.5)	17(1.4)	7(1.0)	21(2.8)	4(1.9)	1(1.7)	0(0.0)	30(1.5)	35(1.5)
22 to 42	53(23.8)	669(62.6)	694(62.2)	457(64.0)	358(29.7)	348(50.2)	411(55.5)	52(25.0)	1(1.7)	1(1.5)	431(21.1)	579(24.1)
43 to 78	108(48.4)	317(29.7)	342(30.6)	169(23.7)	247(20.5)	265(38.2)	252(34.0)	98(47.1)	3(5.0)	5(7.7)	540(26.5)	770(32.0)
79 to 115	55(24.7)	58(5.4)	58(5.2)	58(8.1)	578(47.9)	58(8.4)	55(7.4)	51(24.5)	55(91.7)	58(89.2)	1010(49.5)	984(40.9)
> 115	0(0.0)	1(0.1)	1(0.1)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	10(0.5)	11(0.5)
Missing	0(0.0)	1(0.1)	1(0.1)	0(0.0)	0(0.0)	5(0.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.1)	5(0.2)
Range	1 to 105	1 to 123	1 to 120	1 to 104	1 to 120	1 to 110	1 to 105	1 to 96	10 to 95	4 to 102	1 to 162	1 to 136
Mean	56	43	44	41	63	47	43	55	82	82	67	63
Median	50	42	42	42	72	42	42	49	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.

For the long term studies, the mean treatment duration in P2154 was 11 months in both groups. In P1418, with the primary study P693 included, the mean exposure to ezetimibe and atorvastatin was 11.9 months in the 521 patients.

For patients with HoFH, the mean exposure in P1030 was 82 days and 87 days in the all atorvastatin and ezetimibe + atorvastatin groups, respectively. In P1417 combined with P1030, the mean exposure to the combination was 23.5 months in the 36 patients.

In the short term studies, 51% were male and 87% white. The mean age in the ezetimibe + atorvastatin group was 61.6 years, 69% had a pre-existing vascular disorder and 53% had a cardiac disorder. For P1030 in HoFH, the population treated with the combination had a mean age of 32.2 years, 58% were female and 92% white.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Short term studies

In the core safety pool of 4569 patients, AEs were reported by 34 (56.7%), 41 (63.1%), 756 (37.0%), and 828 (34.5%) patients in the placebo, ezetimibe, atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups, respectively. The exposure-adjusted event rate per 100 patient years was lowest in the ezetimibe + atorvastatin group (209.5) compared to the 305.5, 390.4 and 216.8 in the placebo, ezetimibe, and atorvastatin monotherapy groups, respectively (Table 19).

Table 19. Summary of adverse experiences. Core safety pool.

	Crude Event Rate				Exposure-adjusted Event Rate per 100 Patient-years§				
	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	EZ/All Atorva minus All Atorva Difference (95% CI‡)
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)	305.50	390.39	216.82	209.54	3.21(-18.03, 24.28)
With drug related adverse experiences†	12(20.0)	12(18.5)	213(10.4)	260(10.8)	74.05	67.97	47.65	52.89	7.89(-1.31, 17.09)
With serious adverse experiences	2(3.3)	2(3.1)	46(2.3)	65(2.7)	10.99	10.16	9.59	12.25	2.82(-1.31, 6.90)
With serious drug related adverse experiences	0(0.0)	0(0.0)	3(0.1)	8(0.3)	0.00	0.00	0.62	1.49	1.02(-0.36, 2.59)
Who died	0(0.0)	0(0.0)	2(0.1)	2(0.1)	0.00	0.00	0.41	0.37	0.00(-1.13, 1.08)
Discontinued due to adverse experiences	3(5.0)	3(4.6)	56(2.7)	63(2.6)	16.49	15.33	11.64	11.81	0.10(-4.20, 4.33)
Discontinued due to drug related adverse experiences	2(3.3)	2(3.1)	33(1.6)	36(1.5)	10.94	10.18	6.84	6.72	-0.13(-3.46, 3.11)
Discontinued due to serious adverse experiences	1(1.7)	1(1.5)	13(0.6)	15(0.6)	5.44	5.05	2.68	2.79	0.32(-1.90, 2.47)
Discontinued due to serious drug related adverse experiences	0(0.0)	0(0.0)	3(0.1)	5(0.2)	0.00	0.00	0.62	0.93	0.41(-0.92, 1.81)

EZ=Ezetimibe; All Atorva = Atorvastatin (10, 20, 40, or 80 mg) pooled across all doses.
† Determined by the investigator to be possibly, probably, or definitely drug related.
‡ 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.]

In the ezetimibe + atorvastatin and atorvastatin groups, the specific AEs with an incidence of 2% or more were nasopharyngitis (2.1% versus 1.9%), myalgia (2.5% versus 2.6%) and headache (2.5% versus 2.4%). The similarity of these rates was confirmed by the 95% CI for the exposure-adjusted rate difference which included zero (Table 20).

Table 20. Number (%) of patients with specific adverse experiences (incidence ≥2.0% in all Atorva or EZ 10 mg + all Atorva treatment groups) by Body System Organ Class. Core safety pool.

	Crude Event Rate				Exposure-adjusted Event Rate per 100 Patient-years§				EZ/All Atorva minus All Atorva
	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	Difference(95% CI†)
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)**
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].

AEs of special interest: Preferred terms relating to the AEs of interest were grouped and assessed in the core safety pool as well as studies P2154 and P1030. Effects on the liver and on muscle are discussed under *Safety issues with the potential for major regulatory impact* below.

The incidence of allergic reaction/rash AEs was 1.7%, 3.1%, 1.5%, 1.4% in the placebo, ezetimibe, atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups, respectively. The exposure-adjusted event rates in the ezetimibe + atorvastatin and atorvastatin groups were similar (6.37 versus 6.25).

Gallbladder-related AEs were infrequent with one cholecystitis and one cholelithiasis (0.1%) in the ezetimibe + atorvastatin and one cholelithiasis (0.0%) in the atorvastatin group. The exposure-adjusted event rates were 0.37 and 0.21, respectively.

The incidence of AEs in the gastrointestinal disorders SOC was 13.3%, 21.5%, 9.1% and 8.6% in the placebo, ezetimibe, atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups, respectively. The exposure-adjusted event rate was similar in the ezetimibe + atorvastatin and atorvastatin groups (41.0 versus 41.1). The most frequent events were diarrhoea (1.8% for both) and nausea (1.1% versus 1.9%). The high exposure-adjusted rate in the ezetimibe monotherapy group (81.0) may have been a factor of the small sample size (n=65).

7.4.1.2. Other studies

In the controlled long term study P2154, the AE rate was 70.6% in the ezetimibe + atorvastatin group compared to 66.7% in the all atorvastatin group with a difference of 4.0% (95% CI:-9.9, 19.8). The most frequent AEs were myalgia (8.0% versus 8.9%), back pain (6.5% versus 2.2%), muscle spasms (6.0% versus 0%), arthralgia (6.0% versus 8.9%), extremity pain (6.0% versus 6.7%) and headache (6.0% versus 4.4%). Diarrhoea was more frequent in the ezetimibe + atorvastatin group (3.5% versus 0%).

In the combined studies P693 and P1418, the AE rate was 79%. The most frequent AEs were URTI (17%), arthralgia (11%), headache (10%), myalgia (9%), abdominal pain (9%), musculoskeletal pain (8%) and back pain (7%).In the short term HoFH study (P1030), the rate was slightly higher in the ezetimibe + atorvastatin than then atorvastatin groups (75.0% versus 66.7%, 95% CI for the difference: -21.0, 40.6). The most frequent AE in the short term study was headache (16.7% versus 8.3%) and in the long term extension were headache (28%), anaemia (22%), diarrhoea (19%), influenza (19%), nasopharyngitis (19%) and pharyngolaryngeal pain (19%).

AEs of special interest: In P2154, the rate of allergic reaction/rash AEs was 5.0% and 4.4% in the ezetimibe +atorvastatin and atorvastatin groups, respectively. In the HoFH short term study there was one case of pruritus in each group (4.2% versus 8.3%).

There were no gallbladder-related events in the long term studies or in the HoFH studies. The rate of gastrointestinal SOC AEs was lower with ezetimibe + atorvastatin than atorvastatin in P2154 (17.9% versus 31.1%). In the open label long term study (P1418) the rate was 27%, with abdominal pain and diarrhoea the most frequent gastrointestinal AEs. In the combined P1030 and P1417 studies in HoFH, gastrointestinal disorders SOC AEs were reported in half the patients with diarrhoea and nausea the most common AEs.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Short term studies

In the core safety pool, the rate of treatment-related AEs was 20.0%, 18.5%, 10.4% and 10.8% in the placebo, ezetimibe monotherapy, atorvastatin monotherapy, and ezetimibe + atorvastatin groups, respectively. The exposure-adjusted treatment-related AE rate was similar in the ezetimibe + atorvastatin and atorvastatin groups (52.9 versus 47.7) (Table 19). The most commonly reported treatment-related AEs were myalgia (1.6% versus 1.5%), nausea (0.7% versus 1.0%) and diarrhoea (1.0% versus 0.8%) in the ezetimibe + atorvastatin and atorvastatin monotherapy groups, respectively.

7.4.2.2. Other studies

In the long term study P2154, the treatment-related AE rates were 22.4% and 26.7% in the ezetimibe + atorvastatin and atorvastatin groups, respectively, with myalgia being the most frequent (5.0% versus 4.4%). Myalgia was also the most frequent treatment-related AE in study P1418 occurring in 5.0% of patients.

In the HoFH population the treatment-related AE rate was 66.7% and 75.0% in the two groups, respectively, in the short term study. The most common treatment-related AEs were headache (8.3%) and arthralgia (8.3%) in the short term study and diarrhoea (11%) and xanthoma (11%) in the long term study.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Short term studies

There were four deaths in the core safety pool (1 in P693 and 3 in P112), two in the atorvastatin group (brain stem haemorrhage and myocardial infarction) and two in the ezetimibe +

atorvastatin group (cerebrovascular accident and unknown cause in a patient with a history of myocardial infarction and stroke). None were considered treatment-related.

The SAE rate in the short term studies was 3.3%, 3.1%, 2.3% and 2.7% in the placebo, ezetimibe, atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups, respectively. The exposure-adjusted SAE rate was 11.0, 10.2, 9.6 and 12.3 in these four groups, respectively (Table 19). In the ezetimibe + atorvastatin and atorvastatin groups the most frequent SAEs were myocardial infarction (0.2% versus 0.2%) and chest pain (0.2% versus 0.1%). All other specific SAEs in the ezetimibe + atorvastatin group occurred with a frequency <0.2%.

7.4.3.2. Other studies

There was one additional death in the long term study P1418. The cause of death was complications of a cardiorespiratory arrest on a background of ischaemic cardiomyopathy.

The SAE rate in study P2154 was 8.0% (16/201) and 8.9% (4/45) in the ezetimibe + atorvastatin and atorvastatin monotherapy groups, respectively. The most frequent SAEs were chest pain (1.5% versus 0%) and hypertension (1.0% versus 0%). In the combined studies P693 and P1418, the SAE rate with ezetimibe + atorvastatin was 10% (52/521) with the most frequent being chest pain, angina and coronary artery disorder.

There were two patients (8.3%) with SAEs in the short term study in HoFH with both in the ezetimibe + atorvastatin group. In the combined short and long term studies in this population the SAE rate was 33% (12/36) with the most frequent SAE being coronary artery disease (8%), unstable angina (6%) and chest pain (6%). In the single dose biopharmaceutical studies there was one SAE (study P145) of small intestinal obstruction due to malignant neoplasm.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Short term studies

The discontinuation rate due to AEs was 5.0%, 4.6%, 2.7% and 2.6% in the placebo, ezetimibe monotherapy, atorvastatin monotherapy, and ezetimibe + atorvastatin groups, respectively. The exposure-adjusted rate was similar between the combination and the atorvastatin groups (11.8 versus 11.6). The major SOCs involved were gastrointestinal disorders (0.6% versus 0.9%) and musculoskeletal disorders (0.6% both groups) with the most frequent specific AEs being nausea (0.1% versus 0.3%) and myalgia (0.3% both groups).

7.4.4.2. Other studies

In the long term controlled study P2154, the discontinuation rate due to AEs was slightly higher with ezetimibe + atorvastatin (9.0% versus 6.7%) with musculoskeletal AEs (predominantly myalgia) the main reason (2.5% versus 4.4%). In P693/1418, the AE discontinuation rate in the combination treated patients was 5%. In the HoFH population, the rate was 8% in primary and extension studies combined.

7.5. Laboratory tests

7.5.1. Liver function

See the section on *Safety issues with the potential for major regulatory impact , Liver toxicity* for discussion on liver function.

7.5.2. Kidney function

7.5.2.1. Short term studies

Renal function was assessed by blood urea nitrogen and creatinine. Elevations were infrequent and comparable between groups (Table 21). Post-baseline urinalysis was only conducted in some of the clinical studies and findings were unremarkable.

Table 21. Number of patients exceeding predefined limits for renal function. Core safety pool.

Laboratory Test	Predefined Limit	Treatment	Number†/ Total‡	(%)
Serum blood urea nitrogen (ref range: 5 to 20 mg/dL)	Value< 5 mg/dL	Placebo	0/60	(0.0)
		EZ 10 mg	0/65	(0.0)
		All Atorva	1/1998	(0.1)
		EZ 10 mg + All Atorva	1/2352	(0.0)
	Value> 30 mg/dL	Placebo	2/60	(3.3)
		EZ 10 mg	0/65	(0.0)
		All Atorva	50/1998	(2.5)
		EZ 10 mg + All Atorva	60/2352	(2.6)
Serum creatinine§ (ref range: 0.7 to 1.4 mg/dL)	Value> 2 mg/dL	Placebo	0/60	(0.0)
		EZ 10 mg	0/65	(0.0)
		All Atorva	4/1109	(0.4)
		EZ 10 mg + All Atorva	5/1462	(0.3)

† Number of patients meeting the predefined limit criteria.
‡ Total number of patients with valid values of the laboratory test.
§ Serum creatinine test was not done for Protocols 079, 090 and 112
EZ = Ezetimibe, All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.

7.5.2.2. Other studies

There were no patients in P2154, P1418 or the HoFH studies with serum creatinine above the prespecified limit of >2 mg/dL.

7.5.3. Other clinical chemistry

See Section 7.8.2 *Muscular toxicity* below for discussion on creatinine kinase.

7.5.4. Haematology

7.5.4.1. Short term studies

The rate of haematology parameters falling outside pre-specified ranges was similar between treatment groups (Table 22).

Table 22. Number (%) of patients exceeding the predefined limits for selected haematology tests. Core safety pool.

Laboratory Test	Predefined Limit	Treatment	Number†/ Total‡	(%)
WBC Count (ref range: (4.8 to 10.8x10^9/L))	Value< 3.0x10^9 /L	Placebo	0/60	(0.0)
		EZ 10 mg	0/65	(0.0)
		All Atorva	3/713	(0.4)
		EZ 10 mg + All Atorva	5/696	(0.7)
	Value> 10.8x10^9 /L	Placebo	2/60	(3.3)
		EZ 10 mg	4/65	(6.2)
		All Atorva	24/713	(3.4)
		EZ 10 mg + All Atorva	27/696	(3.9)
Platelet Count (ref range: 150 to 450 x 10 ^{9}/L)	Value< 100x10^9 /L	Placebo	0/60	(0.0)
		EZ 10 mg	0/65	(0.0)
		All Atorva	1/713	(0.1)
		EZ 10 mg + All Atorva	4/696	(0.6)
	Value> 450x10^9 /L	Placebo	0/60	(0.0)
		EZ 10 mg	1/65	(1.5)
		All Atorva	5/713	(0.7)
		EZ 10 mg + All Atorva	2/696	(0.3)
Hematocrit--Female (ref range: 36 to 46%)	Value< 33 %	Placebo	1/31	(3.2)
		EZ 10 mg	1/36	(2.8)
		All Atorva	8/354	(2.3)
		EZ 10 mg + All Atorva	12/349	(3.4)
	Value> 46 %	Placebo	3/31	(9.7)
		EZ 10 mg	1/36	(2.8)
		All Atorva	14/354	(4.0)
		EZ 10 mg + All Atorva	16/349	(4.6)
Hematocrit--Male (ref range: 42 to 54%)	Value< 39 %	Placebo	1/29	(3.4)
		EZ 10 mg	1/29	(3.4)
		All Atorva	26/359	(7.2)
		EZ 10 mg + All Atorva	24/347	(6.9)
	Value> 54 %	Placebo	0/29	(0.0)
		EZ 10 mg	1/29	(3.4)
		All Atorva	2/359	(0.6)
		EZ 10 mg + All Atorva	1/347	(0.3)
Hemoglobin--Female (ref range: 12 to 16 g/dL)	Value< 11 g/dL	Placebo	1/31	(3.2)
		EZ 10 mg	1/36	(2.8)
		All Atorva	7/354	(2.0)
		EZ 10 mg + All Atorva	9/349	(2.6)
	Value> 16 g/dL	Placebo	0/31	(0.0)
		EZ 10 mg	0/36	(0.0)
		All Atorva	1/354	(0.3)
		EZ 10 mg + All Atorva	4/349	(1.1)

Laboratory Test	Predefined Limit	Treatment	Number†/ Total‡	(%)
Hemoglobin--Male (ref range: 14 to 18 g/dL)	Value< 13 g/dL	Placebo	0/29	(0.0)
		EZ 10 mg	1/29	(3.4)
		All Atorva	19/359	(5.3)
		EZ 10 mg + All Atorva	15/347	(4.3)
	Value> 18 g/dL	Placebo	0/29	(0.0)
		EZ 10 mg	1/29	(3.4)
		All Atorva	2/359	(0.6)
		EZ 10 mg + All Atorva	1/347	(0.3)

† Number of patients meeting the predefined limit criteria.
‡ Total number of patients with valid values of the laboratory test.
Hematology tests were not done post-baseline in Protocols 040, 079, 090 and 112
EZ = Ezetimibe, All Atorva = Atorvastatin (10, 20, 40 or 80 mg) pooled across all doses.

7.5.4.2. Other studies

Haematology findings in the long term studies were unremarkable. In the patients with HoFH, there were more men with low haemoglobin (<13g/dL) and low haematocrit (<39%) treated with the combination than with atorvastatin monotherapy (30% versus 0% and 50% versus 0%). Similarly for women low haematocrit (<33%) was more frequent with the combination treatment (43% versus 25%).

7.5.5. Vital signs

There was no integration of data on vital signs. Within the individual studies, the mean change from baseline to study endpoint in weight, heart rate, SBP and DBP was assessed. These vital signs were infrequently affected by study treatment and there were no major differences between treatment groups evident.

7.5.6. Electrocardiograph

ECGs were conducted in the Schering administered studies and there was no integration of data on ECG findings. From review of individual studies, there were few clinically significant changes on ECG and no patterns to suggest an effect of the combination treatment.

7.6. Ezetrol safety data

In the original Ezetrol submission there were pooled safety data from 1675 subjects who received ezetimibe 10 mg co-administered with a statin for a period of 8 to 12 weeks. The rate of SAEs was slightly higher with co-administration that with any statin alone (3.4% versus 2.2%) and there was a marginal increase in AEs leading to treatment discontinuation (5.0% versus 4.1%) and treatment-related AEs (21.2% versus 18.1%). The most frequent treatment-related AEs with co-administration of ezetimibe with a statin were myalgia, headache, fatigue, nausea, abdominal pain, diarrhoea and increased liver enzymes. Compared to statin monotherapy, the most notable risk was increased hepatic transaminases (increased ALT: 1.7% versus 0.6% and increased AST: 1.4% versus 0.4%). There was no evidence found for an increase in risk of clinical or biochemical muscle toxicity compared to statins alone. The Sponsor reported that in the Ezetrol submission there were 295 subjects who received ezetimibe with a statin for at least 12 months. The clinical evaluation report found that the long term safety data was in line with that reported in the short term trials and the rate of increased hepatic transaminases was 0.4% which was no higher than in the short term studies.

7.7. Postmarketing experience

A cumulative summary of post-marketing data relating the co-administration of ezetimibe with a statin and more specifically with atorvastatin was included in Module 5 of the Atozet submission. From October 2002 to December 2010 there were 5516 health care provider reports of ezetimibe with a statin with 22% serious and 78% non-serious. The most frequent ADRs were myalgia, raised CK, diarrhoea, nausea and increased ALT. Within this group, 2342[2] reports were of ezetimibe with atorvastatin with 25% of these serious. The SOCs most frequently affected were investigations (31%), musculoskeletal and connective tissue disorders (29%), gastrointestinal disorders (22%) and general disorders (21%). In the investigation SOC, the most frequent serious ADRs were increased CK, increased ALT, increased AST, increased cholesterol, increased TG and abnormal liver function test. In the musculoskeletal SOC, the most frequent serious ADRs were myalgia, rhabdomyolysis, muscle spasms, muscle weakness and extremity pain. The serious gastrointestinal disorders were abdominal pain, nausea, pancreatitis, vomiting and upper abdominal pain with vomiting. Within the 265 myopathy-related ADRs, 39% were serious and there 3 fatal events (though the sponsor believes it is

[2] Sponsor erratum: "2343"

possible one of these was a duplicate) There were only limited details available on these fatalities. There were 1020 events with hepatobiliary ADR terms, half were serious and 10 fatal. For these 10 deaths information detail was variable and four cases had hepatic ADRs included in the cause of death (one hepatic failure and cirrhosis, one vanishing bile duct syndrome with cirrhosis, one autoimmune hepatitis and cirrhosis and one breast cancer with liver metastases).

There were 29 reports of drug interactions in patients treated with ezetimibe and atorvastatin. Most (62%) related to ezetimibe and atorvastatin. Five reports related to drugs listed on the ezetimibe label (cyclosporine, coumadin anticoagulants, rosuvastatin, oral contraceptive). There were another 5 cases which involved fusidic acid, creatine, atenolol, varenicline and carbamazepine which are not on the product label.

7.8. Safety issues with the potential for major regulatory impact

7.8.1. Liver toxicity

Hepatitis-related AEs (grouped preferred terms) were assessed. In the core safety pool, the rate of hepatitis-related AEs was 0.0% (one case of hepatitis with haemolytic anaemia in 2403 patients) in the ezetimibe + atorvastatin and 0.1% (two cases of cholestasis in 2041) in the atorvastatin monotherapy group. There were also 0.6% (14/2356) and 0.5% (11/2006) of patients in the two groups respectively with consecutive ALT or AST ≥3x ULN, with two patients in the ezetimibe + atorvastatin group classified as potential Hy's law cases (one in study P692 and one in P693) (Table 23). Transaminase elevations were found to return to near normal for the majority of cases on treatment cessation. Changes in GGT, ALP and total BR showed unremarkable differences between groups (Table24).

Table 23. Inferential analysis of Tier 1 AEs-Effects on the liver. Core safety pool.

	Crude Event Rate				Exposure-adjusted Event Rate per 100 Patient-years					
	Placebo	EZ 10 mg	All Atorva	EZ 10 mg + All Atorva	Placebo	EZ 10 mg	All Atorva	EZ 10 mg + All Atorva	EZ/All Atorva minus All Atorva‡	
									Difference (95% CI)	p-Value
	m/n(%)	m/n(%)	m/n(%)	m/n(%)						
ALT or AST										
≥3xULN, consecutive§	0/60(0.0)	0/65(0.0)	11/2006(0.5)	14/2356(0.6)	0.00	0.00	2.28	2.62	0.35(-1.77, 2.43)	0.721
≥5xULN, consecutive§	0/60(0.0)	0/65(0.0)	5/2006(0.2)	4/2356(0.2)	0.00	0.00	1.04	0.75	-0.20(-1.72, 1.15)	0.739
≥10xULN, consecutive§	0/60(0.0)	0/65(0.0)	0/2006(0.0)	1/2356(0.0)	0.00	0.00	0.00	0.19	0.20(-0.59, 1.06)	0.317
ALT										
≥3xULN, consecutive§	0/60(0.0)	0/65(0.0)	9/2006(0.4)	11/2356(0.5)	0.00	0.00	1.87	2.06	0.28(-1.63, 2.15)	0.757
≥5xULN, consecutive§	0/60(0.0)	0/65(0.0)	5/2006(0.2)	4/2356(0.2)	0.00	0.00	1.04	0.75	-0.20(-1.72, 1.15)	0.739
≥10xULN, consecutive§	0/60(0.0)	0/65(0.0)	0/2006(0.0)	1/2356(0.0)	0.00	0.00	0.00	0.19	0.20(-0.59, 1.06)	0.317
AST										
≥3xULN, consecutive§	0/60(0.0)	0/65(0.0)	10/2006(0.5)	7/2356(0.3)	0.00	0.00	2.08	1.31	-0.80(-2.77, 0.92)	0.330
≥5xULN, consecutive§	0/60(0.0)	0/65(0.0)	2/2006(0.1)	2/2356(0.1)	0.00	0.00	0.41	0.37	-0.00(-1.17, 1.05)	0.998
≥10xULN, consecutive§	0/60(0.0)	0/65(0.0)	0/2006(0.0)	1/2356(0.0)	0.00	0.00	0.00	0.19	0.20(-0.59, 1.06)	0.317
Hepatitis-related AEs	0/60(0.0)	0/65(0.0)	2/2041(0.1)	1/2403(0.0)	0.00	0.00	0.41	0.19	-0.19(-1.32, 0.75)	0.574
Potential Hy's Law Condition†	0/60(0.0)	0/65(0.0)	0/2006(0.0)	2/2355(0.1)	0.00	0.00	0.00	0.37	0.40(-0.38, 1.35)	0.157

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 postbaseline, if parameter is a laboratory parameter]) x 100.

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].

‡P-values and confidence Intervals are based on exposure-adjusted event rate using the Miettinen & Nurminen method with study as stratification factor.

§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.

†Potential Hy's Law Condition - Serum ALT or serum AST elevations ≥3 x ULN, with serum alkaline phosphatase ≤2 x ULN and total bilirubin (TBL) >2 x ULN (criteria for Hy's Law based on draft FDA guidance on drug-induced liver injury issued October 2007).

Table 24. Number of patients exceeding predefined limits for Gamma-Glutamyl Transferase, Alkaline Phosphatase and Total Bilirubin. Core Safety Pool.

Laboratory Test	Predefined Limit	Treatment	Number[†]/ Total[‡]	(%)
Gamma-Glutamyl Transferase (ref range: 5 to 29 mIU/mL)	Value> 50 mIU/mL	Placebo	4/60	(6.7)
		EZ 10 mg	5/65	(7.7)
		All Atorva	223/2006	(11.1)
		EZ 10 mg + All Atorva	218/2356	(9.3)
Alkaline Phosphatase[§] (ref range: 32 to 72 mIU/mL)	Value> 125 mIU/mL	Placebo	0/60	(0.0)
		EZ 10 mg	1/65	(1.5)
		All Atorva	18/1109	(1.6)
		EZ 10 mg + All Atorva	6/1462	(0.4)
Total Bilirubin (ref range: 0.1 to 1.1 mg/dL)	Value> 1.5 mg/dL	Placebo	2/60	(3.3)
		EZ 10 mg	0/65	(0.0)
		All Atorva	36/2006	(1.8)
		EZ 10 mg + All Atorva	42/2356	(1.8)

[†] Number of patients meeting the predefined limit criteria.

[‡] Total number of patients with valid values of the laboratory test.

[§] Alkaline phosphatase test was not done for Protocols 079, 090 and 112

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

In the long term study P2154, there was one hepatitis-related AE in the ezetimibe + atorvastatin group (0.5%) and none in the atorvastatin monotherapy group. There were two patients in the ezetimibe + atorvastatin group with ALT/AST ≥3x ULN though no patients had a consecutive increase in ALT or AST. The rate of ALT/AST 2x to <3x ULN was higher with the combination (6.5% versus 2.2%). Other liver function parameters had unremarkable between group differences in this study. In studies P0693/P1418, there were 2/518 patients (<0.1%) with consecutive ALT/AST ≥3x ULN with one occurring in the extension study.

In the HoFH study P1030, there was one case of consecutive ALT/AST ≥3x ULN in the ezetimibe + atorvastatin group (4.2% versus 0.0%) while the rate of any ALT/AST ≥3x ULN was the same between groups (8.3% versus 8.3%). In addition to this one case of elevated transaminases, there was also one case of fatty liver in the extension study.

7.8.2. Muscular toxicity

Myopathy was defined as presence of muscle pain and/or weakness with CK elevation ≥10x ULN. In the core safety pool, there was one myopathy case in the combination group and one case of muscle pain (attributed to exercise) with elevated CK (≥10x ULN) in the atorvastatin group. There were no reported cases of rhabdomyolysis. The rate of AEs of elevated CK (0.8% versus 0.6%) and the rate of CK ≥10x ULN (0% versus 0.1%) was similar between groups. There was however one additional case of CK ≥10x ULN in the ezetimibe + atorvastatin group which was not captured as testing was conducted at a local laboratory. The rate of lower elevations of CK (3x to <5x ULN: 0.5% versus 0.6%, and 5x to <10x ULN: 0.1% versus 0.4%) were comparable between groups.

In study P2154, there were no cases of CK ≥10x ULN and there were four cases (2.0%) in the combination group with CK elevation between 3x and <10x ULN. One case of CK ≥10x ULN in P1418 was attributed to exercise. For patients with HoFH, there were no cases of CK ≥5x ULN in the short term study while there was one case of CK >10x ULN without muscle symptoms in the extension study that was felt unrelated to treatment.

7.9. Other safety issues

7.9.1. Safety in special populations

Age: In the short term studies, when treated with the combination ezetimibe + atorvastatin, patients aged ≥65 years had fewer AEs than those aged <65 years (29.7% versus 39.0%) while the SAE rate was the same (2.7% in both age groups). In the ≥75 year old age group (n=291) compared to those aged <75 years, the AE rate (30.9% versus 34.9%) and SAE rate (3.4% versus 2.6%) were similar, with a slightly higher rate of discontinuation due to an AE (4.8% versus 2.3%).

Gender: For those treated with ezetimibe + atorvastatin in the core safety pool, the AE rate (36.2% versus 32.8%), SAE rate (2.1% versus 3.3%) and discontinuation rate due to AEs (3.1% versus 2.2%) were similar between women and men. The pattern of AEs was similar between the genders.

Race: The majority of subjects in the core safety pool were white with only 144 black and 47 Asian. While there were no major differences evident between these groups, the numbers in the non-white groups were too small to draw conclusions.

7.9.2. Safety related to drug-drug interactions and other interactions

No data were submitted. Drug interactions are a safety concern particularly due to the metabolism of atorvastatin by CYP3A4. This and other drug interactions are listed on the product information.

7.9.3. Pregnancy and lactation

Both ezetimibe and atorvastatin are contraindicated in pregnancy, in women planning to become pregnant and in lactating women. Therefore this contraindication should apply to the composite pack.

7.9.4. Overdose and withdrawal/rebound

There were no reported cases of overdosage with co-administered ezetimibe and atorvastatin. In study P2173R the withdrawal of ezetimibe therapy from coadministration with atorvastatin resulted in lipid parameters returning to pre-treatment baseline levels. There was no evidence of rebound and no notable adverse effects.

7.10. Evaluator's overall conclusions on clinical safety

In the [information redacted] submission, safety data were collated from 11 clinical studies of which seven were short term (6 to 14 weeks) controlled trials which included 4569 patients with 2403 randomised to ezetimibe 10 mg + atorvastatin (all doses). The median duration of exposure in these studies was 8 weeks. There were two long term 12 month studies: one controlled with 246 patients and one open label uncontrolled with 432 patients. There was also one small short term study and a two year open label extension study in 36 patients with HoFH with mean exposure duration of 23.5 months.

In the short term pooled data, the atorvastatin monotherapy population was a similar size to the combination group (n=2041), while the ezetimibe monotherapy group was small (n=65). Consequently, the evaluator has made, in general, comparisons of AE rates between the combination and atorvastatin monotherapy.

In the short term studies, the exposure-adjusted adverse event rate was no higher in patients treated with the combination than in those receiving monotherapy or placebo. Overall the safety profile of the combination of ezetimibe with atorvastatin was in line with that seen with the individual components. The most frequent AEs in the ezetimibe + atorvastatin and atorvastatin group were nasopharyngitis (2.1% versus 1.9%), myalgia (2.5% versus 2.6%) and headache (2.5% versus 2.4%). In the controlled long term study, the most frequent AEs were myalgia

(8.0% versus 8.9%), back pain (6.5% versus 2.2%), muscle spasms (6.0% versus 0%), arthralgia (6.0% versus 8.9%), extremity pain (6.0% versus 6.7%) and headache (6.0% versus 4.4%).

Gallbladder-related events were infrequent (0.1% versus 0.0%) and allergic reactions/rash occurred at similar rates to atorvastatin monotherapy (1.4% versus 1.5% short term and 5.0% versus 4.4% long term). Gastrointestinal disorders occurred at a similar rate to the atorvastatin monotherapy group in the short term studies with the most frequent being diarrhoea (1.8% in both groups) and nausea (1.1% versus 1.9%). With long term treatment the rate increased (17.9%) but was less than with atorvastatin monotherapy (31.1%).

Effects on kidney function and haematology parameters were infrequent and similar between the combination and atorvastatin monotherapy. The combination therapy did not appear to have any clinically significant effect on vital signs or ECG results.

Hepatitis related events were infrequent (one case short term and one long term) in the ezetimibe + atorvastatin treated patients. In the short term studies, the rate of consecutive ALT/AST ≥3x ULN was similar to atorvastatin (0.6% versus 0.5%). With longer term treatment there was an indication of a slightly higher rate of low level (2 to <3x ULN) ALT/AST rise (6.5% versus 2.2%). It is noted that the safety evaluation of Ezetrol noted that there was a higher incidence of clinically important (≥3x ULN) hepatic transaminase elevation with ezetimibe co-administration with a statin compared to statin monotherapy (increased ALT: 1.7% versus 0.6% and increased AST: 1.4% versus 0.4%).

In the short term studies, the rate of AEs of elevated CK (0.8% versus 0.6%), the rate of CK ≥10x ULN (0% versus 0.1%) and the rates of lower levels of elevated CK were similar between the combination and atorvastatin monotherapy. In the three long term studies, there were two cases CK ≥10x ULN which were not attributed to study treatment.

There were 4 deaths in the short term studies, with 2 in the ezetimibe + atorvastatin group, with one further death in a long term study. None was considered treatment-related. The exposure-adjusted SAE rate (per 100 patient years) in the short term studies (12.3) was mildly higher than atorvastatin (9.6). The most frequent SAEs were myocardial infarction and chest pain.

Study discontinuation due to AEs was low (2.6% versus 2.7%) in the short term studies and increased in the controlled long term study (9.0% versus 6.7%). The main reasons were musculoskeletal and gastrointestinal disorders. The discontinuation rate in the short term studies was lower than that reported in with ezetimibe and any statin in the Ezetrol submission (5.0%).

Safety was assessed in the elderly (≥65 years and ≥75 years) and by gender with no increased risk seen in older patients or for either gender. Numbers of non-Caucasians were too low to draw conclusions.

Withdrawal of ezetimibe treatment from co-administration with atorvastatin was assessed with no notable adverse effects.

Although the numbers were small, the AE profile appeared similar in the HoFH population.

Post-marketing data of 2342[3] reports with the combination of ezetimibe and atorvastatin found the most frequent ADRs were myalgia, raised CK, diarrhoea, nausea, increased ALT. There were 3 fatal myopathy-related and 10 fatal hepatobiliary related ADRs though details were lacking.

Overall, the safety data from the [information redacted] submission, which related to ezetimibe with atorvastatin, were consistent with those reported in the Ezetrol submission which related to ezetimibe with any statin.

[3] Sponsor erratum: "2343"

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of the combination of ezetimibe and atorvastatin in the proposed usage were:

- Efficacy in reducing LDL-C, and in terms of the proportion reaching NCEP ATP LDL-C target levels, which was greater than either monotherapy. Efficacy was also demonstrated for reduction of TC, TG, non-HDL-C and Apo B.
- Efficacy with ezetimibe and atorvastatin 10, 20 and 40 mg was greater than monotherapy atorvastatin which had been titrated to the next respective dose.
- Efficacy was maintained for up to 1 year without evidence of tolerance or rebound on cessation of ezetimibe.
- Efficacy was seen in patients with primary hypercholesterolaemia and with HoFH.
- Safety data indicated no new safety signals with the combination compared to atorvastatin monotherapy. The treatment was generally well tolerated and the adverse event-related discontinuations were low.

8.2. First round assessment of risks

The risks of ezetimibe and atorvastatin in the proposed usage were:

- Gastrointestinal adverse effects including diarrhoea, nausea and abdominal pain.
- Muscular toxicity, either clinical or biochemical, that is well known to be associated with statins. This did not, however, appear greater than with atorvastatin monotherapy with the exception of the addition of adverse event of muscle spasms.
- Increased liver transaminases. The data indicated a similar risk to monotherapy atorvastatin in the short term with a possible small increase in risk in the longer term. It is noted that the ezetimibe evaluation found the risk to be greater for the combination than for statin monotherapy.
- Little clinical data on non-Caucasians.
- There were no data to indicate that adding ezetimibe to statin therapy will improve cardiovascular outcomes compared to a statin alone.

8.3. First round assessment of benefit-risk balance

EMA guidelines on fixed dose combination products clearly state that the scientific principles for a FDC also apply to the assessment of the combination pack products. The dossier, as submitted, only referenced clinical data from the original ezetimibe submission (Ezetrol). It did not utilise or reference any of the data from the ezetimibe and atorvastatin[information redacted]. As a consequence, the sponsor failed to provide the most appropriate clinical data for evaluation of a composite pack.

The correspondence between the sponsor and the TGA indicated that the sponsor's rationale for using only the Ezetrol data was that, as ezetimibe is currently indicated for use with a statin, no additional clinical data were required for the composite pack submission. The evaluator does not agree with this. The principal reason for this is that the composite pack is, to all intents and purposes, a fixed dose combination product and therefore all data which throw light on how the two monotherapies interact when used in combination are relevant. This is supported by the Sponsor's statement that the clinical rationale for the composite pack is that "having both

products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed". Thus the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The evaluator, therefore, believes that the composite pack must satisfy all the requirements to be met by a fixed dose combination. This means that additional efficacy and safety data are necessary to support the combined use and that the data in the [information redacted] submission are relevant and appropriate and should have formed part of this dossier.

Furthermore, the data provided in the ezetimibe submission are inadequate for supporting approval of a composite pack of ezetimibe with atorvastatin due to the lack of long term efficacy and safety data with this combination. In fact, the Clinical Overview in Module 2 summarised efficacy data on only 94 patients who were treated from 12 to <18 months with co-administered ezetimibe and any statin.

The evaluator did however, have access to the [information redacted] and in this dossier the sponsor included clinical efficacy and safety studies with [information redacted] ezetimibe and atorvastatin, including two long term safety studies.

When assessing the available data from both Ezetrol and [information redacted] submissions, one of the major deficiencies was the lack of clinical data linking the versions of atorvastatin. The studies in the [information redacted] dossier were conducted using the atorvastatin Lipitor available from the US. In the[information redacted] dossier, dissolution profiles and physicochemical/chemical evidence indicated that the Lipitor from the US and the Lipitor sourced from Australia were identical. The proposed composite pack includes Atorvastatin SZ (Sandoz). In order to bridge between the clinical trials with US Lipitor and Atorvastatin SZ, bioequivalence would need to be demonstrated. If other versions of atorvastatin were used in the ezetimibe submission studies, then similar bioequivalence data would also be needed.

The combination of ezetimibe and atorvastatin has demonstrated a level of efficacy which is above the one achievable by a single substance and this has been achieved with an acceptable safety profile which is comparable to atorvastatin monotherapy. Of clinical relevance, efficacy has been demonstrated while keeping the atorvastatin dose lower. This may potentially decrease safety risks associated with higher statin doses.

This improved benefit-risk balance, together with the complementary mechanisms of action of the two components, meet the EMA guideline criteria to justify the use of the combination. The sponsor has estimated that 25,000 patients were being prescribed the combination in Australia in 2009 so there is a clinical place for the treatment. The sponsor's justification for the composite pack is that "*having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed. In addition, a composite pack would reduce the cost to patients, as patients will only pay for one PBS co-payment instead of two*." Lipid lowering therapy is an area which has poor long term compliance. The composite pack may offer convenience to patients and may stimulate awareness, however it is not certain that this will result in increased compliance and there has been no data submitted to support this possibility.

The proposed indication - *EZETROL PLUS ATORVA is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia* - is too broad and suggests use as first line therapy. This combination therapy should be used as substitution for patients already treated with atorvastatin and ezetimibe, or in patients not adequately controlled with atorvastatin or ezetimibe and in whom an additional agent is being considered. This change would put the product in line with Vytorin (ezetimibe + simvastatin) and also with that proposed for the [information redacted]. The evaluator proposes the following wording:

EZETROL PLUS ATORVA is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate:

- *Patients not appropriately controlled with atorvastatin or ezetimibe alone; or*
- *Patients already treated with atorvastatin and ezetimibe.*

The data for the combination use are sufficient to maintain the indication in homozygous familial hypercholesterolaemia (HoFH) - *EZETROL PLUS ATORVA is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).*

The sponsor has proposed to have four strengths of ezetimibe/atorvastatin in composite packs: 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg. This is appropriate as, due to treatment needing to be titrated to lipid levels, all atorvastatin doses should be available.

The proposed trade name of 'Ezetrol plus Atorva' uses the word 'plus' which could imply superiority of the product over other products. While there are clinical data indicating improved LDL-C reduction with the addition of ezetimibe to atorvastatin compared to monotherapy, there are fewer comparative data with other products. The evaluator recommends an alternate trade name be proposed.

The risks of liver toxicity have been adequately outlined in the PI with monitoring of liver function recommended before treatment initiation and periodically thereafter and dose reduction or withdrawal if transaminases increase. The risks of muscle toxicity are not adequately outlined in the PI as data have been cut and pasted from the two individual product PIs and not combined to make it relevant to a combination product. The monitoring of CK has been recommended based on clinical symptoms or in groups at risk of myopathy. The evaluator agrees with these recommendations. Due to the inherent risks, the evaluator believes that myopathy secondary to lipid lowering agents should be an added contraindication to treatment with this product.

In terms of other risks with ezetimibe and atorvastatin, the draft PI has adequately incorporated all the relevant sections of the approved monotherapy PIs, although fails to reference the combination therapy and in most instances refers to one or other monotherapy. Overall, the proposed PI is has numerous inadequacies and needs to be rewritten. As the evaluator contends the appropriate data are from the specific ezetimibe and atorvastatin clinical studies, two main deficiencies in the PI are not using the efficacy and safety data from these studies in the Clinical Trial section and Adverse Effects sections.

There is currently no available evidence on cardiovascular outcomes with the combination of ezetimibe and a statin and so, while it may be anticipated that the improved lipid reduction with the addition of ezetimibe to atorvastatin will translate into improved cardiovascular outcomes, this remains speculative. A statement regarding this lack of data needs to be included in the PI.

[information redacted]

In summary, the data in the dossier from the Ezetrol submission are insufficient to support the application for the composite pack. Nevertheless, if clinical data submitted for the [information redacted] submission are used, then there are sufficient positive efficacy and safety data, including long term data, to support the combined use of ezetimibe and atorvastatin. A major deficiency still remains the lack of bioequivalence data to bridge between the proposed Atorvastatin SZ in the composite pack and the US Lipitor used in the clinical trials. Finally, the proposed PI is inadequate and needs substantial modifications and inclusions, the justification for the need of a composite pack or two currently registered products is not clinically compelling and the trade names needs to be altered. Given these issues, the evaluator finds the benefit-risk balance of Ezetrol plus Atorva given the proposed usage, is unfavourable.

8.4. First round recommendation regarding authorisation

The evaluator recommends rejection of authorisation of Ezetrol plus Atorva. The grounds for rejection are:

- inadequate provision of clinical efficacy and safety data in the dossier;
- a lack of bioequivalence data between atorvastatin SZ and atorvastatin used in the clinical trials;
- a product information which needs substantial modifications; and
- a non-compelling clinical justification for the product.

9. Clinical questions

9.1. Pharmacokinetics

The most appropriate clinical data on which to base efficacy and safety decisions for the combination product are the data in the [information redacted] submission. The proposed composite pack includes Atorvastatin SZ, while the relevant clinical trials in the [information redacted] submission [information redacted] were conducted with Lipitor sourced in the US. If available, information needs to be provided to allow bridging of the data from the studies with US Lipitor to Atorvastatin SZ, otherwise comparable clinical effects cannot be assumed. A summary of which atorvastatin product has been used in the clinical trials in both the Ezetrol and[information redacted] submissions and a discussion on the bioequivalence of these products to Atorvastatin SZ needs to be provided.

Are there any data on the pharmacokinetics of ezetimibe and atorvastatin in different races? This should be provided as well as be included in the PI.

9.2. Efficacy

The Sponsor has stated that the clinical rationale for the composite pack is that *"having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed"*. Thus, the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The composite pack is then, to all intents and purposes, a fixed dose combination product and the evaluator believes that it must satisfy all the requirements to be met by a fixed dose combination. This is supported by EMA guidelines on fixed dose combination products which clearly state that the scientific principles for a FDC also apply to the assessment of the combination pack products. Could the sponsor clearly and precisely articulate all its reasons for not including the [information redacted] efficacy data as part of the original submission.

9.3. Safety

For the same reasons as outlined in the question above, could the sponsor clearly and precisely articulate all its reasons for not including the [information redacted] safety data as part of the original submission.

10. Second round evaluation of clinical data submitted in response to questions

10.1. Pharmacokinetics

10.1.1. Agency question

The most appropriate clinical data on which to base efficacy and safety decisions for the combination product are the data in the [information redacted] submission.

10.1.1.1. Sponsor's response

"Merck Sharp & Dohme (Australia) Pty Limited (MSD) does not concur with the evaluator's statement that the most appropriate data are that of the [information redacted] *submission. MSD would like to confirm the efficacy and safety data for the co-administration of ezetimibe and atorvastatin for the composite pack are based on the original approval of EZETROL [information redacted]. MSD believes that these data provided sufficient evidence for efficacy and safety for the composite pack*."

MSD also stated that it was their intention after approval to update the PI for the composite pack with additional data from the [information redacted] submission. The Sponsor believes the [information redacted] submission provides "*supporting rather than pivotal data for co-administration for ezetimibe and atorvastatin*". The [information redacted] data were not included as part of the submission as "*co-administration of ezetimibe and atorvastatin is an approved indication*."

The sponsor included tabulation of the clinical studies from the original submission and the supplied [information redacted] submission.

10.1.1.2. Evaluator's response

The Sponsor has now submitted the [information redacted] data in relation to this application. It is again noted that sufficient long term efficacy and safety data for the combined use of ezetimibe and atorvastatin was located in the [information redacted] dossier (studies P2154 and P1418) and not the Ezetrol dossier.

10.1.2. Agency question

The proposed composite pack includes Atorvastatin SZ, while the relevant clinical trials in the [information redacted] submission [information redacted] were conducted with Lipitor sourced in the US. If available, information needs to be provided to allow bridging of the data from the studies with US Lipitor to Atorvastatin SZ, otherwise comparable clinical effects cannot be assumed. A summary of which atorvastatin product has been used in the clinical trials in both the Ezetrol and [information redacted] submissions and a discussion on the bioequivalence of these products to Atorvastatin SZ needs to be provided.

10.1.2.1. Sponsor's response

The evidence for bridging of Lipitor sourced in the US to the Atorvastatin SZ is based on two steps. Firstly, comparison testing of the US Lipitor and Australian Lipitor that was included in the Atozet submission. Comparability was demonstrated including on dissolution. [information redacted] Secondly, bioequivalence of Atorvastatin SZ to Australian Lipitor was demonstrated in the marketing application for Atorvastatin SZ. [information redacted]

10.1.2.2. Evaluator's response

These data are acceptable for demonstrating the two step bridging between the US Lipitor used in the Atozet submission clinical trials and the proposed Atorvastatin SZ to be included in the composite pack.

10.1.3. Agency question

Are there any data on the pharmacokinetics of ezetimibe and atorvastatin in different races? This should be provided as well as be included in the PI.

10.1.3.1. Sponsor's response

As per the Ezetrol PI, there were no pharmacokinetic differences between Blacks and Caucasians based on the meta-analysis of the PK studies. The atorvastatin PI does not contain information on racial PK differences. For coadministration of ezetimibe and atorvastatin, the PK studies included only Caucasians and the efficacy studies had only small sample sizes in non-Caucasian subgroups. The core safety pool examined safety in Whites, Blacks and Asians and found no meaningful differences in adverse experiences between the race subgroups, though again subgroup numbers were small.

10.1.3.2. Evaluator's comments

There are minimal clinical data on non-Caucasians. This needs to be included in the PI, as it has not been done following recommendations in the first round of evaluation.

10.2. Efficacy

10.2.1. Agency question

The Sponsor has stated that the clinical rationale for the composite pack is that *"having both products contained in one calendar pack would increase the awareness and emphasise the clinical importance of taking both medications concurrently and at the same time when both medications are co-prescribed"*. Thus, the clear intention behind the composite pack is that both products are to be always taken together for the one purpose. The composite pack is then, to all intents and purposes, a fixed dose combination product and the evaluator believes that it must satisfy all the requirements to be met by a fixed dose combination. This is supported by EMA guidelines on fixed dose combination products which clearly state that the scientific principles for a FDC also apply to the assessment of the combination pack products. Could the sponsor clearly and precisely articulate all its reasons for not including the [information redacted] efficacy data as part of the original submission.

10.2.1.1. Sponsor's response

"As stated previously MSD believes that the data in the original EZETROL approval provide sufficient evidence for efficacy and safety. These are approved medicines at approved dosages in an approved regimen."

"These data are enhanced by the relevant clinical trials from the [information redacted] *submission now included here. The findings in these studies did not differ from the findings in the original Ezetrol submission and as proposed for the composite pack originally".*

The Module 2 and 5 data from the [information redacted] submission were included with the response and the PI has been updated in the Clinical Trial and Adverse Effects sections.

10.2.1.2. Evaluator's response

In the round one evaluation, the data from the original Ezetrol submission were considered along with the data from the [information redacted] submission, the latter having been provided in response to the s31 questions. Together these provide sufficient clinical efficacy data on which to base a decision for the composite pack.

10.3. Safety

10.3.1. Agency question

For the same reasons as outlined in the question above, could the sponsor clearly and precisely articulate all its reasons for not including the [information redacted] safety data as part of the original submission.

10.3.1.1. Sponsor's response

"For the same reasons outlined above, safety data from the extra co-administration studies were not included as part of the original submission for this ezetimibe and atorvastatin composite pack. In addition, periodic safety update reports submitted for EZETROL covering the period 17 April 2003 to 16 October 2006 immediately after registration and more recent PSURs submitted during the recent CKD evaluation did not reveal any major new safety signals for ezetimibe and atorvastatin co-administration.

Any significant safety data has been incorporated into the EZETROL PI via safety-related notifications and these safety data are reflected in the proposed Composite Pack PI.

However, MSD concurs with the TGA that these extra supporting data would enhance the composite pack submission. MSD proposes to include the extra information regarding co-administration in the proposed Composite Pack PI."

10.3.1.2. Evaluator's response

In the round one evaluation, the data from the original Ezetrol submission were considered along with the data from the [information redacted] submission, the latter having been provided in response to the s31 questions. Together these provide sufficient clinical safety data on which to base a decision for the composite pack.

11. Second round benefit-risk assessment

11.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ezetimibe and atorvastatin composite pack in the proposed usage are unchanged from those identified in the First Round assessment.

11.2. Second round assessment of risk

After consideration of the responses to clinical questions, the risks of ezetimibe and atorvastatin composite pack in the proposed usage are unchanged from those identified in the First Round assessment.

11.3. Second round assessment of benefit-risk balance

The Sponsor's responses to the questions raised after the first round of evaluation have satisfied a number of the submission's deficiencies. Data from the [information redacted] submission were provided. This allowed full evaluation of the combination of ezetimibe and atorvastatin in a variety of clinical situations. It also provided the necessary long term efficacy and safety data which were lacking in the Ezetrol dossier.

The Sponsor has explained the bioequivalence linkage path between the atorvastatin products used in the clinical programs. This is via two steps from the US Lipitor to the Australian Lipitor and from the Australian Lipitor to Atorvastatin SZ (now referred to as MSD Atorvastatin). The evaluator believes this is satisfactory.

The Sponsor has proposed new trade names as the use of the word “plus” in EZETROL PLUS ATORVA was not felt acceptable. The two alternative trade names are "ATOZET COMPOSITE PACK" and "ZETEZE". [information redacted] Atozet Composite pack is a preferable name to Ezetrol Plus Atorva, however it is recommended Zeteze has the words “Composite Pack” as well. The pack dosage needs to be clear to ensure there is no confusion or prescribing errors.

The draft product information now includes updated clinical trial data which cover all relevant studies. The Adverse Effects section has also been revised and now refers to relevant pooled safety data from co-administration of ezetimibe and atorvastatin. The revised product information, however, failed to address a number of the recommendations and therefore still needs a significant amount of revision.

The other major deficiency still outstanding is the proposed indication. The first round evaluation found the proposed indication too broad as it suggested use could be as a first line therapy. It is recommended that use be limited to substitution for patients already treated with atorvastatin and ezetimibe or to patients not adequately controlled with atorvastatin or ezetimibe and in whom an additional agent is being considered. The revised indication proposed by the evaluator was:

Primary Hypercholesterolaemia

TRADENAME is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate:

- *Patients not appropriately controlled with atorvastatin or ezetimibe alone; or*
- *Patients already treated with atorvastatin and ezetimibe.*

Homozygous Familial Hypercholesterolaemia (HoFH)

TRADENAME is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

This change was not adopted and there was no discussion provided by the Sponsor as to why this was the case.

The submission provided considerable positive clinical efficacy data and acceptable safety data for co-administration of ezetimibe with atorvastatin, although the evaluator still maintains that having the products in one pack would provide minimal additional clinical benefit. It may, however, improve compliance. The Sponsor has adequately addressed the other issues raised in the first round evaluation and, given this, the evaluator finds the benefit-risk balance of ezetimibe and atorvastatin in a composite pack for the treatment of primary hypercholesterolaemia is favourable. The product information still has outstanding issues to be addressed and the proposed indication needs to be altered to ensure the combination is not used as first line therapy.

12. Second round recommendation regarding authorisation

The evaluator recommends of approval of authorisation of the composite pack of ezetimibe 10 mg with atorvastatin (10 mg, 20 mg 40 mg or 80 mg) subject to:

- The Sponsor satisfactorily addressing all the comments.
- Alteration of the proposed indication as outlined above.

The rationale for the differing recommendation from that made after the first round of evaluation i is that the major outlined deficiencies have been addressed. These included the

provision of clinical data from the [information redacted] submission and the provision of information which allowed bridging between the US Lipitor used in the clinical trials and Atorvastatin SZ (MSD Atorvastatin) in the composite pack.

13. References

1. Committee for medicinal products for human use (CHMP) (2004). Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders. CPMP/EWP/3020/03. London.
2. Committee for medicinal products for human use (CHMP) (2009). Guideline on clinical development of fixed combination medicinal products. CPMP/EWP/240/95 Rev 1.

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