Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ezetimibe / Simvastatin

Proprietary Product Name: Vytorin

Sponsor: Merck Sharp and Dohme (Australia) Pty Limited

February 2013

TGA Health Safety Regulation

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- 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.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of indications
Decision:	Proposed Extension of Indication withdrawn. Revisions to Product Information, including to *Dosage and Administration* and *Clinical Trials* sections, approved
Date of Decision:	27 July 2012
Active ingredients:	Ezetimibe and Simvastatin
Product Names:	Vytorin10/10, Vytorin10/20, Vytorin 10/40, Vytorin10/80
Sponsor's Name and Address:	Merck Sharp and Dohme (Australia) Pty Limited. Locked Bag 2234. North Ryde NSW 1670. Australia
Dose form:	Fixed dose combination tablet
Strengths:	Ezetimibe/simvastatin 10/10 mg; 10/20 mg, 10/40 mg, 10/80 mg
Container:	Blister pack
Pack sizes:	5, 10 and 30 tablets
Approved Therapeutic use:	Unchanged
Route of administration:	Oral
Dosage:	One tablet daily. The following amendments to the dosage recommendations for Vytorin were approved: *Patients with Renal Impairment/Chronic Kidney Disease* *In patients with mild renal insufficiency (estimated GFR ≥ 60 mL/min/1.73 m^2), no dosage adjustment is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate < 60 mL/min/1.73 m^2), the dose of VYTORIN is 10/20 mg once a day in the evening. In such patients, the use of higher doses should be closely monitored (see PRECAUTIONS, Characteristics in Patients (Special Populations), and CLINICAL TRIALS.)*
ARTG Numbers	98100, 98111, 98115, 98117

Product background

Vytorin is a fixed-dose combination of ezetimibe and simvastatin. Ezetimibe inhibits the intestinal absorption of cholesterol. It is orally active and its molecular target is the sterol transporter, Niemann-Pick C1-Like (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active b-hydroxyacid form which has potent activity in inhibiting 3 hydroxy-3methylglutaryl CoA reductase (HMG-CoA reductase) which catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Merck Sharp and Dohme (Australia) Pty Limited submitted two applications concurrently, one for Vytorin, a fixed-dose combination of ezetimibe + simvastatin (described in this AusPAR) and one for Ezetrol, ezetimibe tablets for administration together with simvastatin tablets (described in a separate AusPAR). Both applications are for an extension of indication to include risk reduction of major cardiovascular events in patients with chronic kidney disease (CKD). Both Vytorin and Ezetrol (alone or in combination with statins) are currently indicated for the treatment of hypercholesterolaemia. The proposed extension of indication for both products is supported by the results of the ***S****tudy of* ***H****eart* ***a****nd* ***R****enal* ***P****rotection* (SHARP). Although both applications had identical clinical data, there are differences between the two in how the results of the SHARP study ought to be reflected in the respective Australian Product Information documents.

Vytorin was registered in Australia January 2005. The currently approved indications for Vytorin are:

> "***Primary Hypercholesterolaemia****:*
> *Vytorin is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:*
>
> · *Patients not appropriately controlled with a statin or ezetimibe alone.*
>
> · *Patients already treated with a statin and ezetimibe.*
>
> ***Homozygous Familial Hypercholesterolaemia (HoFH):***
> *Vytorin is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis)."*

The individual components of Vytorin, when taken together, are also registered (since 2005) for the same indication.

This AusPAR describes the sponsor's application to extend the indications for Vytorin to include:

· ***Prevention of Major Cardiovascular Events in Chronic Kidney Disease.***
Vytorin is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease.

Changes to the Product Information (PI), including additions to the *Clinical Trials* and *Dosage and Administration* sections were also proposed, to take into account the additional indication.

Regulatory status

The product received initial ARTG Registration on January 2005. The international regulatory status regarding similar applications (as of May 2012) is as shown below in Table 1.

Table 1. International regulatory status

Country	Date	Description of Approved Changes
USA	Submitted: 25 March 2011 Approved: 24 January 2012	The proposed new indication for patients with CKD was not accepted. This decision was unexpected, in view of the unanimous positive recommendation received from the FDA Endocrinologic and Metabolic Drugs Advisory Committee on 2 November 2011 to approve an indication for VYTORIN for reducing risk of cardiovascular events in predialysis patients. Information from the SHARP study has been included in dosage and administration, warnings and precautions, adverse reactions, use in specific populations and the clinical studies sections of the US Product Information.
EU	Submitted: 25 April 2011 Approved: 20 April 2012	The proposed new indication for patients with CKD was not accepted. Therapeutic indications (section 4.1) has been modified. This section no longer contains a statement that a beneficial effect of INEGY (i.e. VYTORIN) on cardiovascular morbidity and mortality has not been demonstrated. Information from the SHARP study has been included in Posology and method of administration, Special warnings and precautions for use, Undesirable effects, Pharmacodynamic properties (Clinical trials), including the following statement under Clinical trials (page 19 of the EU-SPC): *"INEGY has been shown to reduce major cardiovascular events in patients with chronic kidney disease; however, incremental benefit of INEGY on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has not been definitively established".*
Canada	N/A as not registered	N/A
New Zealand	Submitted: 12 Dec 2011	Evaluation ongoing
Switzerland	Submitted: 3 June 2011	Evaluation ongoing

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Extracted from the Summary of the Clinical Evaluation Report. Sub-headings, figures and tables may be included for readability.

Introduction

The cholesterol absorption inhibitor ezetimibe, the HMG-CoA reductase inhibitor simvastatin and the combination Vytorin are currently approved in Australia. Ezetimibe, administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apo-lipoprotein B (Apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Ezetimibe, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH. Ezetimibe is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Simvastatin is approved as an adjunct to diet for treatment of hypercholesterolaemia. Simvastatin is indicated in patients at high risk of coronary heart disease (CHD) (with or without hypercholesterolaemia) including patients with diabetes, history of stoke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.

Vytorin is indicated as an adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG and non-HDL-C, and to increase HDL-C in adult and adolescent (10 to 17 years of age) patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia. Vytorin is also indicated for the reduction of elevated total-C and LDL-C levels in adult and adolescent (10 to 17 years of age) patients with HoFH.

This application proposes to extend the indications for Vytorin to an additional population group and disease state. The support for development of such an indication comes from multi-centre randomised trials of statins in patients with heart disease but without chronic kidney disease (CKD). These have shown that lowering LDL-cholesterol (LDL-C) with a statin by 1 mmol/L (approximately 39 mg/dL) reduces the risk of a coronary event by about 25% and of an ischemic stroke by approximately the same amount. Meta-analyses have also confirmed this with a reduction in major vascular events (MVEs) of 20% for every reduction in LDL-C by 1mmol/L. However, there is little data examining whether other medications that are not statins but also reduce LDL have the same effect on clinical outcomes, and indeed whether this effect can be extrapolated to other disease states such as CKD. This evidence base is further lacking because even in the statin studies of patients with known cardiovascular disease (in which CKD patients are known to be highly represented), patients with CKD were excluded. For example in the *Heart Protection Study*[1], only 128 patients had a serum creatinine concentration between 150-200 µmol/L

1 Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

in men (130-200 µmol/L for women). However, retrospective *post hoc* analyses of high dose statin studies (for example, the *Treat to New Targets* study[2] where 80 mg versus 10 mg atorvastatin was compared in patients with both CKD and CHD) a significant reduction in first major cardiovascular event was seen.

It was thus hypothesised that patients with CKD that took the combination of two medications that lowered LDL (that is, both ezetimibe and simvastatin) would have more reduction in LDL than those on statin alone. Further that this would translate into an improved clinical benefit. In a small study[3] ezetemibe had been shown to provide an additional mean reduction in LDL-C of approximately 21% when added short-term to therapy with a statin in a population with CKD.

Subsequently to the commencement of the *Study of Heart and Renal Protection* (SHARP) study[4], the *German Diabetes and Dialysis Study* (Study 4D) in 1255 subjects with Type 2 diabetes mellitus receiving haemodialysis were randomised to atorvastatin 20 mg or placebo[5]. Disturbingly for people believing there was a clear clinical relationship of LDL-C to outcome, a LDL-C reduction of 42% versus 1.3% occurred after 4 weeks in patients allocated to atorvastatin versus placebo, but there was no significant difference in the risk of the primary endpoint in subjects allocated to atorvastatin. Similar outcomes were seen in the just-reported *Assessment of Survival and Cardiovascular Events* (AURORA) study, in a population of people requiring haemodialysis and receiving either rosuvastatin or placebo, despite a 43% reduction in LDL-C in the rosuvastatin group[6].

It was postulated that the lack of clinical outcome differences could have been a function of the fact that the groups studied in these two recently published studies had severe renal function (requiring haemodialysis). This group may be different to other people with CKD as they are more likely to have death from a number of other factors other than atherosclerotic events. Further, *post hoc* analyses of these two negative statin studies suggested that there could be a benefit of LDL lowering on some of the cardiovascular outcomes in a group with less severe renal impairment

There is much other data supporting aspects of some of this hypothesis including observational studies showing that dyslipidemia is associated in humans with CKD[7,8,9,10] and therefore it could assume that improving it may improve CKD. There is also data on statins and effect on glomerular filtration rate (GFR), both worsening and improving.

2 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C. et al., Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352(14):1425-35.

3 Landray M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J. et al., The Second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: A randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis 2006;47(3):385-95.

4 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.

5 Wanner C, Krane V, Marz W, Olschewski M, Mann JFE, Ruf G. et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Eng J Med 2005;353(3):238-48.

6 Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J. et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360(14):1395-407

7 Hunsicker LG, Adler S, Caggiula A, England BK, Green T, Kusek JW. et al. Predictors of the progression of renal disease in the modification of diet in renal disease study. Kid Int 1997;51:1908-19.

8 Manttari M, Tiular E, Alkoski T, Manninen V. Effects of hypertension and dyslipidemia on the decline in renal function. Hypertension 1995;26:670-5.

9 Muntner P, Coresh J, Smith C, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kid Int 2000;58:293-301.

10 Krolewski AS, Warram JH, Christlieb AR. Hypercholsterolemia-a determinant of renal function loss and deaths in IDDM patients with nephropathy. Kidney Int 1994;45(Suppl 45):S-125-S-131

Further the clinical relevance of improving GFR is unknown, although it would seem plausible that this could improve quality of life and lengthen time until dialysis is required. There is animal data on lipids and CKD (publications discussed in *Efficacy* section) and literature support for small parts or for the corollary of the hypothesis, but no clear evidence to date.

All of this data has however shaped the hypothesis regarding the clinical benefit that further LDL lowering may have in a population of people with CKD that is not end-stage. SHARP is thus the pivotal study is this application. It was designed to evaluate whether lipid-lowering therapy with a statin (simvastatin 20 mg) together with another LDL lowering agent (ezetimibe 10 mg) for 4 to 5 years would reduce MVEs in patients with CKD but with no history of myocardial infarction (MI) or coronary revascularisation procedures at baseline.

SHARP was reviewed and implemented by the *Clinical Trial Service Unit* (CTSU) in the Nuffield Department of Clinical Medicine at the University of Oxford, funded by a joint venture of Merck and Schering-Plough (the two companies later merged in November 2009 under the Merck name). An independent data and safety monitoring committee was provided with unblinded safety analyses at regular intervals.

SHARP was double-blind and enrolled over 9000 CKD patients without MI or coronary revascularisation in 18 countries, with median follow-up in survivors of 4.9 years. The dose of ezetimibe 10 mg together with simvastatin 20 mg (ezetimibe/simvastatin 10/20 mg) was used for this study.

Formulation

No changes are proposed to the approved formulation of Vytorin tablets.

Guidance

A number of references were used to guide this evaluation, including the following regulatory Guidelines:

- European Medicines Agency, September 1998 CPMP/ICH/363/96, ICH Topic E9. Statistical Principles for Clinical Trials, Step 5. *Note for guidance on statistical principles for clinical trials* (CPMP/ICH/363/96)
- European Medicines Agency, June 2005 CPMP/EWP/191583/2005. Committee of Medicinal Products for Human Use. *Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention*.
- European Medicines Agency, February 2009. CPMP/EWP/240/95 Rev.1. Committee of Medicinal Products for Human Use. *Guideline on clinical development of fixed combination medicinal products.*
- European Medicines Agency, September 2008 EMEA/CPMP/EWP/311890/2007. Committee of Medicinal Products for Human Use. *Guideline on the evaluation of medicinal products for cardiovascular disease prevention.*
- European Medicines Agency, July 2004 CPMP/EWP/3020/03. Committee of Medicinal Products for Human Use. *Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders.*
- European Medicines Agency, May 2001 CPMP/EWP/2330/99. Committee for Proprietary Medicinal Products. *Points to consider on application with 1. Meta-analysis; 2. One pivotal study.*

Scope of the clinical data

The clinical data comprised three company study reports of controlled clinical studies pertinent to the claimed indication:

1. MRL (Merck Research Laboratories) Clinical Study Report (CSR), Multicenter study: *Study of Heart and Renal Protection* (SHARP – the pivotal study) (Protocol 044).
2. MRL CSR (Synopsis), Multicenter study: *A Randomised Double-Blind Trial of the Effects on Coronary Heart Disease of Standard Versus Larger Blood Cholesterol Reductions with Statin Therapy and of Blood Homocysteine Reductions with Folate Based Therapy* (Protocol 158 MK-0733). [This study was previously submitted to the TGA for an application regarding simvastatin].
3. MRL CSR (Synopsis), Multicenter study: *A Randomized Study of the Effects on Mortality and Morbidity of HMG-CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Artery Disease*. (Protocol 102 MK0733). [This study was previously submitted to the TGA for an application regarding simvastatin].

It should be noted that a large number of studies relating to statins, simvastatin, ezetimibe, CKD and cardiovascular disease (CVD) were submitted. These were used by the evaluator to validate concerns regarding rationale, degree of cholesterol lowering and expected safety outcomes but were not formally evaluated.

The first study referred to above is the pivotal one for this application. It is a Phase V study, which has in part been published. The relevance of the other two is that they provide safety information from large randomised clinical trial data on statins.

Summary of SHARP

Efficacy overview

This study was designed to examine the efficacy of LDL cholesterol lowering with two medications that lower LDL in different ways, in a population of adults with chronic kidney disease. The study met the primary endpoint of efficacy in reducing major vascular events in this population.

Safety overview

There were a number of areas of safety that were focused on in this study, and focused on in the evaluation of this study, due to previously raised concerns with statin or ezetimibe in the areas of cancer, myopathy and rhabdomyolysis, and transaminitis. There were > 4000 patients on Vytorin in this study. Myopathy, rhabdomyolysis and transaminitis occurred more frequently in the treatment groups as expected but the only new concerns were over an almost significant difference in incidence of hypoglycaemia between the two groups. Specifically:

1. There were no significant differences between the ezetimibe/simvastatin 10/20 mg and placebo groups on all-cause mortality, or on any specific cause of death.
2. Cancer development has always been a difficult surveillance issue in a trial due to the lag time of cancer development (however this was >4 year study). In this study, there were no significant differences in the incidence of cancer overall or at any particular site, or in cancer mortality.
3. On an on-treatment basis, the incidence of myopathy including rhabdomyolysis in the ezetimibe/simvastatin group was 0.17%, compared to 0.065% in the placebo group. This higher incidence of myopathy and rhabdomyolysis is further discussed in the safety section.
4. The number of patients during the first year of treatment with post-baseline elevations in alanine aminotranferase (ALT) and/or aspartate aminotransferase

(AST) >3 times the upper limit of normal (ULN) was twice as high in the ezetimibe/simvastatin group than placebo. Following randomisation and throughout the study there was higher number in the treatment than the control group.

5. There were no significant effects on the incidence of new onset diabetes.
6. The overall incidence of serious adverse events and adverse events leading to discontinuation of study medication was similar in the two groups. No other new adverse effects of ezetimibe/simvastatin were reported.

Ethics and Governance

This study was conducted in conformance with Good Clinical Practice (GCP) standards. Country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research were adhered to. Monitoring involved both visits from the nurse monitor to collaborating centers and the remote monitoring of data quality. All Independent Ethics Committees reviewed and approved the protocol and applicable amendments.

SHARP was independently coordinated by the International Coordinating Center based at the Clinical Trial Service Unit (CTSU) and Epidemiological Studies Unit (Oxford University), working with 7 Regional Coordinating Centers (RCCs) with patients randomised at 380 centers in 18 countries. The number of randomised patients were: Australia (1,043), Austria (111), Canada (505), China (994), Czech Republic (191), Denmark (258), Finland (93), France (264), Germany (1,678), Malaysia (701), Netherlands (108), New Zealand (285), Norway (194), Poland (160), Sweden (219), Thailand (253), United Kingdom (UK) (1,987), USA (394). Merck & Co., Inc. provided financial support.

The CTSU was responsible for the organisation and conduct of the study, analysis of the data and publication of the study results. Each RCC was responsible for the administrative support of Local Clinical Centers (LCCs) and oversaw ethics approvals.

Paediatric data – Pediatric Investigation Plan (PIP) waver

The submission included an application to the European Union (EU) for Inergy (which is known as Vytorin in Australia). In this document there was a *"discussion of anticipated similarities and differences of the effect of ezetimibe/simvastatin for the prevention of cardiovascular events in paediatric patients with chronic kidney disease"*.

This application included a discussion agreeing that the lipid lowering effect of ezetimibe co-administered with simvastatin in adolescents appears to be similar to the one in adults. However that symptomatic atherosclerosis disease in paediatric CKD populations is uncommon. Therefore demonstration of the prevention of cardiovascular events in this population would be difficult.

Regarding, the additional effect of ezetimibe on LDL lowering in adolescents, there was a summary in that document under *"Clinical Studies in Paediatric Patients"* where in a multi centre, double-blind, controlled study with adolescents 10 to 17 years with HeFH was undertaken. Those with baseline LDL-C levels 4.1-10.4 mmol/l were randomised to either Ezetrol (ezetimibe) 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered Ezetrol and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks and open-label co-administered Ezetrol and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

At Week 6, Ezetrol co-administered with simvastatin (all doses) significantly reduced total-C and LDL-C compared to simvastatin (all doses) alone. At Week 53, the end of the open label extension, the effects on lipid parameters were maintained. However although efficacy in additional LDL lowering effect was evident, the safety and efficacy of Ezetrol

co-administered with doses of simvastatin above 40 mg daily was not evaluated. Additionally as the long-term efficacy of therapy with Ezetrol in patients below 17 years of age to reduce morbidity and mortality in CKD has not been studied and with the majority of childhood CKD having a different etiology to adult CKD, specifically with vascular disease playing less of a role, evidence along the lines of SHARP in an adult population (examining outcomes) for the paediatric population will be a challenge.

Thus a product-specific waiver for all subsets of the paediatric population was agreed by the European Medicines Agency (EMA) on the grounds *"that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients*".

> ***Evaluator comment:*** It is noted that the requested extension of indication for this current application does not specify age. The age group recruited in the SHARP study was > 40 years, and this application has not submitted any further data for children[11].

Good clinical practice

The pivotal study in this application (SHARP) was conducted in conformance with Good Clinical Practice (GCP) standards. Data sheets from those monitoring visits and lists of investigators are included in the CSR.

Pharmacokinetics

There were no PK studies to evaluate.

Pharmacodynamics

There were no new pharmacodynamic (PD) studies undertaken. However there was PD information collected in the pivotal SHARP study in the lipid parameters. The importance of these PD markers is in the correlation of these with clinical outcomes. The relationship of these parameters to clinical outcomes in this study is discussed in both the efficacy and safety sections.

Efficacy

Dosage selection for the pivotal studies

The dose for SHARP was chosen based on analysis of the predicted LDL-C reduction (45-50%) that was assumed (from previous clinical trial data) to translate into the appropriate clinical outcome. Investigators were also cognisant of the risk of myopathy with each of simvastatin and ezetimibe alone, an effect that was likely to be increased using both LDL-lowering agents together, especially when used in a CKD population, a population with a high risk of myopathy in observational studies. Myopathy may partially be determined by a genetic factor (organic anion transporter (OAT) receptor) in a few patients but increasing dose is also a strong risk factor.

11 The sponsor noted in their response to the clinical evaluation report that the Vytorin PI states, under Paediatric Use, that "Treatment with Vytorin is not recommended."

Chronic kidney disease in adults

Pivotal efficacy study - The SHARP study

Study design, objectives, locations and dates

SHARP was a randomised, controlled, double dummy study, undertaken across 18 countries, primarily to assess the benefit of two medications that lower LDL *via* different mechanisms on vascular outcomes in CKD. The study planned to enroll 9000 adults with various stages of CKD including maintenance dialysis at baseline (about a third). Patients were randomised in a 4:4:1 ratio to ezetimibe/simvastatin 10/20 mg (Arm 2) versus placebo (Arm 1) versus simvastatin 20 mg (Arm 3) daily. The simvastatin Arm was used for safety only, and after one year patients initially randomised to simvastatin 20 mg daily were re-randomised to ezetimibe/simvastatin 10/20 mg (Arm 3b) versus placebo (Arm 3a) for the remainder of the trial.

Patients allocated to simvastatin 20 mg who had an MI, revascularisation procedure, or renal transplant during the first year of the trial were re-randomised, and their baseline status was updated.

Design

11792 people were screened. After screening and prior to randomisation, 11364 potentially eligible patients entered a run-in period during which they received one placebo-combination tablet and one placebo-simvastatin tablet daily for approximately 6 weeks. The 9686 eligible patients who completed the run-in phase were then randomised to 1 of 3 treatment arms in a 4:4:1 ratio (4193 in ezetimibe/simvastatin, 4191 in placebo and 1054 in simvastatin arms). Follow-up visits were scheduled at 2 and 6 months, and then every 6 months, during a scheduled treatment period of at least 4 years.

Table 2, taken from the CSR, shows the subject disposition across the three arms. Final randomisation refers to the period at the end of 1 year where 886 of the 1054 simvastatin patients were re-randomised to either ezetimibe/simvastatin (n = 4650) or placebo (n = 4620). 4547 ezetimibe/simvastatin and 4519 placebo patients completed the study, with equal proportions of non-completers in both groups due to morbidity and mortality. There was a 2.2% incomplete follow-up in both groups.

Table 2. SHARP study - Subject/patient disposition.

	Ezetimibe/ simvastatin 10/20 mg	Placebo	Simvastatin 20 mg	Total
Screened	---	---	---	11,792
Entered Run-In	---	---	---	11,364
Attended Randomization Visit	---	---	---	9,686
Initial Randomization	**4,193†**	**4,191†**	**1,054†**	**9,438**
Male	2,626 (63%)	2,618 (62%)	656 (62%)	5,900
Female	1,567 (37%)	1,573 (38%)	398 (38%)	3,538
Final Randomization	**4,650†**	**4,620†**	**---**	**9,270**
Male	2,915 (63%)	2,885 (62%)	---	5,800
Female	1,735 (37%)	1,735 (38%)	---	3,470
Discontinued Study Drug*	1,563 (33.6%)	1,696 (36.7%)	---	---
SAE, Likely Drug-Related	17 (0.4%)	12 (0.3%)	---	---
Other SAE	297 (6.4%)	307 (6.6%)	---	---
NSAE	165 (3.5%)	131 (2.8%)	---	---
Other Reason	1,084 (23.3%)	1,246 (27.0%)	---	---
Complete Follow-Up	4,547 (97.8%)	4,519 (97.8%)	---	---

* More than one reason may apply
† Mean age 62 years

Objectives

There were three study objectives. It is noted that these were updated prior to unblinding due to the lower than expected event rate of one of the factors included in the composite outcome.

Primary objective: To assess the effects of lowering LDL-C with combined ezetimibe/simvastatin 10/20 mg daily versus placebo on the time to a first MVE in approximately 9000 patients with CKD, of whom around two-thirds were intended to be pre-dialysis and one third on dialysis at randomisation. MVE was a composite of non-fatal MI or cardiac death, non-fatal or fatal stroke, or any revascularisation (excluding dialysis access procedures).

Secondary objective: To assess the effects of ezetimibe/simvastatin 10/20 mg on:

- progression to end stage renal disease (ESRD; among pre-dialysis patients);
- various causes of death;
- major cardiac events (defined as non-fatal MI or cardiac death);
- stroke - both overall and subtypes;
- and hospitalisation for angina.

Tertiary objective: To assess effects of ezetimibe/simvastatin 10/20 mg on:

- hospital admission for heart failure, site-specific cancers;
- the development of diabetes among patients without diabetes at baseline;
- revision of vascular access for dialysis;
- and various other reasons for hospital admission.

Inclusion and exclusion criteria

Inclusion criteria: Men or women aged 40 years and over with advanced CKD pre-dialysis blood creatinine ≥ 150 µmol/L (1.7 mg/dL) in men, or ≥ 130 µmol/L (1.5 mg/dL) in women with no known history of MI or coronary revascularisation. Patients were eligible for randomisation if the patient's nephrologist did not believe that there was a definite indication for or contraindication to an HMG-CoA reductase inhibitor. Further that all inclusion criteria were satisfied and no exclusion criterion applied.

Exclusion criteria: Patients were excluded if they met any of the following criteria:

- Definite history of MI or coronary revascularisation procedure;
- Functioning renal transplant, or living donor-related transplant planned;
- Less than 2 months since presentation as an acute uremic emergency (but may be entered later, if appropriate);
- Definite history of chronic liver disease, or abnormal liver function (that is, ALT > 1.5 ULN or, if ALT not available at the LCC, AST > 1.5 times ULN). Patients with a history of hepatitis were eligible provided these limits were not exceeded;
- Evidence of active inflammatory muscle disease (for example, dermatomyositis, polymyositis), or creatine kinase (CK) > 3 times ULN;
- Definite previous adverse reaction to a statin or to ezetimibe;
- Concurrent treatment with a contraindicated drug (HMG-CoA reductase inhibitor, fibric acid derivative, nicotinic acid, macrolide antibiotic (erythromycin, clarithromycin), systemic use of imidazole or triazole antifungals, protease-inhibitors, nefazodone, cyclosporine, ezetimibe);

- Child-bearing potential (that is, premenopausal woman not using a reliable method of contraception);
- Known to be poorly compliant with clinic visits or prescribed medication;
- Medical history that could limit the individual's ability to take trial treatments for the duration of the study (for example, severe respiratory disease, history of cancer other than non-melanoma skin cancer, or recent history of alcohol or substance misuse).

Study treatments

Initially, subjects were randomly allocated to placebo, simvastatin 20 mg or ezetimibe/simvastatin 10/20 mg. Subjects initially randomised to simvastatin were re-allocated to ezetimibe/simvastatin or placebo at the end of 1 year. Other subjects continued on ezetimibe/simvastatin or placebo as originally randomised.

Efficacy variables and outcomes

The main efficacy variables (as specified in the protocol) were:

Primary:

- To assess the effects of lowering LDL-C with combined ezetimibe 10 mg and simvastatin 20 mg daily versus placebo on the time to a first 'MVE'.

Secondary:

- To assess the effects of ezetimibe/simvastatin 10/20 mg on: progression to ESRD (among pre-dialysis patients); various causes of death; major cardiovascular events (defined as non-fatal MI or cardiac death); stroke both overall and subtypes; and hospitalisation for angina.
- To assess the effects of major vascular effects among particular subgroups of patients.

Tertiary:

- To assess effects of ezetimibe/simvastatin 10/20 mg on: hospital admission for heart failure; site-specific cancers; development of diabetes among patients without diabetes at baseline; revision of vascular access for dialysis; and various other reasons for hospital admission.[12]

The key outcome specified in the Statistical Analysis Plan (SAP)

The key outcome specified in the SAP was the Major Atherosclerotic Event (MAE), defined as the combination of MI, coronary death, ischemic stroke, or any revascularisation procedure (that is, excluding non-coronary cardiac deaths and strokes confirmed to be haemorrhagic from the original protocol-defined MVE outcome).

Other subsidiary comparisons were also recommended:

a) Analysis of the protocol-defined primary outcome of MVE, and also MVE in all randomised patients (Arms 2 + 3b versus Arms 1 + 3a);

b) An analysis of the separate components of the composite MAE;

c) An analysis of the rate of ESRD in pre-dialysis patients, defined as commencement of long-term dialysis or transplantation.

A number of tertiary analyses were also specified including analysis by subgroup including baseline LDL-C, total cholesterol and waist circumference, and type of stroke.

12 The sponsor noted the Study Report also states the following tertiary objective: SHARP also aims to extend the information provided by the second SHARP pilot study (UK HARP II) on the safety of adding ezetimibe to simvastatin among patients with CKD. This will be achieved by comparing ezetimibe/simvastatin with simvastatin alone after 1 year of treatment.

The primary, secondary and tertiary efficacy analyses (as per protocol) conducted at the end of the trial are documented in the CSR. It is important however to note that the primary outcome specified in the protocol (MVE) differs from the key outcome specified in the SAP (MAE). This addition occurred because blinded examination of MVE showed that about one third of the MVE events were either non-coronary cardiac deaths or haemorrhagic strokes. The study investigators became aware during the trial (from published data such as Study 4D[13] and the *Assessment of Survival and Cardiovascular Events* (AURORA) study[14] that these events are less likely to be prevented by LDL lowering therapy in a CKD group. Further the mean LDL reduction at the midpoint of the trial was less than expected, so a relative risk reduction of 13% in the original primary outcome of MVE only was anticipated, significantly under-powering the SHARP study (66% power at p = 0.01) to detect this difference.

The Steering Committee stated that the key outcome in the SAP was to be on the effects on all randomised patients (that is, Arms 2 + 3b versus Arms 1 + 3a) of ezetimibe/simvastatin 10/20 mg versus placebo on the overall incidence of first MAE rather than MVE. So MAE is MVE without non-coronary cardiac deaths and haemorrhagic stroke.

The inclusion of all randomised patients, that is, all those who were originally allocated to simvastatin for 1 year (that is, Arm 3b versus Arm 3a), in the comparison, was also recommended by the Committee to increase power (the number of subjects (n) increases to 9270 from 8384). Table 3 summarises the difference in the protocol primary outcomes and the SAP key outcomes.

Table 3. SHARP study – SAP and protocol key outcomes.

Main Outcome (Primary/Key)	Protocol	SAP
Composite Endpoint	MVE	MAE
Endpoint components	Major cardiac events (MI, cardiac death); any stroke, any revascularisation procedure	Major coronary events (MI, coronary death), ischaemic stroke, any revascularisation procedure
Analysed population	Arm 2 versus Arm 1 (n = 8384)	Arm 2 + 3b versus Arm 1 + 3a, (n = 9270)
Differences in MVE/MAE	n is smaller (excludes original Arm 3 group). Includes non-coronary cardiac death and haemorrhagic stroke	Includes Arm 3, excludes non-coronary cardiac death and haemorrhagic stroke

13 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.

14 Wanner C, Krane V, Marz W, Olschewski M, Mann JFE, Ruf G. et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Eng J Med 2005;353(3):238-48.

It should also be noted that the sponsor did not approve these protocol changes and subsequently reported both the per-protocol findings, followed by the SAP analyses.

Randomisation and blinding methods

A standard randomisation method, using a 4:4:1 ratio as described above in *Design*, and double-dummy technique was used. The 4:4:1 method was used due to concerns for safety of LDL lowering in this population and inclusion of an arm that was allocated simvastatin only.

Analysis populations

The populations in the analysis are discussed under the *Statistical methods* section, below.

Sample size

This study needed to recruit patients with CKD but without CHD. Extrapolating from observational studies and other statin studies, a primary outcome rate of MVE of around 3% per annum was expected. An event rate of around 5% in dialysis patients was expected (which would account for about one-third of patients), giving an average annual event rate of about 3.7%. At least 1100 MVE would be needed to occur for the study to have approximately 90% power to detect a 20% proportional reduction in MVEs at probability (p) < 0.01 (2-sided).

Further, it was expected that randomisation to ezetimibe/simvastatin would produce an average reduction in LDL-C over the whole study of at least 1 mmol/L, compared to placebo, taking into account potential compliance issues, the lower LDL in CKD and dialysis patients specifically and that a percentage of non CHD cardiac events would not be affected by LDL lowering in this CKD population. Overall a 1 mmol/L reduction in LDL was assumed to lead to a 20% reduction in MVE during the study, based on statin studies and a recent meta-analysis[15].

Using *Heart and Renal Protection* (HARP-1; the pilot study for SHARP) and *Reduction of Endpoints in Non-Insulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan* (RENAAL[16]) study data the cumulative incidence of ESRD was expected to be 20% at 4 years which would give the study over 95% power to detect a 20% proportional reduction in the risk of ESRD at 2p (two-sided p value) < 0.01.

> ***Evaluator comment*:** Although it is known that low LDL is a risk factor for mortality in CKD, the hypothesis discussed here supporting the sample size for the study is plausible. There were two unknowns prior to the commencement of this study: whether LDL lowering *per se* as opposed to using ezetimibe would have the same benefit on reduction in outcomes seen in the statin studies and further, what the effect of LDL lowering would be on outcomes in a population with CKD. A further important question regarding the magnitude of the clinical benefit of dual ezetimibe/simvastatin as opposed to simvastatin alone in this population group could not be studied with the trial design of this study.

15 Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J. et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360(14):1395-407

16 The RENAAL study was set up to analyse the effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy (http://www.nejm.org/doi/full/10.1056/NEJMoa011161). There was an absolute risk reduction of 3.6% in the composite outcome (doubling of the serum creatinine concentration, end-stage renal disease, or death) in the losartan group as compared with placebo group, however within this composite there was no effect on death.

Statistical methods

Analyses were performed using intention-to-treat (ITT) principle for all efficacy and safety analyses except for analyses of myopathy/rhabdomyolysis and hepatitis - analysed using both an ITT and an on-treatment approach. Log-rank methods were employed for analysis of time-to-event endpoints to calculate average event rate ratios, confidence intervals (CI) and two-sided p-values.

As discussed above, an update was made to the statistical methods after the lower than expected reduction in LDL-C and higher non-coronary events and haemorrhagic strokes in the MVE was seen. This update was finalised on 20 August, 2010, blind to results by allocated treatment for clinical outcomes[17].

In this update increased numbers of patients were now included (9270 from 8384) and the new definition of MAE was used, increasing the power for the study. For example, the power for an 18% proportional reduction in MAE was estimated at 84% based on 8400 patients originally randomised to ezetimibe/simvastatin versus placebo and 88% on adding patients who were randomly allocated between ezetimibe/simvastatin versus placebo following initial allocation to simvastatin alone for 1 year. This is in contrast to a 66% power to detect a difference of 13% between Arms 1 and 2 using the protocol-defined outcomes.

Thus efficacy populations analysed differed for the protocol and the SAP (see also *Study treatments*, above). Specifically, the primary analysis defined in the original protocol involved comparisons of MVE in ezetimibe/simvastatin 10/20 mg versus placebo among those originally allocated to receive either ezetimibe/simvastatin 10/20 mg or placebo at the beginning of the study (Arms 1 and 2). However the adjusted analysis in the SAP-specified key outcome was the analysis of MAE, in all patients allocated to ezetimibe/simvastatin 10/20 mg or placebo at any time point in the study (including the simvastatin 1 year Arm). Thus it included MAE that occurred after the first year of follow-up in Arms 3a and 3b. Events that had occurred in Arm 3 prior to re-randomisation were not added to the randomised comparison of ezetimibe/simvastatin versus placebo, but were used to update the baseline status at the time of re-randomisation of patients originally allocated to Arm 3. Stratified log-rank method was employed for analysis of time-to-event endpoints to calculate event rate ratios, CIs and 2-sided p-values. Specifically, log ranked observed (O) minus expected (E) values and their variances were calculated for each of the two comparisons, and the overall log-rank statistic was derived as the ratio of the sum of the (O-E) and to the sum of the variances of (O-E) from each comparison. These were used to derive the stratified risk ratio (RR), CI and 2-sided p value.

Measurement and comparison of the amount and effect of LDL-C reductions at 1 year were calculated by taking the mean absolute difference in LDL-C between those allocated active treatment and those randomised to placebo in a particular subgroup. This weighting was multiplied by the log-rank (O-E) for each subgroup (variance by weighting squared). The RR per 1.0 mmol/L reduction in LDL-C was then calculated using the weighted parameters. Difference in change in biochemical efficacy parameters was undertaken using t-tests.

The SAP describes methodology for the evaluation of the separate components of the MAE (which also used the Hochberg procedure). For the interpretation of tertiary comparisons, multiple hypotheses testing which included timing, duration and severity was adjusted for.

17 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.

Participant flow

This is most clearly described by viewing the flow chart in Figures 1 and 2, below.

> ***Evaluator comment***: There appears to be 168 patients unaccounted for at the completion of year 1 (simvastatin Arm), that is, they were not re-allocated.

Figure 1. SHARP study - participant flow.

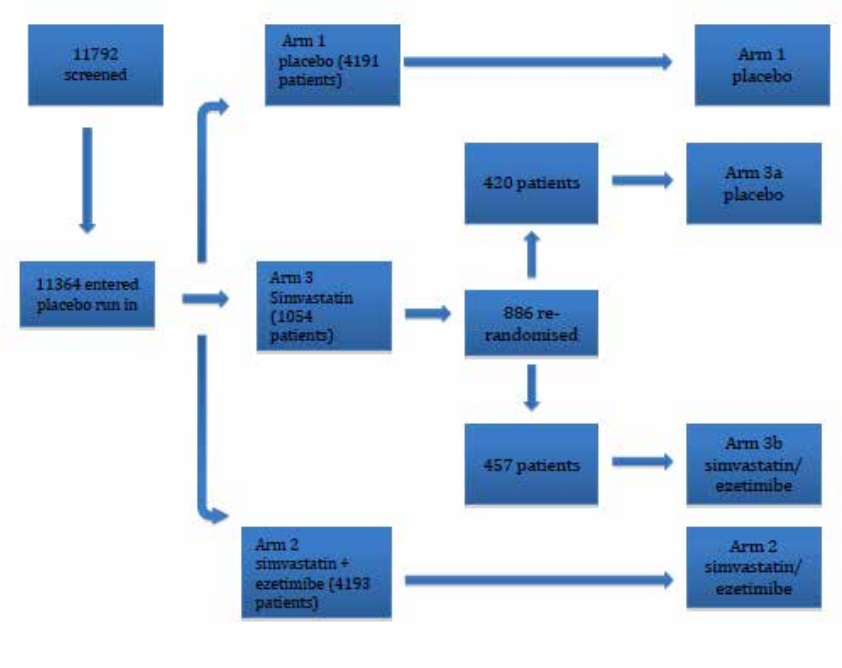
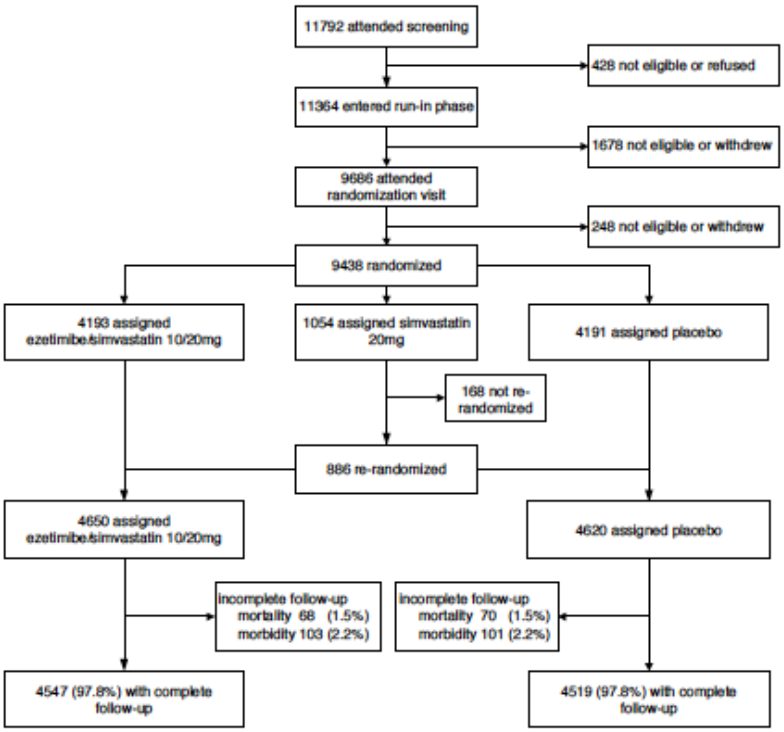


Figure 2. SHARP Study – summary of patient accounting.



Incomplete follow-up includes those without direct contact (in person or by telephone) at the scheduled final visit and with less than 4 years of follow-up.

Major protocol violations/deviations

Overall there was a change made to the analysis in the protocol as described because of a lower number of events, and a lower achievement of LDL targets than expected. This has been expanded in the above section.

Regarding protocol violations, one patient aged 39 was randomised (inclusion criteria specified age ≥ 40). This was reported as a protocol violation, and a sponsor's *Protocol Waiver* was issued to allow the patient to continue. The patient was included in all analyses.

Treatment was unblinded during the first year of the study in 6 (0.14%) patients allocated to ezetimibe/simvastatin 10/20 mg, and 5 (0.12%) patients allocated to placebo because of a serious adverse event (SAE). No patients allocated to simvastatin 20 mg were unblinded.

Overall, 24 (0.52%) patients in the ezetimibe/simvastatin and 16 (0.35%) in the placebo groups were unblinded before the end of the study, all due to a SAE that was attributed to study treatment. However of the 40 suspected serious adverse reactions (SSARs), 7 (4 in the ezetimibe/simvastatin group and 3 in the placebo group) were later 'downgraded'.

Baseline data

This is most clearly demonstrated by Table 4 (which shows the baseline characteristics of the 3 groups) read in conjunction with Table 5 (from the SHARP Collaborative group publication that enables examination of dialysis status in each of the demographic characteristics).

Table 4. SHARP Study – baseline characteristics at the time of first randomisation (number and percentage or mean ± SD)

Baseline Characteristic	Ezetimibe/ simvastatin 10/20 mg (N=4193) n (%)	Simvastatin 20 mg (N=1054) n (%)	Placebo (N=4191) n (%)
Prior vascular disease			
Coronary disease	138 (3%)	39 (4%)	122 (3%)
Peripheral arterial disease	276 (7%)	62 (6%)	272 (6%)
Cerebrovascular disease	303 (7%)	77 (7%)	281 (7%)
At least one of the above 3 conditions	633 (15%)	158 (15%)	608 (15%)
None	3560 (85%)	896 (85%)	3583 (85%)
Diabetes			
No	3241 (77%)	813 (77%)	3255 (78%)
Yes	952 (23%)	241 (23%)	936 (22%)
Gender			
Male	2626 (63%)	656 (62%)	2618 (62%)
Female	1567 (37%)	398 (38%)	1573 (38%)
Age at randomization (years)	62 ± 12	62 ± 12	62 ± 12
40-49	865 (21%)	211 (20%)	848 (20%)
50-59	1037 (25%)	266 (25%)	1039 (25%)
60-69	1123 (27%)	280 (27%)	1131 (27%)
70+	1168 (28%)	297 (28%)	1173 (28%)
Current smoker			
No	3637 (87%)	903 (86%)	3641 (87%)
Yes	556 (13%)	151 (14%)	550 (13%)
Diastolic BP (mmHg)	79 ± 13	79 ± 12	79 ± 13
<80	2040 (49%)	534 (51%)	2091 (50%)
≥80 <90	1263 (30%)	324 (31%)	1191 (28%)
≥90 <100	640 (15%)	138 (13%)	658 (16%)
≥100	241 (6%)	55 (5%)	236 (6%)
Systolic BP (mmHg)	139 ± 22	139 ± 22	139 ± 22
<140	2175 (52%)	549 (52%)	2178 (52%)
≥140 <160	1269 (30%)	318 (30%)	1263 (30%)
≥160 <180	561 (13%)	142 (13%)	559 (13%)
≥180	182 (4%)	45 (4%)	184 (4%)

Table 5. SHARP Study – baseline characteristics, overall and by renal status at randomisation.

	Not on dialysis	On dialysis	All patients
Number randomized	6382	3056	9438
Renal diagnosis			
Glomerulonephritis	1063 (17%)	689 (23%)	1752 (19%)
Diabetic nephropathy	916 (15%)	477 (16%)	1393 (15%)
Hypertensive or renovascular disease	1334 (22%)	482 (16%)	1816 (20%)
Cystic kidney disease	690 (11%)	374 (12%)	1064 (12%)
Pyelonephritis/obstructive nephropathy	413 (7%)	202 (7%)	615 (7%)
Other known cause	911 (15%)	373 (12%)	1284 (14%)
Unknown cause	796 (13%)	403 (13%)	1199 (13%)
Unavailable	259	56	315
Age, y			
Mean (SD)	62.3 (11.7)	58.9 (11.8)	61.2 (11.9)
40-49	1099 (17%)	825 (27%)	1924 (20%)
50-59	1516 (24%)	826 (27%)	2342 (25%)
60-69	1794 (28%)	740 (24%)	2534 (27%)
70+	1973 (31%)	665 (22%)	2638 (28%)
Sex			
Men	3954 (62%)	1946 (64%)	5900 (63%)
Women	2428 (38%)	1110 (36%)	3538 (37%)
Physical measurements			
Systolic blood pressure, mm Hg	139 (21)	139 (24)	139 (22)
Diastolic blood pressure, mm Hg	80 (13)	78 (13)	79 (13)
Body mass index, kg/m^2	27.4 (5.5)	26.4 (5.8)	27.1 (5.6)
Waist circumference, cm	96.7 (14.8)	97.0 (15.7)	96.8 (15.1)
Smoking			
Current smoker	791 (12%)	475 (16%)	1266 (13%)
Prior diseases*			
Angina	212 (3%)	77 (3%)	289 (3%)
Peripheral arterial disease	371 (6%)	229 (7%)	600 (6%)
Cerebrovascular disease	464 (7%)	187 (6%)	651 (7%)
Any vascular disease	933 (15%)	437 (14%)	1370 (15%)
Diabetes	1429 (22%)	650 (21%)	2079 (22%)
Ethnic group			
White	4567 (72%)	2206 (72%)	6773 (72%)
Black	130 (2%)	146 (5%)	276 (3%)
Chinese	1031 (16%)	109 (4%)	1140 (12%)
Other Asian	528 (8%)	442 (14%)	970 (10%)
Other/not specified	126 (2%)	153 (5%)	279 (3%)

Mean (SD) or number (percentage) shown.
*Cerebrovascular disease includes stroke and transient ischemic attack. Any vascular disease is defined as a history of angina, peripheral arterial disease, or cerebrovascular disease at the screening visit.

In summary, there were no clinically important differences between treatment groups for baseline characteristics of patients in the first randomisation. Importantly, mean LDL-C concentration was significantly lower among patients on dialysis than those who were not (100 mg/dL versus 111 mg/dL, respectively; $p < 0.0001$).

Results for the primary efficacy outcome

Main efficacy Outcomes

a) Protocol-specified primary outcome

This is the effect of ezetimibe/simvastatin 10/20 mg versus placebo on MVEs in all patients except those originally allocated to simvastatin alone, or MVE in Arm 2 versus Arm 1. Compared to placebo (Arm 1, n = 749/4191), ezetimibe/simvastatin 10/20 mg (Arm 2, n = 639/4193) reduced the risk of MVE by 16% (RR 0.84, 95% CI 0.75-0.93, p = 0.001).

The RR of ezetimibe/simvastatin 10/20 mg versus placebo on the components of MVE in all patients including those originally allocated to simvastatin was 0.85, 95% CI 0.77-0.94, p = 0.0012 (SAP subsidiary outcome).

b) SAP 'key outcome' (MAE)

In the SAP, the 'key outcome' is the first occurrence of MAE, defined as major coronary events (coronary death or non-fatal MI), ischemic stroke, or any revascularisation procedure, in all patients randomised to ezetimibe/simvastatin 10/20 mg (Arms 2 + 3a)

or placebo (Arms 1 + 3b). This outcome occurred in 526/4650 versus 619/4260 (that is, RR 0.83, 95% CI 0.74-0.94, p = 0.0022).

Thus the direction, RR, CI and significance of the primary endpoint are similar regardless of whether MVE or MAE is used, even though the power of the study was much less for the MVE than the MAE analysis.

Results for other efficacy outcomes

SAP subsidiary efficacy comparisons

Subsidiary and tertiary comparisons were made in all patients randomised to ezetimibe/simvastatin (Arms 2 + 3b, n = 4650) versus placebo (Arms 1 + 3a, n = 4620) as per the Steering Committee recommendations. Further analyses were also performed on the primary outcome MVE.

a) MVE in all patients randomised:

The risk of MVE in all patients randomised was reduced by 15% (RR 0.85, 95% CI 0.77-0.94, p = 0.0012). This compares to 16% (RR 0.84, 95% CI 0.75- 0.93, p = 0.001) if just Arm 2 versus 1 is compared as per primary outcome efficacy analysis above.

b) Results for the protocol-specified components of primary outcome (MVE) in all randomised patients (Arms 2 + 3b Versus Arms 1 + 3a) were:

- major cardiovascular events (RR 0.90, 95% CI 0.78–1.04, p = 0.16);
- total stroke (RR 0.81, 95% CI 0.66–0.99, p = 0.038);
- ischaemic stroke 2.5% versus 3.4% (RR 0.72 95% CI 0.57-0.92, p = 0.0073);
- haemorrhagic stroke 1% versus 0.8%; (RR 1.21 CI 0.78-1.86; p = 0.4);
- unknown cause of stroke 0.4% versus 0.4% (RR 0.94 95% CI 0.49-1.79, p = 0.85);
- any revascularisation procedure (RR 0.79, 95% CI 0.68–0.93, p = 0.0036).

There was a 27% reduction in risk (p = 0.0027) of coronary revascularisation procedure and non-significantly fewer (10%, p = 0.36) non-coronary revascularisation procedures (non-coronary vascular surgery/intervention, non-traumatic amputation).

Total stroke is a component of MVE, while for MAE, haemorrhagic stroke was excluded.

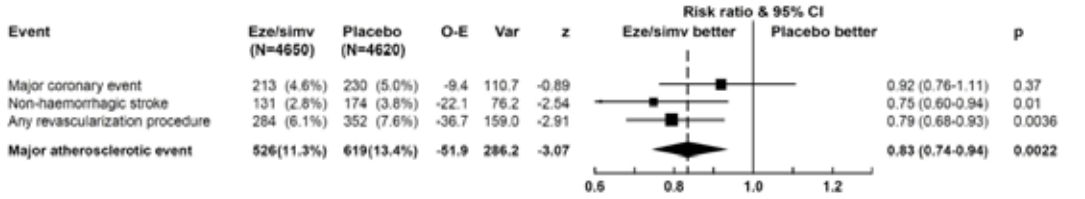
Elements of MVE (protocol) not included as components of MAE are other, that is, non-CHD cardiac death and haemorrhagic stroke, which are tertiary endpoints and for which there was no statistical difference between the groups.

c) For the components of MAE in all randomised patients (refer to Figure 3):

- major coronary events, RR 0.92, 95% CI 0.76–1.11, p = 0.37;
- non-haemorrhagic stroke, RR 0.75, 95% CI 0.60–0.94, p = 0.01;
- any revascularisation procedure, RR 0.79, 95% CI 0.68–0.93, p = 0.0036.

The RR should be compared with b) above.

Figure 3. SHARP Study – Effect of ezetimibe/simvastatin 10 mg/20 mg versus placebo on the components of MAE in all randomised patients (Arms 2 + 3b versus Arms 1 + 3a)



The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

The risk reductions in non-haemorrhagic stroke and any revascularisation procedure both remain statistically significant after applying the Hochberg procedure to the uncorrected p-values displayed here: corrected p = 0.022 and 0.011, respectively.

Thus for both MAE or MVE, and bearing in mind the issues with attaching clinical weight to the breakdown of a composite endpoint, the effects on MAE and MVE appear to be driven by a benefit from ezetimibe/simvastatin on stroke and revascularisation procedures.

> ***Evaluator comment*:** This point is important as the request for extension of indication is reduction in cardiovascular outcomes – see further breakdown in a) in the section below.

Secondary endpoints in protocol

a) With respect to the effects of ezetimibe/simvastatin 10/20 mg on: progression to ESRD (among pre-dialysis patients); various causes of death; major cardiac event (defined as non-fatal MI or cardiac death); stroke both overall and subtypes; and hospitalisation for angina:

- There was no significant effect on the risk of ESRD (commencement of long-term dialysis or transplantation among pre-dialysis patients): RR 0.97, 95% CI 0.89-1.05, p = 0.41. Thus treatment with ezetimibe/simvastatin 10/20 mg did not reduce the progression of renal insufficiency according to this measure;
- There was no difference in overall and cause-specific mortality, vascular deaths, or deaths due to heart disease. There were fewer deaths attributed to ischemic stroke (30 [0.6%] versus 41 [0.9%]) in the combination therapy group, and slightly more deaths due to haemorrhagic stroke (27 [0.6%] versus 23 [0.5%]), although these numbers are small. The mortality section is presented in more detail in the *Safety* section, below;
- Major cardiac events (part of the composite endpoint) - there was a non-significant difference (10%, p = 0.16) for major cardiac events (cardiac death and non-fatal MI) in the ezetimibe/simvastatin group;
- Stroke (part of the composite endpoint) – there was a 19% risk reduction for total stroke (p = 0.038) in the ezetimibe/simvastatin as compared to placebo group;
- Hospitalisation for angina – the risk was the same in both groups.

b) With respect to the effects of major vascular effects among particular subgroups of patients, there were numerically fewer vascular deaths in patients randomised to ezetimibe/simvastatin 10/20 mg versus placebo, although the difference was not significant (RR 0.93, 95 % CI 0.80-1.07; p = 0.30), with fewer deaths due to heart disease (RR 0.93, 95% CI 0.78-1.10; p = 0.38) and stroke (RR 0.87, 95% CI 0.63-1.20, p = 0.39).

Tertiary endpoints

With respect to the effects of ezetimibe/simvastatin 10/20 mg on: hospital admission for heart failure; site-specific cancers; development of diabetes among patients without diabetes at baseline; revision of vascular access for dialysis; and various other reasons for hospital admission, the number of patients hospitalised for angina was the same in both groups; and there were non-significant trends towards a reduction in the risk of transient ischemic attack, hospitalisation for heart failure, and haemodialysis access revision.

SAP tertiary efficacy comparisons

1). There was no significant difference between the groups when undertaking a subgroup analysis, except when analysed according to their baseline lipid profile and body weight. However after adjusting for reduction in LDL, statistical significance was only seen for total cholesterol (trend p = 0.02) and waist circumference (p = 0.05) in the MAE group and total baseline cholesterol in the MVE (trend p = 0.02).

2). Ezetimibe/simvastatin reduced the risk of stroke by 19% (RR 0.81, 95% CI 0.66–0.99, p = 0.038). For ischemic stroke the RR was 0.72, 95% CI 0.57–0.92, p=0.0073, for stroke of unknown type the RR was 0.94, 95% CI 0.49–1.79, p=0.85, and for haemorrhagic stroke the RR was 1.21, 95% CI 0.78–1.86, p = 0.40.

Evaluator comment: This finding is consistent with the statin data on strokes.

3). There was no significant heterogeneity of the effect on MAE and MVE among the subgroups specified.

4). There was a trend towards a greater effect of treatment in patients without a history of atherosclerotic disease (who accounted for 85% of the study population). There was also no significant heterogeneity due to the presence or absence of diabetes, another condition in which treatment with statins has been shown to be beneficial[18].

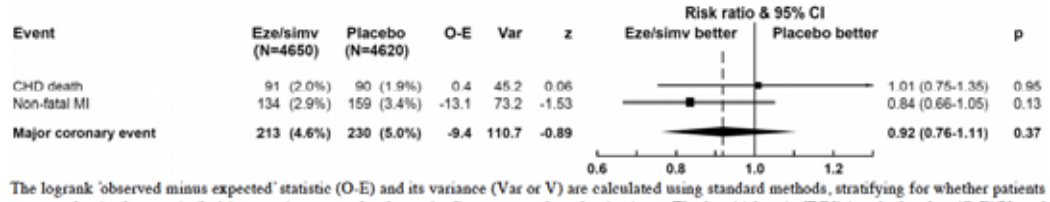
5). Because two previous studies of lowering LDL-C with statins in patients on dialysis were negative (Study 4D and AURORA), an analysis of dialysis status was undertaken. There was no significant heterogeneity, but the point estimates of MVE and MAE reduction were greater in the pre-dialysis patients. The reduction in LDL-C was also greater in the pre-dialysis patients (at the 2.5 years midpoint, net of placebo 0.96 mmol/L versus 0.60 mmol/L in the dialysis patients), although the predialysis population had higher mean baseline LDL-C (2.9 mmol/L, 111 mg/dL versus 2.6 mmol, 100 mg/dL) and better compliance (70% at 2.5 years) than the dialysis patients (57% at 2.5 years).

Further when the risk reductions were weighted for the LDL-C reduction, the observed risk reduction differences narrowed between pre-dialysis and dialysis patients, for both MVE and MAE.

6). *Major coronary event:* There was no difference in number of coronary events between the combination and the placebo groups, as can be seen by Figure 4.

18 Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

Figure 4. SHARP Study – Breakdown of major coronary event in all randomised patients (Arms 2 + 3b versus Arms 1 + 3a)



The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

Summary of other heterogeneity, subgroup analysis

Apart from body mass index (BMI) and waist circumference in the case of MAE, there was no significant heterogeneity on the effect of treatment on either MVE or MAE when subgroups including age, sex, race, prior atherosclerotic disease, diabetes, smoking status, blood pressure, haemoglobin, concomitant medication, or measures of renal disease and function in pre-dialysis patients were considered. The trend test for LDL-C approached statistical significance in the case of MAE and was significant for MVE. There was a significant trend test result indicating a greater reduction in risk in patients with higher baseline total and non-HDL-cholesterol, and apo-lipoprotein B, without adjusting for multiple comparisons.

After weighting the RRs in the efficacy endpoints according to the reductions in LDL-C the trends for MAE were much reduced, and remained only statistically significant (before accounting for multiple testing) only for total cholesterol and waist circumference. For MVE, only the trend by baseline total cholesterol remained conventionally significant after accounting for LDL-C differences. Thus, no particular subgroup in SHARP obtained more or less benefit, other than that variation among subgroups in the absolute reduction of LDL-C.

Other efficacy studies

There were no new clinical pharmacology studies, including those that provided PK or PD data. There were a number of other references in the clinical part of the dossier which were not evaluated although the information was analysed to check consistency of pivotal data results.

Meta-analysis

No meta-analysis data was submitted for evaluation. There was a published meta-analysis, from the *Cholesterol Clinical Trialists* (CTT) group[19].

Additional supporting literature

Other reports pertinent to the claimed indications are:

MRL CSR (Synopsis), Multicenter study: *A Randomised Double-Blind Trial of the Effects on Coronary Heart Disease of Standard Versus Larger Blood Cholesterol Reductions with Statin Therapy and of Blood Homocysteine Reductions with Folate Based Therapy* (Protocol 158 MK-0733). [This study was previously submitted to the TGA for an application regarding simvastatin].

19 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

MRL CSR (Synopsis), Multicenter study: *A Randomized Study of the Effects on Mortality and Morbidity of HMG-CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Artery Disease.* (Protocol 102 MK0733). [This study was previously submitted to the TGA for an application regarding simvastatin].

There were no new clinical pharmacology studies, including those that provided pharmacokinetic or pharmacodynamic data.

Evaluator's conclusions on clinical efficacy for extension of indication

There are slight differences only in the interpretation of the efficacy data depending on whether the protocol primary outcome or SAP key outcome are used. Further, the analyses with Arms 1 and 2, as specified in the protocol, as opposed to adding Arms 3a and 3b, do not appear to change the interpretation of the results. This is likely to be contributed to by the fact that Arm 3 combined only had 886 patients, 9.6% of the total patient population of 9270 randomised to ezetimibe/simvastatin or placebo.

Summary of main findings

The main efficacy finding is that the combination ezetimibe/simvastatin 10/20 mg significantly reduced:

- the protocol defined primary endpoint, which was MVE - excluding patients originally randomised to simvastatin alone, and
- the 'key outcome' of the SAP, which was MAE in all randomised patients.

The point estimate and CI of the risk reduction are similar for MVE analysed in the whole patient population, or MVE in all randomised patients (a subsidiary comparison specified in the SAP).

Summary of other efficacy data

In analysis of the composite of MVE, the major (in terms of size, direction and significance) drivers of the reduction in MVE in the composite appear to be stroke and any revascularisation procedure. Reduction of 'major cardiac event' was not significant. Similarly, in the analysis of the effect of the combination versus placebo on the individual components of the MAE (undertaken in all randomised patients) significance was seen in non-haemorrhagic stroke, and any revascularisation procedure, but not on major coronary events. Slightly more patients allocated to ezetimibe/simvastatin suffered a haemorrhagic stroke 45 (1.0%) versus 37 (0.8%) in the placebo group, of which 27 and 23, respectively, were fatal. Although the numbers are small and the difference not significant, this observation of an increase in the risk of haemorrhagic stroke has been reported in studies of statins in the literature. But because the effect of the combination on ischaemic stroke was beneficial, the overall effect of treatment on stroke taken as a whole was statistically significantly positive, and was a contributor to the composite outcome.

However it should be noted that analysis of the composite of MAE was not analysed in the same patient set (Arms 1 and 2) as the primary endpoint and was not pre-specified in protocol. Further, that SHARP was powered to show an effect on the composite main endpoints (with somewhat greater power for MAE than MVE) but was underpowered for the individual components.

The principal renal outcome measure was progression to ESRD; this risk was not altered by taking ezetimibe/simvastatin.

Almost a quarter of the randomised patients died during the course of the study; but there was no mortality benefit allocated to ezetimibe/simvastatin or for deaths overall or

divided by cause, including vascular death (although this was not powered for vascular death).

Overall conclusion regarding efficacy

These data thus support a request to extend the use of the ezetimibe/simvastatin combination to reduce MVEs in patients over 40 years with CKD, who have not had revascularisation or a MI. They do not appear to support a benefit in a particular subgroup, a benefit on progression to end stage renal disease or a mortality benefit.

Safety

Studies providing evaluable safety data

In the pivotal SHARP study the protocol pre-specified that unblinded information on a limited number of safety outcomes were to be reviewed by the Steering Committee after each patient had completed 1 year of follow-up. However the SAP (finalised on 20 August 2010) indicated that the main safety analyses would be slightly different to those specified in the protocol, for the Arm 3 group. Specifically, that safety would involve comparisons of simvastatin versus ezetimibe/simvastatin versus placebo after the first year, ezetimibe/simvastatin versus placebo during the whole time period for Arms 1 and 2, and for the follow-up period after the second randomisation for Arms 3a and 3b.

Thus the 4193 patients allocated to ezetimibe/simvastatin (Arm 2), the 1054 patients allocated simvastatin alone (Arm 3) and the 4191 patients allocated to placebo (Arm 1) were compared (Arm 2 and Arm 3, Arm 2 and Arm 1, and Arm 3 and Arm 1).

The protocol also specified that central analysis of blood lipid concentrations on a random sample at 2.5 years and all at 4 years was to be undertaken and compared in an unblinded manner.

These data have been published[20].

Pivotal efficacy study

The SHARP investigators applied the ITT principle to all analyses of safety (as well as efficacy). Where applicable, RRs and associated statistics were calculated using the same log rank method as in the efficacy analyses, discussed under *Statistical methods*, above.

All safety data includes adverse events (AEs) regardless of whether or not a patient was taking study medication at the time the event occurred, apart from tables on myopathy and hepatitis, which counted only those patients allocated to ezetimibe/simvastatin who were actually compliant (in 'on treatment') with study medication, and to exclude patients in the placebo group who were taking non-study statin.

Safety was evaluated in two time periods.

1. Study treatment at 1 year (as discussed above) - 9438 patients during the first year of follow-up for all arms;
2. Data at whole follow-up for Arms 1 and 2, and for the period after 1 year till study completion for Arms 3a and 3b - 9270 patients.

Note: 168 of the 1054 patients in Arm 3 were not re-randomised at completion of year 1.

20 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.

During the conduct of SHARP, the occurrence of pre-specified SAEs of interest would mandate that all available information pertaining to the event be reviewed by CTSU clinicians (blinded to study treatment). These then adjudicated the event as described in the Standard Operating Procedure (SOP) for event adjudication.

In the pivotal efficacy study (SHARP), the following safety data were collected:

- *General AEs*. Apart from SAEs only AEs of special interest, or that led to discontinuation of study treatment were recorded. Non-serious AEs (NSAEs) were not routinely collected in SHARP unless they led to study discontinuation.
- *AEs of particular interest*:
  - cause specific mortality
  - development of diabetes mellitus, a tertiary endpoint in both the protocol and the SAP assessed by reports of diabetes as an SAE and by the initiation of diabetic medications in patients not known to have diabetes mellitus at randomisation
  - cancer
  - hepatitis
  - biliary disease
  - pancreatitis
  - events reported as myopathy, muscle symptoms or rhabdomyolysis
  - CK elevations > 10 times ULN
  - other adverse experiences
- SAEs

The occurrence of SAEs was sought at each study visit. LCC staff decided whether a SAE was related to study medication. CTSU confirmed that all potentially treatment-related SAEs with the LCC to confirm that the event was an SAE and thought likely to be related to study treatment.

- Laboratory tests

These were performed in 10% of random subsamples at 1 year and 4 years, and in all patients at 2.5 years. The main analysis was the effects of ezetimibe/simvastatin versus placebo on:

  - total cholesterol
  - LDL-C
  - HDL-cholesterol
  - non-HDL-cholesterol
  - triglycerides
  - apo-lipoprotein-B
  - apo-lipoprotein-A1
  - proteinuria (albumin:creatinine ratio)
  - creatinine
  - cystatin C

Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as a primary outcome.

Adverse events

All adverse events

Pivotal study - First year

Table 5 shows the suspected SAEs during the first year of treatment on each of the 3 arms of the study. Overall 468 (11.2%) in the ezetimibe/simvastatin versus 111 (10.6%) in the simvastatin 20 mg and 440 (10.6%) in the placebo groups complained of muscle pain. Other AEs are summarised in Table 6.

Table 6. SHARP study – suspected serious adverse experience reactions during the first year of treatment in each arm of the study.

	Ezetimibe/ simvastatin 10/20 mg (N=4193)	Simvastatin 20 mg (N=1054)	Placebo (N=4191)
Suspected Serious Adverse Reaction	n	n	n
CK>10 ≤40xULN, muscle symptoms[†]	1	0	1
CK>40xULN, no muscle symptoms	0	0	1
Cholelithiasis	1	0	0
Acute pancreatitis-drug induced	1	0	0
Gastritis	0	0	1
Difficulty controlling INR	1	0	0
Eczema/dermatitis	1	0	0
Psoriasis	0	0	1
Allergic or anaphylactic reaction	0	1	1
Total	**5 (0.12%)**	**1 (0.09%)**	**5 (0.12%)**

[†] These patients meet the criteria for myopathy, as traditionally defined and used by Merck.
Note: Suspected serious adverse reaction refers to an unwanted or harmful reaction that is considered by the reporting investigator to be both serious and thought likely to be directly related to the study treatment based upon information from the patient and/or the patient's physician.

It should be noted that the definitions of myopathy and rhabdomyolysis were slightly different between the sponsor (reflected in the protocol) and the Steering Committee (reflected in the SAP). This is reflected in Table 7, below for safety data at 1 year (this is Table V from the SHARP Steering Committee publication[21]). The Merck definition of myopathy is CK elevation > 10 times ULN plus unexplained muscle pain or weakness, which was used in the study report. The definition of rhabdomyolysis used in the study report is myopathy with CK > 40 times ULN.

21 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.

Table 7. SHARP Study - safety at 1 year (Table V from the SHARP Steering committee publication)

	Placebo	Simvastatin only	Ezetimibe plus simvastatin	P*	P†
Number randomized	4191	1054	4193		
Muscle pain	393 (9.4%)	103 (9.8%)	430 (10.3%)	.19	.68
CK					
>5× but ≤10 × ULN					
Asymptomatic	11 (0.3%)	5 (0.5%)	16 (0.4%)	.44	.88
Muscle symptoms present	3 (0.1%)	1 (0.1%)	1 (0.0%)	.62	.86
>10× but ≤40 × ULN					
Not on dialysis‡					
No end-organ damage§					
Asymptomatic	0 (0.0%)	1 (0.1%)	0 (0.0%)	–	.46
Muscle symptoms present	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–
With end-organ damage§	4 (0.1%)	0 (0.0%)	1 (0.0%)	.37	1.0
On dialysis‡					
Asymptomatic	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
Muscle symptoms present	0 (0.0%)	0 (0.0%)	1 (0.0%)	1.0	1.0
>40× ULN					
Not on dialysis‡					
With end-organ damage§	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–
Persistently elevated liver transaminases‖	5 (0.1%)	0 (0.0%)	7 (0.2%)	.77	.39
Hepatitis¶					
Infective	6 (0.1%)	1 (0.1%)	6 (0.1%)	1.0	1.0
Noninfective	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
No cause identified	1 (0.0%)	1 (0.1%)	2 (0.0%)	1.0	1.0
Complications of gallstones					
Acute pancreatitis	5 (0.1%)	0 (0.0%)	4 (0.1%)	1.0	.70
Other complications	19 (0.5%)	3 (0.3%)	17 (0.4%)	.87	.77
Hospitalization with gallstones#	4 (0.1%)	4 (0.4%)	2 (0.0%)	.68	.02
Pancreatitis					
Acute (excluding gallstones)	7 (0.2%)	1 (0.1%)	2 (0.0%)	.18	1.0
Chronic	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–

* Test of difference between ezetimibe/simvastatin combination therapy and placebo.
† Test of difference between ezetimibe/simvastatin combination therapy and simvastatin only.
‡ At the time of presentation with raised CK.
§ End-organ damage is defined as acute initiation of dialysis or a >20% rise in serum creatinine. Among patients already on dialysis, it is not possible to determine if end-organ damage has occurred.
‖ At least 2 consecutive ALT or AST >3× ULN without other indication of hepatitis.
¶ Infective hepatitis—definite evidence of an infective cause; noninfective hepatitis—definite evidence of a noninfective cause; no cause identified—includes cases with negative viral serology result and those with no viral serology result available.
# With no reported complications.

Muscle AEs during the first year of treatment

At each follow-up or early recall visit, patients were asked whether they had developed muscle pain or weakness. In addition, CK was measured at each study visit and whenever there was unexplained muscle pain. Study medication was stopped if the CK was persistently > 5 times ULN and associated with unexplained muscle pain, or if CK > 10 times ULN with unexplained muscle pain.

There were no significant differences in CK elevations, muscle symptoms or the development of renal damage in 4193 patients allocated to ezetimibe/simvastatin for the first year compared to 1054 allocated to simvastatin and 4191 on placebo. Elevations in CK > 10 times ULN but < 40 times ULN occurred in 11 patients, 4 (0.10%) randomised to ezetimibe/simvastatin, 1 (0.09%) patient allocated to simvastatin 20 mg, and 6 (0.14%) patients allocated to placebo.

In the first year of treatment, 2 patients developed myopathy 1 randomised to ezetimibe/simvastatin and 1 to placebo. These patients had CK elevations > 10 times and £ 40 times ULN, respectively. As defined in the protocol there were no cases of rhabdomyolysis in the first year, see Table 8, below, and Table 7 above.

Table 8. SHARP Study – Muscle safety data at one year in patients allocated to placebo, simvastatin 20 mg and ezetimibe/simvastatin 10/20 mg

Event	Ezetimibe/ simvastatin 10/20 mg (N=4193) n (%)	Simvastatin 20 mg (N=1054) n (%)	Placebo (N=4191) n (%)
CK >5 but ≤10×ULN			
Asymptomatic	17 (0.41%)	5 (0.47%)	11 (0.26%)
Muscle symptoms	1 (0.02%)	1 (0.09%)	3 (0.07%)
Subtotal:	**18 (0.43%)**	**6 (0.57%)**	**14 (0.33%)**
CK >10 but ≤40×ULN			
Not on dialysis			
No renal damage			
Asymptomatic	0 (0.00%)	1 (0.09%)	0 (0.00%)
Muscle symptoms	0 (0.00%)	0 (0.00%)	0 (0.00%)
With renal damage			
Asymptomatic	1 (0.02%)	0 (0.0%)	3 (0.07%)
Muscle symptoms	0 (0.0%)	0 (0.0%)	1 (0.02%)
On dialysis			
Asymptomatic	2 (0.05%)	0 (0.00%)	2 (0.05%)
Muscle symptoms	1 (0.02%)	0 (0.00%)	0 (0.00%)
Subtotal:	**4 (0.10%)**	**1 (0.09%)**	**6 (0.14%)**
Asymptomatic	3 (0.06 %)	1 (0.09%)	5 (0.12%)
Muscle symptoms	1 (0.02%)	0 (0.0%)	1 (0.02%)
CK >40×ULN			
Not on dialysis			
No renal damage			
Asymptomatic	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle symptoms	0 (0.00%)	0 (0.00%)	0 (0.00%)
With renal damage			
Asymptomatic	0 (0.0%)	0 (0.0%)	1 (0.02%)
Muscle symptoms	0 (0.0%)	0 (0.0%)	0 (0.00%)
On dialysis			
Asymptomatic	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle symptoms	0 (0.00%)	0 (0.00%)	0 (0.00%)
Subtotal:	**0 (0.00%)**	**0 (0.00%)**	**1 (0.02%)**
Asymptomatic	0 (0.0%)	0 (0.0%)	1 (0.02%)
Muscle symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)

Patients are counted only once in this table. If a patient had more than one report of elevated CK, the highest CK is reported in this table.
Minor differences between this table and the corresponding table in the SHARP baseline paper (American Heart Journal 2010;160:785-94) are attributable to the use of slightly different rules for censoring events.

Adverse effects related to liver, gallbladder and pancreas during the first year of treatment

Persistently elevated transaminases occurred in 13 (0.31%), 1 (0.09%), and 6 (0.14%) patients in the ezetimibe/simvastatin, simvastatin, and placebo groups, respectively. There were 4 cases of hepatitis of non-infective or of unknown etiology; 2 (0.1%) were in the ezetimibe/simvastatin group and 2 (0.05 %) in placebo. The results in Table 7 are different to the CSR, however there is no difference in the conclusions.

Pivotal study – safety for the whole period

This includes the safety of ezetimibe/simvastatin 10/20 mg versus placebo in the entire period – that is, Arms 1 and 2 for the whole period, and Arm 3 after the end of year 1 (when this Arm was reallocated to Arm 1 or 2, as 3a and 3b).

1. Cause specific mortality

This includes overall and cause-specific mortality, including CHD mortality, vascular mortality and non-vascular mortality in all patients ever randomised to ezetimibe/simvastatin versus placebo.

Almost a quarter (24%) of the randomised patients died during the course of the study. About one third of the deaths were due to vascular causes. The numbers of deaths overall and of deaths by cause were not significantly different in patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo. Specifically there were no significant differences between the ezetimibe/simvastatin and placebo groups in mortality from specific non-CHD or non-vascular causes, including cancer.

2. Development of diabetes and complications of diabetes

There was no difference in risk of developing new diabetes between ezetimibe/simvastatin or placebo (RR 1.06, 95% CI 0.85-1.32; p = 0.59).

There was a non statistically significant but numerically larger significant complication rate among patients with diabetes mellitus allocated to ezetimibe/simvastatin 10/20 mg than placebo (83/4650) versus (67/4620), p = 0.56. Hypoglycemic episodes were more common in patients with diabetes at baseline who were randomised to ezetimibe/simvastatin, the difference almost reaching statistical significance (RR 1.50, 95% CI 0.99-2.28, p = 0.06)

3. Cancer

A safety concern surrounding ezetimibe has been possible effects on the risk of cancer, which was raised by the *Simvastatin and Ezetimibe in Aortic Stenosis* (SEAS) study in 2008[22]. The total number of patients with any incident cancer did not differ between ezetimibe/simvastatin 10/20 mg and placebo. For deaths from any incident cancer, the RR was 1.15 (95% CI 0.90-1.48) and for deaths from any cancer including the pre-randomisation cohort, the RR was 1.17 (95% CI 0.92-1.48). The only site in SHARP where there was a difference in the combination arm as compared to placebo was the bowel/intestine (53 versus 35), without any adjustment for multiplicity.

4. Muscle safety

Overall, approximately 21% of all patients reported muscle pain at during the study (21.5% in the ezetimibe/simvastatin group and 20.9% in the placebo group). More patients in the ezetimibe/simvastatin group compared to the placebo group discontinued treatment because of muscle pain: 49 (1.1%) versus 28 (0.6%).

Myopathy occurred in 8 (0.17%) patients taking ezetimibe/simvastatin and 3 (0.065%) on placebo (and not taking a non-study statin) in an 'on treatment' analysis. Of these cases, 4 in the ezetimibe/simvastatin group and none in the placebo group had rhabdomyolysis, while none of the 3 cases of myopathy in the placebo group were deemed to be rhabdomyolysis. All 8 patients in whom myopathy including rhabdomyolysis developed while taking ezetimibe/simvastatin recovered after stopping study medication. These case histories (including whether muscle pain was present or absent) and further analyses are reported in the CSR.

Overall incidence of CK elevation on routine testing in all patients allocated to ezetimibe/simvastatin versus placebo (Arms 2 + 3b versus Arms 1 + 3a) was similar for CK > 5 £ 10 times ULN, > 10 £ 40 times ULN, and > 40 times ULN.

22 Nissen SE. Analyses of cancer data from three ezetimibe trials. N Engl J Med 2009;360(1):86-7.

5. Hepatitis

In an ITT analysis, hepatitis was reported in 21 (0.45%) patients allocated to ezetimibe/simvastatin 10/20 mg and 18 (0.39%) patients allocated to placebo. There were similar numbers of cases of infective hepatitis, non-infective hepatitis and hepatitis with no cause identified in both groups. An on-treatment analysis was undertaken which showed that there was no difference in the numbers or proportions of patients who developed hepatitis, overall or from different causes for 19 (0.41%) in ezetimibe/simvastatin versus 18 (0.39%) in placebo groups.

6. Pancreatitis and gallstones

There was a similar risk of complications of gallstones, hospitalisations for gallstones or pancreatitis, regardless of treatment. Specifically the number of patients who developed complications of gallstones, or who were hospitalised with gallstones (without complications) and the number of patients who developed pancreatitis as a complication of gallstones, or pancreatitis without gallstones was similar. Acute pancreatitis as a complication of gallstones was similar and pancreatitis without gallstones occurred in less of the ezetimibe/simvastatin than the placebo group.

Treatment-related AEs

Non-fatal SAEs

There was no significant difference in the number of events between the ezetimibe/simvastatin group and placebo, and the only difference that came close to significance was 'any endocrine' event. This occurred in 58/4650 (1.2%) of people taking ezetimibe/simvastatin versus 39/4620 (0.8%) in the placebo group (RR 1.47 (0.99-2.19) p = 0.06.

SAEs attributed to study treatment

There were 20/4650 of these events in the ezetimibe/simvastatin and 13/4620 in the placebo Arm. The most common were CK elevations > 10 times ULN, observed in 7 patients allocated to ezetimibe/simvastatin 10/20 mg and 4 on placebo. SSARs led to discontinuation of study treatment in 17 (0.4%) patients allocated to ezetimibe/simvastatin 10/20 mg and 12 (0.3%) on placebo. Serious AEs that led to discontinuation of study treatment before the scheduled were similar between the two groups. Listed below are the details of the cases of SAEs from ezetimibe/simvastatin documented in the CSR:

- myopathy: n = 4
- pancreatitis: n = 3
- rhabdomyolysis: n = 3
- interstitial nephritis: n = 1
- hepatitis: n = 1
- diarrhoea: n = 1
- dermatitis: n = 2
- cholelithiasis: n = 1
- angioedema: n = 1
- gastrointestinal haemorrhage: n = 1

Deaths and other SAEs

In the pivotal SHARP study, 24% of the randomised subjects died during the course of the study, with about one third of the deaths due to vascular causes. There were no statistically significant differences in mortality between patients allocated to ezetimibe/simvastatin or placebo, for deaths overall or divided by cause, specifically vascular death or non-vascular death and overall mortality.

Discontinuation due to AEs

There were more non significant AEs that led to study drug discontinuation in patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo, largely due to muscle pain (49/4650 in ezetimibe/simvastatin versus 28/4620 in placebo), abnormal safety blood results (43/4650 in ezetimibe/simvastatin versus 28/4620 in placebo), and reported skin symptoms (19/4650 in the ezetimibe/simvastatin versus 8/4620 in placebo). The total number of patients stopping study medication due to any AE, whether serious or not, or drug-related or not, was 479 (10.3%) of patients allocated to ezetimibe/simvastatin and 450 (9.7%) of patients allocated to placebo.

As discussed above, 5 patients taking ezetimibe/simvastatin (compared to 4 patients taking placebo) had non-infective hepatitis. Of the 5 study medication was permanently discontinued in 3 patients and transaminases improved in all. Study medication was temporarily discontinued and then restarted in the other 2 patients with transaminases remaining below 3 times ULN back on study treatment. The 2 patients with hepatitis of unknown etiology had their study drug stopped temporarily and transaminases remained below 3 times ULN when restarted on medications.

Patients stopping study medication due to an AE accounted for about one third of the non-compliant patients.

Laboratory tests

Liver function

Elevation in transaminases in first year of treatment

Elevated transaminases were defined as elevations > 3 times ULN in ALT and/or AST on 2 consecutive visits. The number of patients during the first year of treatment with post-baseline elevations in ALT and/or AST > 3 times ULN[23] were higher in the ezetimibe/simvastatin group (43/4170 (1.0%)) than simvastatin alone (6/1051 (0.6%)) and placebo (22/4166 (0.5%)).

Elevation in transaminases following randomisation

Following randomisation, 105 (2.3%) patients allocated to ezetimibe/simvastatin and 76 (1.7%) allocated to placebo had at least one elevation of ALT and/or AST > 3 times ULN. Throughout the study, the incidence of elevations in transaminases > 3 times ULN was greater in patients allocated to ezetimibe/simvastatin versus placebo.

Table 8 shows the number of patients with persistently elevated transaminases, the incidence of which was low (< 1%) and similar in both treatment groups. In 14 (0.30%) patients allocated to ezetimibe/simvastatin and 10 (0.22%) patients allocated to placebo, consecutive elevations in transaminases were associated with hepatitis.

23 The sponsor commented that these elevations were not necessarily persistent.

Table 9. SHARP Study – Number (%) patients with ALT and/or AST > 2 times ULN: All patients randomised to ezetimibe/simvastatin 10/20 mg versus placebo (Arms 2 + 3b versus Arms 1 + 3a)

Degree of Elevation	Ezetimibe/simvastatin 10/20 mg n/N (%)	Placebo n/N (%)
>2 ≤3×ULN	162 /4615 (3.51%)	112 /4587 (2.44%)
>3 ≤5×ULN	66 /4615 (1.43%)	49 /4587 (1.07%)
>5 ≤10×ULN	29 /4615 (0.63%)	15 /4587 (0.33%)
>10×ULN	10 /4615 (0.22%)	12 /4587 (0.26%)

Kidney function

The deterioration of renal function and progression to ESRD was covered in the *Efficacy* section, as a secondary endpoint.

Other clinical chemistry

Non-serious laboratory adverse experiences were not captured. Measurement of other chemistry such as albumin and phosphate was measured and documented (with comparison between the three groups). There were no concerns reported.

Clinical evaluation of laboratory tests

The listing of values from specific laboratory safety tests, including abnormal laboratory values by patient are in the CSR. Specifically, further evaluation of the laboratory tests CK, ALT, and AST increases are covered; but they are not covered here because there are no further safety concerns in these reports over and above what has been covered in the sections on myopathy and liver function above.

LDL-C lowering

At the initial randomisation and at the approximate study midpoint of 2.5 years, all patients were scheduled to have lipids measured with a subsample of 10% also scheduled to have lipids measured centrally at 12 and 48 months after randomisation. The lipid analyses were done on an ITT basis, so non-attendees were assumed to have stopped taking the study medication and had their baseline measurement imputed for the scheduled lipid measurement (and those with no baseline measurement were not included in the analyses).

LDL-C was measured to examine a number of factors, including compliance, to repower the analysis of the study by the Steering Committee when it was apparent that the LDL lowering seen would not be sufficient to translate into the reduction in clinical endpoints that had powered the study, and to compare if efficacy and safety effects were related to changes in LDL.

Of note is that the mean reduction in LDL (in mmol and % reduction) was affected by the baseline lipid value. For example, when patients were divided by approximate tertiles according to their baseline lipid values at 2.5 years the difference between the mean reduction in LDL-C in patients allocated to ezetimibe/simvastatin and those allocated to placebo was 0.63 mmol/L (32%), in patients with baseline LDL-C < 2.5 mmol/L, 0.86 mmol/L (31%) in patients with baseline LDL-C ≥ 2.5 < 3.0 mmol/L, and 1.07 mmol/L (29%) in patients with baseline LDL-C ≥ 3.0 mmol/L.

With regard to compliance, this became a major issue for the study. For example, adherence to the allocated treatment declined (dropouts) as the study progressed, and an increasing number of patients took a non-study statin (drop-ins), which closed the difference in LDL-C between the ezetimibe/simvastatin and placebo treatment groups, from 1.09 mmol/L (42 mg/dL, 39%) at 1 year to 0.78 mmol/L (30 mg/dL, 29%) at 4 years.

At 1 year, compliance was already an issue with 25% of all surviving patients allocated to ezetimibe/simvastatin taking less than 80% of the allocated medication. At 2.5 years, only 66% of the patients allocated to ezetimibe/simvastatin 10/20 mg were taking at least 80% of the study medication and another 6% were taking a non-study statin; in addition, 9% of the patients allocated to placebo were taking non-study statin. At 2.5 years of follow-up, 72% of the ezetimibe/simvastatin group was receiving lipid-lowering treatment versus 9% of the placebo group, which is equivalent to a 'net' difference of 63%. This would have resulted in a larger mean difference in LDL (1.35 mmol/L) than was seen in the trial.

Analysing the LDL-C in Arm 3 with the ezetimibe/simvastatin group at year 1 (1054 subjects) it can be seen that the ezetimibe component accounted for 31% of the LDL-C reduction achieved with the combination ezetimibe/simvastatin.

Creatine kinase

CK tends to be higher in patients with CKD, seen also in the SHARP study. CK was measured at every follow-up visit. Overall incidence of CK elevation on routine testing in all patients allocated to ezetimibe/simvastatin versus placebo was similar for CK > 5 £ 10 times ULN, > 10 times £ 40 times ULN, and > 40 times ULN. 47 patients (1.0%) allocated to placebo had at least one CK value between 5 times and 10 times ULN, and an additional 21 (0.46%) patients had an elevation > 10 times ULN.

Haematology

Haematology tests were not an endpoint of the study and no AEs were reported that required an analysis of haematology laboratory measures.

Electrocardiograph (ECG)

ECG testing was not an endpoint of the study and no AEs were reported that required an analysis of ECG measurements.

Vital signs

There were no differences in blood pressure between the treatment groups. BMI also did not change throughout the trial, with similar values between the two groups.

Pregnancy

Women of childbearing potential were excluded from the trial.

Post-marketing experience

Both components of Vytorin have been marketed for up to 8 years, and the combination is also marketed in Australia. No new post marketing data were submitted.

Safety issues with the potential for major regulatory impact

There were no newly identified issues demonstrated in the SHARP study. Standard pharmacovigilance processes as stated in the RMP are appropriate.

Liver toxicity

Elevations in transaminases with both components are recognised. This study is consistent with other studies in terms of the frequency for adverse liver events.

Haematological toxicity

No new issues were reported.

Serious skin reactions

There were more AEs from skin in the combination group, however these were not serious.

Cardiovascular safety

No new issues were reported.

Unwanted immunological events

No new issues were reported.

Other safety issues

Safety in special populations

This combination was studied in adults over 40 with CKD. It was not studied in other special populations.

Safety related to drug-drug interactions and other interactions

There was no new evidence presented here.

Safety in this CKD population

There has been a concern for a period of time regarding the efficacy and safety of using medications that lower LDL in a population such as CKD, where low cholesterol is associated with mortality. However, in this study, there was no overall effect on mortality.

Evaluator's overall conclusions on clinical safety

Summary

SHARP was a clinical trial in a CKD population without symptomatic atherosclerotic disease at baseline, who received combination therapy with ezetimibe and simvastatin or placebo. They did not receive sequential treatment of ezetimibe added to simvastatin. During this study almost one quarter of the patients died, and approximately one third of the pre-dialysis patients developed ESRD. However, there was no significant difference in development of ESRD or mortality between the ezetimibe/simvastatin and placebo groups.

Further using the protocol analysis, there was not any significant difference in the overall number of AEs between the ezetimibe/simvastatin group or placebo, and the only difference that came close to significance was 'any endocrine' event, p = 0.06. Serious AEs that led to discontinuation of study treatment before the scheduled time were similar between the two groups.

The overall incidence of CK elevation on routine testing in all patients allocated to ezetimibe/simvastatin versus placebo was similar for CK > 5 £ 10 times ULN, > 10 times £ 40 times ULN, and > 40 times ULN.

Of concern:

- The number of patients during the first year of treatment with post-baseline elevations in ALT and/or AST > 3 times ULN[24] were higher in the combination group than simvastatin alone and placebo (1.0%, 0.6% and 0.5% respectively). Similarly, persistently elevated transaminases occurred in 13 (0.31%), 1 (0.09%), and 6 (0.14%) of patients in ezetimibe/simvastatin, simvastatin, and placebo groups, respectively.
- The results in Table 6, above, are different to the CSR, however there is no difference in the conclusions. This is said to be due to the slightly different censoring but it may be helpful to have some conclusions around this.

24 The sponsor noted that these elevations were not necessarily persistent.

- There were more non-significant AEs that led to study drug discontinuation in patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo, largely due to muscle pain, abnormal safety blood results and reported skin symptoms. The total number of patients stopping study medication due to any AE, whether serious or not, or drug-related or not, was marginally higher in the ezetimibe/simvastatin than placebo group, including discontinuation because of muscle pain and myopathy.
- Myopathy and rhabdomyolysis occurred more often in patients taking ezetimibe/simvastatin than placebo.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ezetimibe/simvastatin in the proposed usage are:

- Reduction in the risk of MVEs

This is slightly different to the sponsor's request to extend the indication for ezetimibe/simvastatin "*..to reduce the risk of major cardiovascular events in patients with CKD…*" Strict application of the data would request the extension be granted to patients with CKD Class III-V without prior MI or coronary revascularisation to reduce MVEs.

First round assessment of risks

The risks of ezetimibe/simvastatin in the proposed usage are:

- Small number of excess cases of myopathy and rhabdomyolysis
- Higher risk of ALT and/or AST > 3 times ULN
- Lack of knowledge over the efficacy benefit over simvastatin or ezetimibe alone

First round assessment of benefit-risk balance

The benefit-risk balance of ezetimibe/simvastatin 10/20 mg daily in adults > 40 years with CKD in patients without prior MI or revascularisation, is favourable because it reduces MVEs; and the risks in this study are those known to be associated with the profiles of simvastatin and ezetimibe individually.

First round recommendation

It is recommended that the extension of indication for Vytorin to reduce the risk of major cardiovascular events in patients with CKD be approved. However alternate wording such as that discussed in the section on *First round benefit-risk assessment*, above, should be considered.

List of questions

The clinical evaluator recommended the following six questions required discussion from the sponsor:

Question 1: In the SHARP study it is noted that 168 out of the 1054 patients in Arm 3 were not re-randomised at the completion of year 1. What were the reasons for this? For each reason please specify the relevant number of patients. What were the consequences for the final analysis of the SHARP study flowing from this incomplete randomisation?

Question 2: Table V in the SHARP publication[25] presents safety findings which are different from those which are presented in the CSR after 1 year and a footnote to the Table states that these differences are attributable to the use of slightly different rules for censoring events and a more precise categorisation of gallstone events. Please clarify in considerably more detail the "slightly different rules for censoring events" as well as the "more precise categorisation of gallstone events". Are any of the differences affected in any way by any differences in definition between SAP and protocol safety? Is there any possibility that any of the differences may have clinical significance? If so, please clarify in detail.

Question 3: What would the efficacy and safety data have shown if the simvastatin Arm had been continued for the entirety of the study? This would have provided information on the additional benefit of ezetimibe to simvastatin therapy, with regard to both efficacy and safety. Therefore, apart from other statin data in CKD, does the sponsor have data on the clinical benefits/side effects of simvastatin in CKD after 4-5 years? Please provide a detailed summary of these data.

Question 4: What was the final power of the SHARP study to evaluate the primary composite endpoint with a 2-sided p value? Please provide all details and working which show how this final value for the power of the study was derived.

Question 5: Does the sponsor have or know of any data which relate to the safety and any efficacy of ezetimibe in CKD with statins other than simvastatin? Please provide a detailed summary of these data and then compare and contrast these data with the known data for the combination of ezetimibe and simvastatin in CKD.

Question 6: Routine risk minimisation activities: The submitted EU Risk Management Plan (RMP) and the Australian Specific Annex did not provide any specific information detailing the ongoing safety concerns and how these are to be addressed in the EU SPC and the Australian PI respectively. Consequently please detail the routine risk minimisation activities proposed in the draft Australian PI for the specified ongoing safety concerns, as well as identifying and justifying any differences to the EU SPC.

Question 7: In addition to requesting the sponsor address the above questions, the TGA advised the sponsor that additional safety considerations may be raised by the clinical and nonclinical evaluators. It was important to ensure that the information provided in response to these included a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations raised in the clinical or nonclinical requests for information, the sponsor is requested to provide information that is relevant and necessary to address the issue in the RMP.

25 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94. Table V in this publication is titled Safety at 1 year by initial randomized treatment at allocation and is Table 6 in this AusPAR.

Summary of sponsor's response to the *List of questions*

Response to Question 1

In the SHARP study, Arm 3 patients received simvastatin alone for one year. They were re-randomised only if they attended a study clinic visit at (or after) the 1 year time point. A total of 168 (16%) participants in Arm 3 were not re-randomised at one year, and the reasons given for this were summarised in the CSR as follows:

- 46 (4%) died prior to re-randomisation
- 103 (10%) stopped treatment during the first year
- 19 (2%) did not attend clinic for re-randomisation

The baseline characteristics (at the first randomisation) of the 168 patients who were allocated to Arm 3 but not re-randomised are shown in Table 10, and it may be seen that these patients were similar to the 9270 included in the final analyses (see Table 11). Consequently, the exclusion of these 168 patients would not be expected to influence the study findings.

Table 10. SHARP study: baseline characteristics at the first randomisation.

Baseline Characteristics and Laboratory Measurements at Initial Randomization of Arm 3 Patients who were not Re-randomized

Baseline characteristic *Number (& percentage) or mean ± SD*	*Arm 3 and not re-randomized (n=168)*
Prior vascular disease	*26 (15%)*
Diabetes	*42 (25%)*
Male	*100 (60%)*
Age at randomization (years)	*63 ± 11*
Current smoker	*23 (14%)*
Diastolic BP (mmHg)	*78 ± 12*
Systolic BP (mmHg)	*138 ± 22*
Total cholesterol (mmol/L)	*4.68 ± 1.20*
LDL cholesterol (mmol/L)	*2.62 ± 0.89*
HDL cholesterol (mmol/L)	*1.08 ± 0.35*
Triglycerides (mmol/L)	*2.17 ± 1.20*
Body mass index (kg/m^2)	*26.5 ± 5.1*
Renal status	
On dialysis	*76 (45%)*
Haemodialysis	*57 (34%)*
Peritoneal dialysis	*19 (11%)*
Not on dialysis	*92 (55%)*
MDRD estimated GFR (ml/min/1.73m^2)Â†‡	*22.5 ± 11.3*
≥60	*0 (0%)*
≥30 <60	*23 (27%)*
≥15 <30	*33 (39%)*
<15	*28 (33%)*
Not available	*8*
Urinary albumin:creatinine ratio (mg/g) [median (interquartile range)]Â†‡	*281 (37 - 1289)*
<30	*17 (24%)*
≥30 ≤300	*20 (28%)*
>300	*35 (49%)*
Not available	*20*

† Percentages exclude participants for whom data were not available for that category.
‡ For patients not on dialysis.

Table 11. SHARP study - baseline characteristics at latest randomisation

Baseline Characteristics and Laboratory Measurements at Latest Randomization in the 9270 Participants

Baseline characteristic	*Arm 2+3b Eze/simv (n=4650)*	*Arm 1+3a Placebo (n=4620)*
Number (& percentage) or mean ± SD		
*Prior vascular disease**	*711 (15%)*	*682 (15%)*
*Diabetes**	*1054 (23%)*	*1040 (23%)*
Male	*2915 (63%)*	*2885 (62%)*
*Age at randomization (years)**	*62 (12)*	*62 (12)*
Current smoker	*626 (13%)*	*608 (13%)*
*Diastolic BP (mmHg)**	*79 (13)*	*79 (13)*
*Systolic BP (mmHg)**	*139 (22)*	*139 (22)*
Total cholesterol (mmol/L)	*4.88 (1.20)*	*4.90 (1.17)*
LDL cholesterol (mmol/L)	*2.77 (0.88)*	*2.78 (0.87)*
HDL cholesterol (mmol/L)	*1.12 (0.35)*	*1.11 (0.34)*
Triglycerides (mmol/L)	*2.31 (1.76)*	*2.34 (1.68)*
*Body mass index (kg/m^2)**	*27.1 (5.7)*	*27.1 (5.6)*
Renal status*		
On dialysis	*1533 (33%)*	*1490 (32%)*
Haemodialysis	*1275 (27%)*	*2363 (27%)*
Peritoneal dialysis	*258 (6%)*	*238 (5%)*
Not on dialysis	*3117 (67%)*	*3130 (68%)*
MDRD estimated GFR (ml/min/1.73m^2)Â†‡*	*26.6 (12.9)*	*26.6 (13.1)*
≥60	*44 (1%)*	*44 (1%)*
≥30 <60	*1100 (37%)*	*1055 (35%)*
≥15 <30	*1246 (41%)*	*1319 (44%)*
<15	*614 (20%)*	*607 (20%)*
Not available	*113*	*105*
Urinary albumin:creatinine ratio (mg/g) [median (interquartile range)]Â†‡	*217 (44-788)*	*196 (43-748)*
<30	*545 (20%)*	*562 (20%)*
≥30 ≤300	*1032 (37%)*	*1076 (39%)*
>300	*1203 (43%)*	*1156 (41%)*
Not available	*337*	*336*

† Percentages exclude participants for whom data were not available for that category.
‡ For patients not on dialysis.
* Variables updated at 1 year for Arm 3a and 3b patients.

Response to Question 2

The differences in the rules applied to Table V of the baseline SHARP paper (published in *Am Heart J* 2010;160: 785-94) and the CSR are summarised in Table 12 below:

Table 12. SHARP Study – Differences between the main publication and the CSR

Summary of Differences in Rules in the SHARP Paper and the CSR

	Reason	SHARP baseline paper: Table V	CSR
1 Year Censoring Date	1	Randomization + 394 days	Whichever was earlier of: - Randomization + 394 days, or - Follow-up 3 (ie, the one year clinic visit)
Definition of the date of a blood test	2	The date of the blood test was used	The date of the follow-up form when the blood test was requested was used
Additional Censoring Rule	3	Persistently elevated transaminases were censored if a hepatitis or other SAE were thought to be responsible	All persistently elevated transaminases were presented subdivided by explanatory causes
Additional Censoring Rule	4	A hepatitis event was censored because of later seroconversion to hepatitis C and is therefore counted in the infective hepatitis row only	No such rule was applied in the CSR
Error	5	Incorrect inclusion of a pre-randomization event (an erratum will be published)	Corrected
Categorization difference	6	Cholecystitis was considered a gallstone complication regardless of cause	Acalculous cholecystitis was not considered a gallstone complication
Additional Censoring Rule	7	If participants had 'acute pancreatitis' and an 'other complication' of gallstones within the first year, only the earlier event would be counted	No such rule was applied in the CSR

Compared to Table V (Table 6 in this AusPAR), the changes to the table titled *Muscle Safety Data at One Year in Patients Allocated to Placebo, Simvastatin 20 mg and Ezetimibe/Simvastatin 10/20 mg* of the CSR include:

- CK > 5 but £ 10 asymptomatic row: an increase from 16 (0.4%) to 17 (0.4%) in the ezetimibe/simvastatin Arm (reasons 1 and 2).
- CK > 10 but £ 40 asymptomatic row: an increase from 1 (0.02%) to 2 (0.05%) in the placebo Arm (reasons 1 and 2).

Compared to Table V, the changes to the table titled *Incidence of Hepatitis, Elevations in Transaminases, Complications of Gallstones, and Pancreatitis During the First Year of Treatment in Patients Allocated to Placebo, Simvastatin 20 mg and Ezetimibe/Simvastatin 10/20 mg* of the CSR include:

- Persistently raised liver transaminases row: an increase from 7 (0.2%) to 13 (0.3%) in the ezetimibe/simvastatin Arm; an increase from 0 (0%) to 1 (0.1%) in the simvastatin alone Arm; and an increase from 5 (0.1%) to 6 (0.1%) in the placebo Arm (reason 3).
- Hepatitis no cause identified row: a decrease from 1 (0.1%) to 0 (0%) in the simvastatin only Arm (reason 4).
- Complications of gallstones, acute pancreatitis row: a decrease from 4 (0.1%) to 3 (0.1%) in the ezetimibe/simvastatin Arm (reason 5).
- Complications of gallstones, other complication row: an increase from 19 (0.5%) to 20 (0.5%) in the placebo Arm (reasons 5, 6 and 7).
- Pancreatitis (without gallstones), acute pancreatitis row: a decrease from 7 (0.2%) to 5 (0.1%) in the placebo Arm (reason 1).

The differences between Table V of the SHARP baseline paper and the tables of the CSR are minor and do not have any bearing on the interpretation of the trial results. The tables in the CSR should be considered the definitive results.

Response to Question 3

Continuation of the simvastatin alone Arm to the end of the study would not have yielded reliable information on the safety and efficacy of adding ezetimibe to simvastatin, because such a comparison would not have had sufficient statistical power to detect the expected differences in major atherosclerotic or MVEs. Such a trial would have had to detect a proportional reduction around one third as large as was observed (because about one third of the absolute LDL-C reduction produced by ezetimibe/simvastatin was contributed by ezetimibe). Consequently, the sample size required for a trial assessing both the effects of ezetimibe/simvastatin versus simvastatin and ezetimibe/simvastatin versus placebo would have required 9 times (that is, the reciprocal of one third squared) as many participants (that is, over 80,000 patients) in order to have similar power to SHARP.

SHARP was designed to address the main clinical question concerning nephrologists which was whether a large reduction in LDL-C could be achieved safely with ezetimibe/simvastatin and whether such a reduction would reduce the risk of MAEs. The question of whether adding ezetimibe to simvastatin yields additional benefit is most appropriately addressed in other populations at higher risk of CHD, as is currently being done in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT trial) among 18,000 patients with an acute coronary syndrome.

Neither the study sponsor (the University of Oxford) nor the company possess any data on the effects of simvastatin in CKD after 4-5 years.

Response to Question 4

Approximate power equals:

$$100 \times \Phi\left(\frac{|p_1 - p_0|}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_0(1-p_0)}{n_0}}} - z_{\frac{\alpha}{2}}\right)$$

where p_1 and p_0 are the proportions of patients in the two arms having a MAE, n_1 and n_0 are the number of randomised patients in the two arms, $Za/2$ is the critical value for the hypothesis test (that is, 1.96 for 2p = 0.05 and 2.576 for 2p = 0.01) and f is the standard normal cumulative distribution function.

Setting $p_1 = 526/4650$, $p_0 = 619/4620$, $n_1 = 4650$ and $n_0 = 4620$ in the above equations gives power estimates of 86% when a = 0.05 and 68% when a = 0.01.

Response to Question 5

Neither the study sponsor nor the company have knowledge of any such reliable data. The data available have been obtained in short term efficacy trials with lipid levels as endpoints, in patients with very mild kidney disease as "SHARP like" patients are excluded from our regular trials.

Response to Question 6

The Australian PI and the European SPC are maintained to contain sufficient information to inform prescribers and patients about the product's risks and to provide guidance with respect to the mitigation of those risks, where applicable. The Australian PI contains robust information regarding the risks specified in the RMP. As the SHARP trial identified no additional risks in the CKD patient population, no additional mitigation activities apart from the Australian PI language are needed for this group. The information in the Australian PI adequately addresses those safety concerns and no additional mitigation activities are considered to be necessary.

To detail the routine risk minimisation activities relating to the ongoing safety concerns raised in the European RMP, a table is provided identifying the specific sections in the proposed Australian PI and the latest approved EU-SPC where each ongoing safety concern has been addressed as a routine risk minimisation activity. Another table provided a side-by-side comparison of text from the proposed Australian PI and the latest approved EU-SPC that is relevant to the listed safety concerns, and justification of any major differences between the documents. Details of the text in the PI and SPC are beyond the scope of this AusPAR and therefore tables cited above and the remainder of the sponsor's response to this question has been omitted from this document.

Response to Question 7

The company does not consider that there have been any safety considerations raised by the clinical evaluator in questions 1 through 5 that would need to be addressed in the RMP.

Second round evaluation of clinical data submitted in response to TGA requests for information

Evaluation of updated CSR for the SHARP study

Questions raised by the Food and Drug Administration (FDA) during their evaluation of the SHARP study resulted in changes needing to be made to the CSR and, as a result, to the proposed Australian PI. The FDA questions were addressed and the CSR subsequently updated by the CTSU at the University of Oxford.

The changes to the CSR from the original study report are fully outlined in an updated CSR provided by the sponsor on request from the TGA and were reviewed by the clinical evaluator. In summary, the most important changes are:

1. A recalculation of the p value for the key study outcome of MAE from p = 0.0022 to p = 0.0021.
2. A change in the numerator for ESRD or 2 times creatinine from 1190 (38.2%) to 1189 (38.1%).

There were other minor changes to the report, predominantly due to:

- Refinement of the way p-values were calculated from z scores that fell between values in the statistical tables
- Correction of a programming error in the calculation of the period into which a given day falls
- Correction of the non-fatal censorship date for 8 patients (this accounted for most of the changes to the figures and tables in the revised CSR)
- Splitting of the "None of the above" row of the reason into subcategories
- Formatting errors during manuscript preparation

These changes were incorporated into updated figures and tables in the CSR. Changes were also made to the text of the SHARP CSR to enable consistency with updated figures and tables. Details of the specific details of the revisions are omitted from this AusPAR.

Other minor changes

In the *Introduction* section of the revised CSR, the number of cardiac deaths in patients with CKD was amended from 15% to 25% and the citation was corrected to read: "*As noted above, atherosclerotic coronary artery disease is not the most common cause of cardiovascular mortality in patients with CKD. Once patients start dialysis, the occurrence of new atherosclerotic CHD is difficult to determine clinically, mainly because symptoms and*

signs of myocardial ischemia can occur in the absence of angiographic coronary artery lesions. Thus only about 25% of cardiac deaths in the United States dialysis programs are attributed to MI, and the rest are classified as sudden death or arrhythmic, or some other cause. It is possible that there are misclassification errors in some of the sudden or arrhythmic deaths and that some of these could be due to MI and vice-versa."

Summary and conclusion regarding revisions to the CSR for SHARP

The details of the changes made to the original CSR are numerous. Overall there are small changes to many of the O-E, HR, CI and p values. These changes are very minor and do not have any effect on the overall findings and interpretation of the SHARP study. There are minor formatting changes to the figures and tables also.

Changes made to the proposed Australian PI as a result of the revisions are all appropriate. There are no further changes that need to be made based on the updated CSR. An additional request however is for the relative risk reduction to be changed to absolute risk reduction (ARR) and the percentage changed accordingly.

Second round assessment of benefits

After consideration of the sponsor's responses to the clinical questions, the clinical evaluator considered the benefits of Vytorin in the proposed usage are as stated above under *First round assessment of benefits*, above.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of:

- Small number of excess cases of myopathy and rhabdomyolysis
- Higher risk of ALT and/or AST >3 times ULN

are unchanged from those identified under *First round assessment of risks*, above.

The sponsor's response documents included a note regarding a potential risk of interstitial lung disease. This relates to the co-administered simvastatin used with ezetimibe in the combination Vytorin, for this indication, and has been highlighted as an *Ongoing safety concern* to be addressed in the PI. The sponsor indicates they have been contacted by the TGA in a separate regulatory communication regarding update of the relevant section in the PI. Details of these are aspects are beyond the scope of this AusPAR.

Second round assessment of benefit-risk balance

The benefit-risk balance of ezetimibe, given the proposed usage, is favourable.

However it should be noted that in Jan 2012, the FDA did not approve the proposed new indication (reduction in *Major Cardiovascular Events in Chronic Kidney Disease…)* for ezetimibe or the ezetimibe/simvastatin combination (Vytorin) because independent contributions of ezetimibe and simvastatin were not assessed. This point was made in the first round clinical evaluation and comment was sought from the sponsor in the *List of questions*; that is, "*What would the efficacy and safety data have shown if the simvastatin Arm had been continued for the entirety of the study. This would have provided information on the additional benefit of ezetimibe to simvastatin therapy, with regard to both efficacy and safety. Therefore, apart from other statin data in CKD, does the sponsor have data on the clinical benefits/side effects of simvastatin in CKD after 4-5 years? Please provide a detailed summary of these data.*"

The sponsor was unable to resolve this issue due to the design of the study. Specifically the sponsor was able to discuss the fact that the simvastatin Arm was small and that Arm would have been underpowered to examine the effect of interest: "*SHARP was designed to address the main clinical question concerning nephrologists which was whether a large*

reduction in LDL cholesterol could be achieved safely with ezetimibe/simvastatin and whether such a reduction would reduce the risk of MAEs". Further, *"neither the study sponsor (the University of Oxford) nor the company possess any data on the effects of simvastatin in CKD after 4-5 years"*; therefore, additional benefit of addition of ezetimibe to simvastatin is unknown.

Clinical summary and conclusions

There was no new evidence for risk and benefits after the second round assessment. It is recommended that the extension indication for Vytorin is indicated to *reduce the risk of major cardiovascular events in patients with CKD* be approved. However alternate wording such as that discussed in the section on *First round benefit-risk assessment*, above, should be considered. The FDA decision should also be considered.

The clinical evaluator also recommended revisions to the proposed PI; details of these are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP (version 1.0, dated 14 April 2011) which was reviewed by the TGA's Office of Product Review (OPR). The summary of the RMP is presented in Table 13.

Table 13. Summary of RPM. Table continued across two pages.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risk: Rhabdomyolysis/Myopathy	• Routine Pharmacovigilance • Monitor reports of rhabdomyolysis/myopathy and related muscle events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Abnormal Liver Function	• Routine Pharmacovigilance • Monitor reports of abnormal liver function and related hepatic events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Hypersensitivity	• Routine Pharmacovigilance • Monitor reports of hypersensitivity and related allergic events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with warfarin, another coumarin anticoagulant, or fluindione	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with ciclosporin	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with Potent CYP3A4 Inhibitors, including itraconazole, telithromycin, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors and nefazodone	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with fusidic acid	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with grapefruit juice	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with diltiazem	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risk: Drug Interaction with verapamil	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with amlodipine	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with fibrates	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with niacin (≥ 1g/day)	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with danazol	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Identified Risk: Drug Interaction with amiodarone	• Routine Pharmacovigilance	Information for this safety concern is described in the EUSPC.
Important Potential Risk: Pancreatitis	• Routine Pharmacovigilance • Monitor reports of pancreatitis and related pancreatic events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Potential Risk: Cholecystitis/Cholelithiasis	• Routine Pharmacovigilance • Monitor reports of cholecystitis and cholelithiasis and related cholecystitis and cholelithiasis events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Potential Risk: Interstitial Lung Disease	• Routine Pharmacovigilance • Monitor reports of interstitial lung disease and related events from ongoing trials	Information for this safety concern is described in the EUSPC.
Important Potential Risk: Simvastatin Hypersensitivity Syndrome	• Routine Pharmacovigilance • Monitor reports of simvastatin hypersensitivity syndrome and related allergic events from ongoing trials	Information for this safety concern is described in the EUSPC.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Safety Specification

The summary of the *Ongoing safety concerns* as specified by the sponsor is as follows (Table 14):

Table 14. Ongoing safety concerns

Important Identified Risks	Rhabdomyolysis/Myopathy Abnormal liver function Hypersensitivity Drug interaction with: • Warfarin; another coumarin anticoagulant, or fluindione • Ciclosporin • Potent CYP3A4 Inhibitors, including itraconazole; telithromycin; ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors and nefazodone • Fusidic acid • Grapefruit juice • Diltiazem • Verapamil • Amlodipine • Fibrates • Niacin (≥1 g/day) • Danazol • Amiodarone
Important Potential Risks	Pancreatitis Cholecystitis/Cholelithiasis Interstitial Lung Disease Simvastatin Hypersensitivity Syndrome
Important Missing Information	Exposure during pregnancy and lactation Use in children (Limited clinical trial experience in children 10 – 17 years of age. No clinical trial experience in children less than 10 years of age.)

Pursuant to the evaluation by TGA of the clinical aspects of the safety specifications, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance Plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03), are proposed to monitor all the specified Ongoing safety concerns pertaining to the extension of indications.

In addition the sponsor proposes to further monitor the important identified risks: 'Rhabdomyolysis/Myopathy', 'Abnormal liver function' and 'Hypersensitivity' and the important potential risks: 'Cholecystitis/Cholelithiasis', 'Pancreatitis' 'Interstitial Lung Disease' and 'Simvastatin Hypersensitivity Syndrome' *via* the ongoing Study P04103 - IMPROVE-IT. This cardiovascular outcomes study will involve a total of approximately 18,000 patients, of which approximately 9000 individuals (50%) will be exposed to ezetimibe 10 mg/simvastatin 40 mg/day. The IMPROVE-IT trial is projected to have a minimum of a 2.5 year follow-up of all randomised patients and is projected to accumulate approximately 5250 cardiovascular events. Furthermore reports of the following AEs will be monitored, identified and evaluated:

· rhabdomyolysis/myopathy and related muscle events

- abnormal liver function and related hepatic events
- hypersensitivity and related allergic events
- cholecystitis/cholelithiasis and related events
- pancreatitis and related pancreatic events

The sponsor reports that a total of 280 patients have been randomised into this study in Australia (115) and New Zealand (165). The first patient was randomised in Australia on 28 Jun 2006, and currently there are 70 active patients in the study in Australia, and 124 active in New Zealand. The database for the IMPROVE-IT study will be locked in August in preparation of the Data Safety Monitoring Board (DSMB)'s efficacy review of the study currently projected to occur in November 2011 (projected that 75% of 5,250 subjects will have had a minimum of one primary endpoint). The sponsor reports that the DSMB review is not expected to significantly alter the course of the study, which is currently on track to end in May 2013 with a final study report projected for August 2013. A synopsis for this study was provided in Annex 5 of the RMP.

Evaluator's summary regarding the Pharmacovigilance Plan

In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study synopses have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the updated RMP, will be expected in future Post Marketing Safety Update Reports (PSURs).

Risk Minimisation Activities

The sponsor has concluded and provided justification that routine risk minimisation activities for all the specified ongoing safety concerns pertaining to the extension of indications are sufficient. The sponsor's justification and conclusion would appear to be reasonable, and is therefore acceptable.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns (see *Proposed Pharmacovigilance Activities*, above). However, the ongoing Study P04103 – IMPROVE-IT is not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study synopses have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the updated RMP, will be expected in future PSURs.
- The sponsor's justification and conclusion that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient would appear to be reasonable, and is therefore acceptable.
- The sponsor's proposed use of routine risk minimisation activities would appear to be reasonable, and therefore acceptable. However, the sponsor should include the information provided in its correspondence dated 27 January 2012 to the TGA that

relates to the proposed routine risk minimisation, in the summary tables found in the RMP and in the Australian Specific Annex when these documents are next revised.

- In regard to the proposed routine risk minimisation activities, revisions to the PI and Consumer Medicine Information (CMI) are recommended; details of these are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacokinetics

There were no new PK data to be evaluated.

Pharmacodynamics

There were no new specific PD studies undertaken. As noted by the clinical evaluator, there was PD information collected in the pivotal SHARP study with regard to lipid parameters. The importance of these PD markers is in correlating them with the clinical outcomes. This correlation or relationship is discussed under both *Efficacy* and *Safety*.

Efficacy

Chronic Kidney Disease in adults

SHARP was a randomised, controlled, double-dummy study, undertaken across 18 countries, primarily to assess the benefit of two medications, ezetimibe and simvastatin, on vascular outcomes in CKD. There were 11,792 people screened. After screening and prior to randomisation, 11,364 potentially eligible patients entered a run-in period during which they received one placebo-combination tablet and one placebo-simvastatin tablet daily for approximately 6 weeks. The 9686 eligible patients who completed the run-in phase were then randomised to 1 of 3 treatment arms in a 4:4:1 ratio (4191 in the placebo arm [Arm 1], 4193 in the ezetimibe/simvastatin 10/20 mg arm [Arm 2], and 1054 in the simvastatin 20 mg arm [Arm 3]; see Figure 1 of this AusPAR for a diagram of the flow of patients in the study and hence the design).

The simvastatin monotherapy Arm was used for safety evaluation only and after one year patients initially randomised to simvastatin 20 mg daily were re-randomised to either ezetimibe/simvastatin 10/20 mg (Arm 3b) or to placebo (Arm 3a) for the remainder of the trial. Follow-up visits were scheduled at 2 and 6 months and then every 6 months, during a scheduled treatment period of at least 4 years.

There were 4547 patients on ezetimibe/simvastatin and 4519 patients on placebo who completed the study, with equal proportions of non-completers in both groups due to mortality and morbidity. There was a 2.2% incomplete follow-up in each group.

The primary objective was to assess the effects of lowering LDL-C with combined ezetimibe 10 mg and simvastatin 20 mg daily versus placebo on the time to a first MVE in approximately 9000 patients with CKD, of whom about two thirds were intended to be pre-dialysis and one third on dialysis at randomisation. MVE was a composite of non-fatal MI or cardiac death, non-fatal or fatal stroke or any revascularisation (excluding dialysis access procedures). There were a number of secondary and tertiary endpoints.

Included in the study were men or women aged 40 years or over with advanced CKD with a pre-dialysis blood creatinine of at least 150 µmol/L (1.7 mg/dL) in men or 130 µmol/L (1.5 mg/dL) in women with no known history of MI or coronary revascularisation. Thus there were no pre-conditions for study enrolment relating to baseline level of total cholesterol or LDL-C and other parameters. Unfortunately neither Table 3 nor Table 4 (describing baseline characteristics; reproduced above in this AusPAR) summarises the baseline distribution of lipid values (such as total cholesterol, LDL-C or triglycerides) by treatment group. The sponsor is requested, in its response to this Overview to provide tables of such baseline data: as well as mean and range, the baseline lipid data should be arranged by quartiles for each treatment group.

It should be noted that the primary outcome specified in the protocol (MVE) differed from the key outcome specified in the SAP. The latter was the MAE which was defined as the combination of MI, coronary death, ischaemic stroke or any revascularisation procedure (that is, excluding non-coronary cardiac deaths and strokes confirmed to be haemorrhagic from the original protocol-defined MVE outcome). This addition occurred because blinded examination of MVE had shown that about one third of the MVE were either non-coronary cardiac deaths or haemorrhagic strokes. The study investigators had also become aware during the trial that these events were less likely to be prevented by LDL lowering therapy in a CKD group. Also the mean LDL reduction at the midpoint of the trial was less than expected which meant that a relative risk reduction of only 13% in the original primary outcome of MVE could now be anticipated. This resulted in a significant under-powering of the SHARP study (66% at p = 0.01) to detect such a difference.

The Steering Committee stated that the key outcome in the SAP was to be the effect, for all randomised patients (that is, Arms 2 + 3b versus Arms 1 + 3a) of ezetimibe/simvastatin 10/20 mg versus placebo on the overall incidence of first MAE rather than first MVE; MAE is MVE without non-coronary cardiac deaths and haemorrhagic stroke.

The inclusion of all those who were originally allocated to simvastatin for 1 year in the comparison, that is, Arm 3b versus Arm 3a, was also recommended by the Steering Committee. This had the effect of increasing the total number of randomised patients in the analysis from 8384 (the total number in Arms 2 and 1, that is, for the comparison Arm 2 versus Arm 1) to 9270 (the total number in Arms 2, 3b, 1 and 3a, that is, for the comparison Arms 2 + 3b versus Arms 1 + 3a).

It would appear that the sponsor did not approve the protocol changes recommended by the Steering Committee. However, per-protocol results were first reported followed by the results of the SAP outcomes. In its response to this Overview, the sponsor is requested to clarify the need for the Steering Committee to recommend a change in the key outcome to be measured and also to clarify the precise difference between the parameters MAE and MVE. As part of the latter, the sponsor is requested to define precisely what is meant by the term “non-coronary cardiac death”. The sponsor is also requested to provide a detailed discussion of the precise power of the study to achieve each of these endpoints and also to clarify the precise make-up of the populations which were compared in each analysis.

There were no clinically important differences between treatment groups with respect to baseline characteristics of patients as a result of the first randomisation. Mean LDL-C concentration was significantly lower among patients on dialysis than among those not on dialysis (100 mg/dL (2.58 mmol/L) versus 111 mg/dL (2.87 mmol/L), respectively, $p < 0.0001$). The sponsor is requested to confirm that there were also no significant differences between treatment groups following the second randomisation, that is, at the end of the first year when those patients initially randomised to simvastatin 20 mg daily were re-randomised to either ezetimibe/simvastatin 10/20 mg (Arm 3b) or to placebo (Arm 3a) for the remainder of the trial.

Main efficacy outcomes:

- The first was the protocol-specified primary outcome, this being the effect of ezetimibe/simvastatin 10/20 mg versus placebo on MVEs in all patients except those originally allocated to simvastatin alone (that is, on MVE in Arm 2 versus Arm 1). Compared to placebo (Arm 1, MVE = 749/4191 = 17.9%), ezetimibe/simvastatin 10/20 mg (Arm 2, MVE = 639/4193 = 15.2%), reduced the risk of MVE by 16% (RR 0.84, 95% CI, 0.75-0.93, p = 0.001). The ARR appeared to be of the order of 2.7%. The sponsor is requested to state precisely the value of the ARR demonstrated.
- In the SAP, the key outcome was the first occurrence of MAE, defined as major coronary events (coronary death or non-fatal MI), ischaemic stroke or any revascularisation procedure, in all patients randomised to ezetimibe/simvastatin 10/20 mg (Arms 2 + 3a) or placebo (Arms 1 + 3b). This outcome occurred in 526/4650 or 11.3% versus 619/4260 or 14.5%, a relative risk reduction of 17% (RR 0.83, 95% CI 0.74-0.94, p = 0.0022). The ARR appeared to be of the order of 3.2%. Once again the sponsor is requested to state precisely the value of the ARR demonstrated.
- Thus, as noted by the clinical evaluator, the direction, RR, ARR, CI and significance level of each of the primary endpoint analyses were similar.

There were analyses of the protocol-specified components of the primary MVE outcome in all randomised patients with apparently significant reductions in the rates of total stroke, ischaemic stroke and any revascularisation procedure but not in the rates of major cardiovascular events, haemorrhagic stroke or stroke of unknown cause. However, it is uncertain whether there was a pre-determined hierarchy of these components. The sponsor is requested to clarify this issue. For both MVE and MAE, the effects on each appeared to be driven by a benefit on ischaemic stroke (not haemorrhagic) and revascularisation procedures.

There were a number of secondary endpoints and notably amongst these, there was no significant effect on the risk of progression to ESRD (commencement of long-term dialysis or transplantation among pre-dialysis patients) and there were no differences in overall and cause-specific mortality, vascular deaths or deaths due to heart disease. There were also a number of tertiary endpoints. The fact that there was no significant effect on the risk of progression to ESRD raises the question of whether SHARP has demonstrated an actual independent benefit to CKD patients beyond that which may have just been conferred by the lipid lowering effects of ezetimibe, effects for which ezetimibe already has an indication.

After weighting the risk ratios in the efficacy endpoints according to the reductions in LDL-C, the trends for MAE were much reduced and remained only statistically significant (before accounting for multiple testing) only for total cholesterol and waist circumference. For MVE, only the trend by baseline total cholesterol remained significant after accounting for LDL-C differences. Thus, the clinical evaluator concludes, no particular sub-group in SHARP obtained more or less benefit, other than that variation among sub-groups in the

absolute reduction of LDL-C. The Delegate is not entirely certain of the precise meaning of these statements and requests the sponsor to provide some clarification.

Of particular concern is whether or not the findings of the SHARP study actually support a new indication. Are the benefits demonstrated by SHARP really only those conferred by the lipid lowering effects of ezetimibe, effects for which the medicine already has an approved indication? Is there enough evidence to support the existence of a special, specific effect in patients with CKD above and beyond the lipid lowering effect? If there is not sufficient evidence of this sort, then it would be difficult to justify a separate, new indication specifically for those with CKD.

As mentioned by the clinical evaluator, the trends for MAE were much reduced once reductions in LDL-C had been taken into account. Does this in fact imply no benefit or perhaps only a very small benefit in patients with CKD on top of the already approved lipid lowering effect? Does it imply that a proportion only of the benefit claimed is due to the already approved lipid lowering effect with the remainder of this benefit then and only then able to be ascribed to the specific effect in patients with CKD? Is it possible to determine the exact size of each proportion, that is, the proportion of the benefit due simply to the lipid lowering effect and the remainder due to the specific renal effect? Is it possible to see evidence for this specific effect quite independently of the lipid lowering effect of ezetimibe? Is the benefit evenly distributed across the population when that population is stratified by the extent to which lipid levels, for example those of LDL-C, were reduced?

The sponsor was requested to address all of these questions in its response to this Overview, particularly the last question. For example, the sponsor may conduct a *post hoc* analysis which begins by comparing the rate of the primary endpoint in those whose LDL-C was reduced by less than 10% of its baseline value (including those whose LDL-C increased) with those whose LDL-C was reduced by at least 10% of its baseline value and which continues by repeating the analysis by advancing, at each step, the reduction in LDL-C by a further 10%. This means that the second step of the analysis would be to compare the rate of the primary endpoint in those whose LDL-C was reduced by less than 20% of its baseline value (including those whose LDL-C increased) with those whose LDL-C was reduced by at least 20% of its baseline value and that this analysis be repeated across the entire range possible. It is of interest to determine from such an analysis whether there is evidence of consistency of effect across the board, that is, quite independent of the lipid lowering effect.

Summary of efficacy

The data indicates a reduction in MVEs in patients over 40 years of age with CKD who have had not had a revascularisation procedure or a MI. Given the concerns expressed in the preceding paragraph, it can be speculated whether exactly the same benefit would have been demonstrated if SHARP had been conducted in a population of patients all with some other condition, for example, osteoarthritis of the hip. The data does not appear to demonstrate a benefit in any particular sub-group, nor a benefit on progression to end-stage renal disease, nor any mortality benefit.

Safety

Safety was evaluated in two time periods, firstly during the first year of treatment on each of the three arms of the study and then safety for the whole period.

There were no significant differences in CK elevations, muscle symptoms or the development of renal damage in 4193 patients allocated to ezetimibe/simvastatin for the first year compared to 1054 allocated to simvastatin and 4191 on placebo. The numbers of patients during the first year of treatment with post-baseline elevations in ALT and/or AST of > 3 times ULN, that were not necessarily persistent, were higher in the combination

group than in either the simvastatin monotherapy or placebo groups (1.0%, 0.6% and 0.5%, respectively). Persistently elevated transaminases occurred in 13 (0.31%), 1 (0.09%) and 6 (0.14%) in ezetimibe/simvastatin, simvastatin and placebo groups, respectively. There were a total of 4 cases of hepatitis of non-infective or of unknown origin, 2 (0.1%) being in the ezetimibe/simvastatin group and 2 (0.05%) in the placebo group.

Considering safety for the whole period, almost a quarter (24%) of the randomised patients died during the course of the study and about one third of the deaths were due to vascular causes. The numbers of deaths overall and by specific cause were not significantly different in patients allocated to ezetimibe/simvastatin compared with those allocated to placebo.

There was no difference in risk of developing diabetes *de novo* between the two groups.

The total numbers of patients with any incident cancer did not differ between the two groups.

Overall, approximately 21% of all patients reported muscle pain during the study (21.5% of the ezetimibe/simvastatin group and 20.9% of the placebo group. More patients in the former, 49 (1.1%), discontinued treatment because of muscle pain than in the placebo group, 28 (0.6%). Myopathy occurred in 8 (0.17%) patients taking ezetimibe/simvastatin and in 3 (0.065%) on placebo (and not taking a non-study statin). Of these cases, 4 in the ezetimibe/simvastatin group compared with none in the placebo group had rhabdomyolysis. All 8 patients in whom myopathy occurred while taking ezetimibe/simvastatin, including those in whom rhabdomyolysis developed, recovered after stopping study medication.

There were no differences in the numbers or proportions of patients who developed hepatitis, overall or from different causes, the numbers and proportions overall being 19 (0.41%) in the ezetimibe/simvastatin group versus 18 (0.39%) in the placebo group. There were similar risks of complications of gallstones, hospitalisations for gallstones or pancreatitis, regardless of treatment.

There were no significant differences in the numbers of non-fatal SAEs between the two groups.

The total numbers of patients stopping study medication due to any AE, whether serious or not, drug-related or not, were 479 (10.3%) in the ezetimibe/simvastatin group and 450 (9.7%) in the placebo group.

At 1 year, compliance was already an issue with 25% of all surviving patients allocated to the ezetimibe/simvastatin Arm taking less than 80% of the allocated medication. At 2.5 years, this figure had risen to 34%.

Summary of safety

In summary, there were no significant differences in the rates of development of ESRD or of mortality between the ezetimibe/simvastatin and placebo groups. Of some concern and as noted by the clinical evaluator, the numbers of patients during the first year of treatment with post-baseline elevations in ALT and/or AST of > 3 times ULN, that were not necessarily persistent, were higher in the combination group than in either the simvastatin monotherapy or placebo groups (1.0%, 0.6% and 0.5%, respectively). Persistently elevated transaminases occurred in 13 (0.31%), 1 (0.09%) and 6 (0.14%) in ezetimibe/simvastatin, simvastatin and placebo groups, respectively. There were more non-significant AEs that led to study drug discontinuation in patients allocated to the ezetimibe/simvastatin Arm compared with those in the placebo Arm, largely due to muscle pain, abnormal safety blood results and reported skin symptoms. Myopathy and rhabdomyolysis occurred more often in patients taking ezetimibe/simvastatin than in those taking placebo. The incidence of myopathy including rhabdomyolysis in the

ezetimibe/simvastatin group was 0.17%, compared to 0.065% in the placebo group. However, all of these results are consistent with the known AE profile of the combination.

First round risk-benefit balance

The clinical evaluator was of the opinion that the risk-benefit balance of ezetimibe/simvastatin 10/20 mg in adults aged at least 40 years with CKD and without prior MI or revascularisation was favourable because of the reduction in the rate of MVEs and because the risks demonstrated in SHARP were those already known to be associated with simvastatin and ezetimibe individually and in combination. The clinical evaluator noted that the wording of the extension of indications sought by the sponsor referred to 'major cardiovascular events' whereas the term 'MVEs' was the parameter tested and should therefore be the term used. The Delegate agreed and requests comment from the Advisory Committee on Prescription Medicines (ACPM) on this point.

Second round evaluation of clinical data submitted in response to TGA requests for information

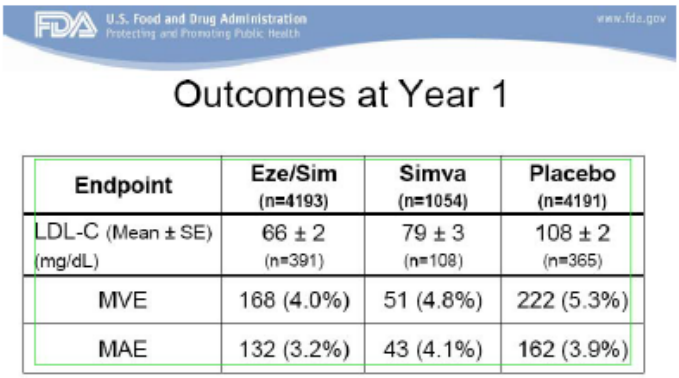
Questions raised by the US FDA during its evaluation of the SHARP data resulted in the need for changes to be made to the CSR. These questions were addressed and the CSR updated by the CTSU at the University of Oxford. In the second round evaluation, the clinical evaluator reviewed the updated CSR. Overall the changes were judged to be minor and not to have any effect on the overall findings and interpretation of the SHARP study. The clinical evaluator also found the sponsor's responses to the clinical questions acceptable, with the exception of one.

In January 2012, the US FDA did not approve the extension of indication, that is, for the reduction in major cardiovascular events in CKD, for either the monotherapy ezetimibe or the ezetimibe/simvastatin combination because the independent contributions of each monotherapy, that is, of ezetimibe and of simvastatin, were not assessed. This issue was echoed in the third clinical question asked of the sponsor by the TGA, namely what would the efficacy and safety data have shown if the simvastatin Arm had been continued for the entirety of the study. Because of the design of SHARP, the sponsor is unable to answer this question.

The EMA's Committee for Medicinal Products for Human Use (CHMP) guideline on *Clinical Development of Fixed Combination Medicinal Products* (CHMP/EWP/240/95 Rev. 1) states, in its section 6.1 that, "*The indications claimed for a fixed combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect or improves the overall benefit risk ratio by mitigating side effects*". In its response to this Overview and to matters raised in the clinical evaluation report (CER) (see *Response from sponsor*, below), the sponsor has discussed the US FDA decision and explained why it was not possible to design SHARP to definitively address the question of separate contributions of the two components in a CKD population.

The results from SHARP at one year show that both ezetimibe and simvastatin contributed to the lowering of LDL-C, with the ezetimibe component contributing approximately 31% of the LDL-C reduction observed with the combination. The US FDA also calculated the outcomes at the end of the first year which showed numerically greater reductions in the rates of both MVE and MAE for the ezetimibe/simvastatin 10/20 mg group compared with those for the simvastatin group. These results are shown in Figure 5, below, obtained from the FDA website at:-
<http://www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/EndocrinologicalandMetabolicDrugsAdvisoryCommitteee/UCM279293.pdf> (slide 75)

Figure 5. SHARP outcomes data at year 1.



Endpoint	Eze/Sim (n=4193)	Simva (n=1054)	Placebo (n=4191)
LDL-C (Mean ± SE) (mg/dL)	66 ± 2 (n=391)	79 ± 3 (n=108)	108 ± 2 (n=365)
MVE	168 (4.0%)	51 (4.8%)	222 (5.3%)
MAE	132 (3.2%)	43 (4.1%)	162 (3.9%)

As acknowledged by the sponsor, the above analysis by the FDA was *post-hoc*. Because of this and the fact that there is a lag time after starting statins before any effect on the rates of vascular events is fully apparent, no firm conclusions can be drawn from the above analysis.

The sponsor also commented in its response to the CER about the mitigation of side effects by use of the combination. The highest dose of simvastatin (80 mg) has been shown to produce a mean 47% lowering of LDL-C in patients with primary hypercholesterolaemia. However, these greater reductions in LDL-C produced by the higher statin doses are at the cost of a dose-related myopathy risk. Patients with CKD are already at increased risk of myopathy. In patients with primary hypercholesterolaemia, the combination of ezetimibe/simvastatin 10/20 mg produces a similar lowering of LDL-C, mean 52%, in 12 week studies to that of simvastatin 80 mg. In SHARP at one year, ezetimibe contributed about one third of the LDL-C lowering effect produced by the ezetimibe/simvastatin combination. Existing evidence suggests that the risk of myopathy with ezetimibe is similar to that of placebo. It should be noted that the fixed-dose combination of ezetimibe 10 mg with simvastatin 20 mg is already approved for the management of hypercholesterolaemia.

The hypothesis for SHARP was that ezetimibe/simvastatin 10/20 mg could be used to improve the benefit/risk profile in CKD patients, by producing a large LDL-C reduction with a significant reduction in cardiovascular events while minimising the risk of myopathy/rhabdomyolysis. The sponsor contends that this rationale was borne out in SHARP by a substantial reduction in LDL-C and a reduction in cardiovascular events with a low incidence of myopathy (0.1% greater than in the placebo group). However, there is still the unanswered concern as to whether the data from SHARP shows robust evidence of some special, specific, presumably renally-mediated effect of ezetimibe/simvastatin 10/20 mg extra to and separate from the combination's lipid-lowering effect.

The Delegate was of the view that, while the lack of precision concerning the relative contributions of ezetimibe and simvastatin to the primary outcome was a deficiency of the SHARP study, that alone does not automatically negate the principal findings of the study. Furthermore, the Delegate accepts the sponsor's arguments concerning the reduction in the rates of myopathy by use of the combination. What the sponsor will need to do, however, is acknowledge this deficiency of SHARP in the PI. However, the Delegate still remained to be convinced that the principal findings of the study really do provide robust evidence of a specific, separate effect in the population of patients with CKD, that is, an effect quite distinct from the already approved lipid lowering effect of the combination. Such a concern goes to the heart of the issue as to whether a new, separate indication is clearly warranted.

Risk management plan

The OPR evaluator was of the opinion that the submitted RMP (version 1.0, dated 14 April 2011, and Australian Specific Annex dated 18 June 2011) is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU RMP is applicable without modification in Australia unless so qualified.

Risk-benefit analysis

The benefit of the combination ezetimibe/simvastatin 10/20 mg in adults aged more than 40 years with CKD and without prior MI or revascularisation is that it reduces the rates of vascular events in the long term. This benefit was consistent in both protocol-defined analysis of MVE and that defined in the SAP, the revised analysis of MAEs. Another benefit was the reduction in the risk of myopathy with the combination compared with the risk which would be associated with higher doses of simvastatin.

There are two major concerns with the robustness of the evidence supporting efficacy. Firstly, there are the concerns of the FDA in relation to the difficulty, if not impossibility, of being able to determine how much of the claimed benefit is due to ezetimibe and how much to simvastatin. These are somewhat mitigated by the results of the *post hoc* analysis in which the FDA calculated the outcomes at the end of the first year and these showed numerically greater reductions in the rates of both MVE and MAE for the ezetimibe/simvastatin 10/20 mg group compared with those for the simvastatin group. However, the analysis was *post hoc* and was only for the first year whereas the SHARP ran on for another few years. Can it be entirely certain that the claimed final benefit could not have also been achieved by simply being on simvastatin 20 mg alone for the duration of the study? There is the other issue of the apparent lack of dose-ranging studies. How can it be entirely certain that the same effect could not have also been achieved by being on a fixed-combination dose of ezetimibe 10 mg/simvastatin 10 mg for the duration of the study?

The second major concern of the Delegate revolves around the issue of whether the results from SHARP genuinely and robustly support a new, separate indication. How certain is it that the primary endpoint achieved in the SHARP study is not simply and wholly due to the already approved lipid lowering effects of the combination of ezetimibe and simvastatin? How robustly do the findings of SHARP support the existence of a special, specific effect in those with CKD extra to and independent of the already approved lipid lowering indications of the fixed-dose combination. The Delegate requests the sponsor to respond to a number of questions on this issue and also to perform a detailed *post hoc* analysis of the primary efficacy endpoint when the patient population is stratified according to the relative extent of reductions in LDL-C (see above).

The risks of the combination of ezetimibe and simvastatin are those well known to be associated with simvastatin and ezetimibe, both individually and in combination. There were no new or greater risks identified.

Given the concerns expressed above, the Delegate was minded at this stage to recommend rejection of the application for an extension of indications but to recommend instead approval of the updating of the PI with the results of the SHARP study, qualified by satisfactory acknowledgement of all the Delegate's concerns about the applicability of the findings of the study. However, if the sponsor is able, in its response to this Overview, to address satisfactorily all those Delegate's concerns (above), then it may be possible for the Delegate to recommend approval of the extension of indications. The two major concerns are firstly the exact apportioning of claimed benefit between the separate components, ezetimibe and simvastatin and secondly as to whether the findings from SHARP robustly support a new, separate indication, one indicative of a benefit which can, without any

doubt, be attributed to a special, specific effect of the combination extra to and independent of the already established lipid lowering effects of the combination. Of these two major concerns, the Delegate would regard the latter as the more important.

Indication

If the extension application is approvable, the Delegate was of the opinion that the term '*major vascular events*' is more appropriate than '*major cardiovascular events*' as it is the term used to define the primary endpoint of the SHARP study. Although SHARP was conducted in adult patients aged more than 40 years, the Delegate considers that inclusion of the latter age restriction in the wording of the indications would be unnecessarily restrictive, particularly for those patients aged close to 40 years, such as those over 30 years of age. However, the Delegate is of the opinion that the extension of indications should apply only to adult patients. Furthermore, entry to the study was restricted to patients with no known history of MI or coronary revascularisation. Thus the Delegate suggested the indications may be amended to the following:

> ***Prevention of Major Vascular Events in Chronic Kidney Disease***
> *Vytorin is indicated to reduce the risk of major vascular events in adult patients with chronic kidney disease and with no known history of myocardial infarction or coronary revascularisation.*

Recommendation

The Delegate proposes, at this stage, to **reject** this submission by Merck Sharp and Dohme (Australia) Pty Limited to register Vytorin 10/20 mg (containing ezetimibe 10 mg and simvastatin 20 mg) based on the efficacy of the product not having been satisfactorily established for the extension of indications as requested (below), for the reasons stated above in the *Risk/Benefit Analysis*.

> ***Prevention of Major Cardiovascular Events in Chronic Kidney Disease.***
> *Vytorin is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease.*

As mentioned above, the Delegate has asked a number of questions of the sponsor. Dependent upon the provision, by the sponsor, of satisfactory answers to all questions asked of the sponsor in this Overview and also upon amendment of the PI document to the satisfaction of the TGA, an approval of the extension of indications (as indicated in the discussion above) may be possible. The Delegate will also need to take into account any advice received from the ACPM. At this stage, the Delegate is prepared to consider the updating of the PI with the results of the SHARP study which takes into account and acknowledges the concerns expressed above in the *Risk/Benefit Analysis*.

The Delegate intends to impose the following specific conditions of registration:

1. The implementation of Risk Management Plan, version 1.0, dated 14 April 2011 with the Australian Specific Annex dated 18 June 2011, and any subsequent updated versions as agreed with the Office of Product Review
2. A condition of registration specifying the lodgement with the TGA, of the final study reports as evaluable data when available of all post-authorisation studies mentioned in the RMP evaluation, in particular the ongoing study P04103 – IMPROVE-IT (IMProved Reduction in Outcomes: Vytorin Efficacy International Trial).

The sponsor should address the following issues in its response to this Overview:

a. Provide an update to the registration status (with dates) for this submission of Vytorin 10/20 mg (ezetimibe 10 mg and simvastatin 20 mg) in the USA, Europe/UK, Switzerland, Canada and New Zealand including any withdrawals, rejections or deferrals.

b. The sponsor is asked to address the major concerns raised by the Delegate in the Risk/Benefit Analysis above.

c. The sponsor is also asked to address all the issues raised by the Delegate, some of which have been asked as questions, some of which are directly linked with the major concerns mentioned at b) above and some of which are not directly linked with those major concerns. These questions/issues are to be found throughout the Overview.

d. The sponsor is requested to provide a list of all ongoing studies involving Vytorin (ezetimibe/simvastatin) and/or either of the monotherapies, ezetimibe or simvastatin.

This Overview was submitted for ACPM advice. In addition to the provision of overall advice regarding the adequacy of the data to support approval, the Committee was also requested to specifically address the following:

1. Does the ACPM agree with the Delegate that, while the lack of precision concerning the relative contributions of ezetimibe and simvastatin to the primary outcome was a deficiency of the SHARP study, that deficiency alone does not negate the principal findings of the study? However in this regard, can it be certain that the claimed benefit could not have been also achieved by being simply on simvastatin 20 mg alone for the duration of the study? Also in this regard, can it be certain that the claimed benefit may not also have been conferred by being on a lower dose of the combination, namely ezetimibe 10 mg/simvastatin 10 mg?
2. Another major concern of the Delegate revolves around the issue of whether the results from SHARP genuinely and robustly support a new, separate indication. How certain is it that the primary endpoint achieved in the SHARP study is not simply and wholly or to a large degree due to the already approved lipid lowering effects of the combination of ezetimibe and simvastatin? How robustly do the findings of SHARP support the existence of a special, specific effect in those with CKD extra to and independent of the already approved lipid lowering indications of the fixed-dose combination? The Delegate has asked the sponsor a number of questions concerning this issue and has also asked the sponsor to undertake a detailed post hoc analysis of the primary endpoint of SHARP when the patient population is stratified according to the extent of LDL-C reductions achieved. These issues will be addressed in the sponsor's response to the Overview. The ACPM is asked for its opinion as to whether the findings from the SHARP study do robustly support a new, separate indication as requested by the sponsor.
3. Does the ACPM agree with the Delegate's acceptance of the sponsor's arguments concerning the reduction in the rates of myopathy by use of the combination?
4. Does the ACPM agree with the Delegate that there will need to be an acknowledgement of the above deficiency in the proposed PI?
5. Does the ACPM agree with the Delegate's slightly amended wording of the Indications? Should the extension of indications be also only applied to those patients with CKD, classes III-V, as suggested by the clinical evaluator?

Response from Sponsor

The sponsor provided an abbreviated (summary) response to the Overview and the CER as well as a detailed response that addressed all issues which were raised in the Delegate's Overview.

Summary response:

Merck Sharp and Dohme concurred with the clinical evaluator's assessment that "*the benefit-risk balance of ezetimibe given the proposed usage is favourable"* and disagrees with the Delegate's proposed action to reject the application. MSD proposes the indication:

> ***Prevention of Major Vascular Events in Chronic Kidney Disease***
> *VYTORIN is indicated to reduce the risk of major vascular events in adult patients with chronic kidney disease.*

The Delegate proposed to restrict the indication to patients with no known history of MI or coronary revascularisation, that is, *VYTORIN is indicated to reduce the risk of major vascular events in adult patients with chronic kidney disease and with no known history of myocardial infarction or coronary revascularization.*

However, the sponsor would strongly recommend that the phrase '*...and with no known history of MI or revascularization*' be omitted from the indication language. CKD patients with known CHD are in fact the CKD patients who would predictably benefit the most from therapy. They were excluded from SHARP because, in Merck's view such patients were considered to be already appropriate for LDL-C lowering treatment irrespective of concurrent CKD, based on existing approved indications for certain statin therapies. It would therefore not have been appropriate to randomise them to a study with a 50% chance of going on placebo for the duration of the trial. It is known from the CTT meta-analyses that patients with clinically overt CHD and those at high risk but without overt disease experience similar magnitudes of relative risk reduction with LDL-C-lowering statin therapy[26,27]. There is no reason to believe this would be different in CKD patients with known CHD, and because the atherosclerotic-event rate is known to be higher in patients who have had a prior atherosclerotic event, it would be expected that the absolute benefit from ezetimibe/simvastatin would be even greater than that observed overall in the SHARP population. Thus, it is very appropriate to extrapolate the findings of SHARP to these very high risk patients, who could not practically be randomised into the trial.

The proposed indication is supported by the results from the SHARP trial evaluating the effects of ezetimibe/simvastatin 10/20 mg in patients with moderate to severe CKD, who are very prone to cardiovascular events; the countries including Australia. With over 9000 patients followed for a median duration of 5 years, SHARP is by far the largest trial of any treatment in CKD patients. The study was conducted by the CTSU in the Nuffield Department of Medicine at Oxford University under the oversight of an independent Steering Committee. CTSU is a recognised leader in the field of large clinical trials in cardiovascular medicine.

The results for the SHARP trial clearly demonstrate that ezetimibe/simvastatin 10/20 mg daily reduces MVEs in CKD, which no other treatment has been shown to do. These results have been peer-reviewed and published in the *Lancet*[28].

The sponsor appreciates the opportunity to respond to the Delegate, as MSD disagrees with the Delegate's proposed action to reject the application. The Delegate outlines two

26 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

27 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

28 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C. et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-92.

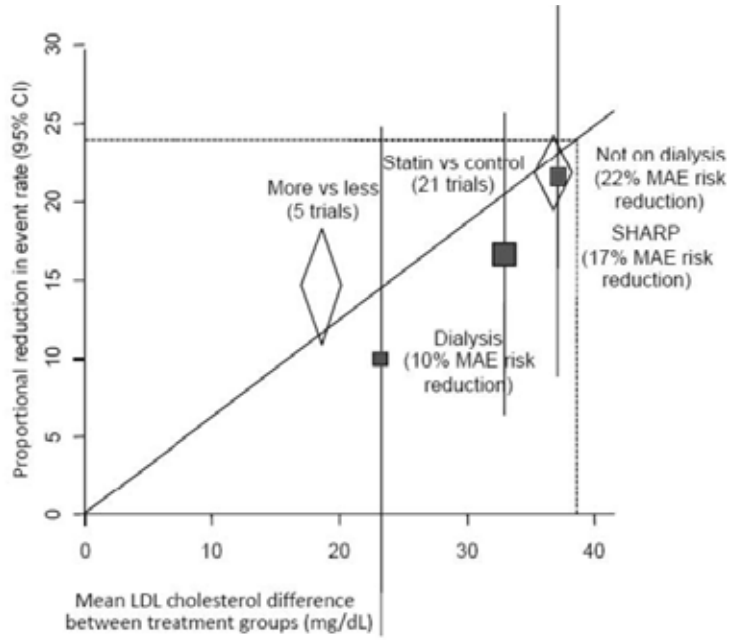
major concerns: (i) it is important to establish that there was a specific effect of the ezetimibe/simvastatin combination on cardiovascular risk reduction independent of LDL-C reduction in order to recommend approval; and (ii) it is not possible from SHARP to establish the relative contributions of ezetimibe and simvastatin to the observed reduction in the primary outcome. The sponsor offers the following comments in response to these concerns:

Cardiovascular risk reduction and LDL-C reduction

The sponsor does not agree that it is necessary to establish that the combination of ezetimibe/simvastatin has effects beyond reducing LDL-C among patients with CKD. The key point is that, prior to SHARP, there was uncertainty about whether to use LDL-lowering therapy among patients with CKD, for three main reasons: (i) LDL-C is not increased and in fact is generally below average, among patients with CKD; (ii) the specific type of cardiovascular disease characteristic of CKD (arterial stiffness, cardiomyopathy, sympathetic overactivity) was not believed to be susceptible to reducing LDL-C; and (iii) there were studies demonstrating inverse associations between cholesterol and mortality in haemodialysis patients. SHARP set out to demonstrate that by reducing LDL-C in CKD, provided that the LDL-C was sufficiently large (by using a potent but safe combination regimen), the expected reductions in atherosclerotic events would be observed in patients with CKD, even in the absence of hypercholesterolaemia. The SHARP investigators hypothesised this because of existing epidemiological studies suggested that reductions in LDL-C are associated with lower risk of vascular events even among those with average or below average LDL-C. SHARP has now demonstrated that this is correct, and that reducing LDL-C still further in a population with average or below average LDL-C is beneficial and safe. The existing label does not ensure that the SHARP results are translated into practice because only a minority of patients with CKD have hypercholesterolaemia.

The contribution of other potentially beneficial factors to reducing risk of cardiovascular events is speculative at this time. The magnitude of the risk reduction observed in SHARP in relation to the degree of LDL-C lowering achieved is consistent with what would be anticipated from the known relationship between absolute reduction in LDL-C and proportional reduction in MVEs with statins. This is seen in Figure 6, below, which superimposes the reductions seen in SHARP on the data from the large CTT meta-analysis of 26 statin trials.

Figure 6. Effect on major vascular/atherosclerotic events by trial-midpoint LDL-C reduction.



SHARP superimposed on the CTT meta-analysis from 26 statin trials. The SHARP point estimates are shown with squares for the entire cohort (17% reduction), and the subgroups of patients who at baseline were not on dialysis (22% reduction) or on dialysis (10% reduction)[29].

While the SHARP findings are entirely consistent with the relationship between reduction in events and reduction in LDL-C seen in statin trials, SHARP is the first and only trial to clearly show this for patients with CKD and to show this with the use of ezetimibe/simvastatin. The reductions in cardiovascular risk demonstrated in SHARP go well beyond the currently approved indications for Vytorin for treating hypercholesterolemia.

The proposed indication is for reducing vascular events, not just reducing cholesterol in hypercholesterolaemic patients. The majority of patients with moderate to advanced CKD are not usually "hypercholesterolaemic" to a degree corresponding to the way the term is usually applied. This is reflected by the fact that the mean LDL-C at baseline for the SHARP population was only 2.8 mmol/L, a level which most physicians would not consider "primary hypercholesterolemia" for which Vytorin is approved.

Patients with moderate to severe CKD have been routinely excluded from most trials investigating LDL-C reduction, chiefly because of concerns about safety. Patients with advanced CKD are known to be more susceptible to the serious side effect of statin-induced myopathy. By using a low dose of simvastatin in combination with ezetimibe, SHARP was able to achieve a large LDL-C reduction (and corresponding substantial event reduction) with a favourable safety profile. It is for these reasons that obtaining an indication for reducing cardiovascular risk in patients with CKD, separate from the existing approved indication for treatment of hypercholesterolemia, is extremely important to facilitate treatment of this high-risk population.

29 Baigent C. Presentation to US FDA Endocrinologic and Metabolic Drugs Advisory Committee: Study of Heart and Renal Protection (SHARP): Safety and Efficacy of Ezetimibe/Simvastatin in Patients with Chronic Kidney Disease (CKD). 2011 Nov 2, 2011:S1, S73-S81 http://www.sharpinfo.org/CTSU_SHARP_FDA_ACM_2011-1102.pptx

With regard to the question of whether the benefit in SHARP is evenly distributed across the population when that population is stratified by the extent to which LDL-C was reduced, this cannot be readily answered. The proposed analysis of looking at event reductions in groups of patients whose LDL-C was reduced by increments of a certain percent (for example, 10%, 20%) would not be statistically valid because it would be a post-randomisation analysis and hence subject to serious bias/confounding. For example, those patients with the largest LDL-C reductions are likely to be those who adhered best to therapy and are also likely to be the less sick patients. For the latter reason, they may be less likely to have certain events. Further detail is provided in the *Detailed response*, below.

The sponsor believes that, based on all that is known about the mechanism of action of both statins and ezetimibe and based on the key meta-analyses of these therapies[30,31], their efficacy for reducing cardiovascular risk is primarily attributable to LDL-C reduction per se and the magnitude of event reduction is proportional to the absolute magnitude of LDL-C reduction achieved. There is no reason to believe that the reductions in atherosclerotic events observed in SHARP would differ from this relationship.

The sponsor believes a new separate indication is warranted given the robustness of the efficacy and safety data and the fact that no alternative therapy for decreasing risk of cardiovascular events in CKD patients has been approved. The current approved indication for the treatment of hypercholesterolaemia does not encompass either the patient group or the clinical outcomes of the SHARP trial. Examples of other products that have obtained an indication to prevent or reduce the risk of cardiovascular events in addition to an indication for the treatment of hypercholesterolaemia include Crestor (rosuvastatin) and Zocor (simvastatin).

Relative contributions of ezetimibe and simvastatin

The other major concern relates to the relative contributions of ezetimibe and simvastatin to the primary outcome.

In SHARP it was important to test the effects of a large reduction in LDL-C, since higher reductions in LDL-C have been shown to produce greater reductions in cardiovascular risk. SHARP was designed to address the main clinical question concerning nephrologists, namely: does a large reduction in LDL-C reduce the risk of vascular disease in patients with CKD, and, importantly, is it safe to reduce LDL-C to low levels in these patients?

The rationale for using ezetimibe in combination with simvastatin in SHARP was also justified by valid therapeutic principles that comply with regulatory guidelines relating to the design of the study specifically in relation to the Section 6.1 of the CHMP guideline on Clinical Development of Fixed Combination Medicinal Products, which states:

"*The indications claimed for a fixed combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect* ***or*** *improves the overall benefit risk ratio by mitigating side effects*".

The first option in the guideline requires determining whether *"the presence of each active substance makes a contribution to the claimed effect".* The combination of ezetimibe with simvastatin produces a lowering of LDL-C comparable to increasing the simvastatin dose to 80 mg[32]. In SHARP at one year, ezetimibe contributed about one third of the LDL-C

30 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

31 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

32 Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40(12):2125-2134i.

lowering effect produced by the ezetimibe/simvastatin 10/20 mg combination. Existing evidence suggests that the risk of myopathy with ezetimibe is similar to placebo.

The results from SHARP at one year show that both ezetimibe and simvastatin contributed to the lowering of LDL-C, with the ezetimibe component contributing approximately 31% of the LDL-C reduction observed with the combination. The FDA performed a *post-hoc* analysis on the outcomes data for one year. While the numerical reductions in events observed at one year were greater for ezetimibe/simvastatin compared with simvastatin, it is acknowledged that reliable conclusions cannot be drawn from these findings. To determine the independent contributions of each active substance to the reduction in cardiovascular risk would have required far greater numbers of patients than the 9000 patients which is already the largest study with any lipid-lowering treatment in CKD.

The design of SHARP aligns to the second option in the fixed combination guidelines: that is, to *"improve the overall benefit risk ratio by mitigating side effects".*

The fixed combination product ezetimibe/simvastatin was not only to achieve greater reduction of LDL-C than that obtainable with simvastatin alone, but more importantly to achieve safety: myopathy (including rhabdomyolysis) associated with simvastatin (and other statins) is dose-related. Unlike statins, ezetimibe was not believed to cause myopathy based on early findings, subsequently confirmed with greater experience[33]. Patients with CKD have an increased risk of myopathy. The delegate acknowledges that the "*important point re mitigation of side-effects*".[sic]

The hypothesis for SHARP was that ezetimibe/simvastatin 10/20 mg could be used to improve the benefit/risk in CKD patients; that it would produce a large LDL-C reduction with a significant reduction in cardiovascular events while minimising the risk of myopathy/rhabdomyolysis. This rationale was borne out in SHARP by a substantial reduction in LDL-C and a reduction in cardiovascular events with a low incidence of myopathy (0.1% greater than in the placebo group).

It will never be possible to specifically demonstrate that ezetimibe alone reduces major cardiovascular events among patients with CKD. In order to demonstrate the incremental effect of ezetimibe on top of a statin in a study like SHARP, it can be estimated that it would need to be 9 times larger (over 70,000 participants) to have sufficient power.

Therefore the premise that the LDL-C lowering attributable to ezetimibe did contribute to the outcomes results is eminently plausible and is supported by several lines of evidence, and provides strong support for the proposed indication in CKD patients. These include: (1) the fact that the degree of event reduction in SHARP was consistent with that anticipated from the total LDL-C reduction achieved, based on the known relationship in the CTT meta-analysis of over 26 statin trials; (2) the findings in SHARP at 1 year are suggestive of an incremental event benefit with ezetimibe/simvastatin 20 mg compared with simvastatin 20 mg monotherapy, although there is insufficient power to draw definitive conclusions.

Other issues raised by the Delegate

See also *Detailed response*, below.

Subgroup analysis including lipid levels: The results of SHARP show equal benefit in the CKD subgroups. This is a very important finding, as it aligns with the evidence that all CKD patients benefit from the treatment, irrespective of severity of renal insufficiency or other factors.

Components of the primary endpoint: No pre-determined hierarchy was assigned.

33 Davidson MH, Maccubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). Am J Cardiol 2006;97:223-8

Outcomes: The independent SHARP Steering Committee (SC) made the decision to change the key outcome to MAE based on findings from other lipid-lowering trials and analyses indicating that the event categories of haemorrhagic stroke and non-coronary death would not be substantively influenced by LDL-C-lowering therapy and thus were not appropriate components of the primary endpoint. The rationale behind the SC decision is explained in detail in the publication that was issued prior to unblinding[34]. Further detail is provided in the *Detailed response*, below.

Second randomisation: The sponsor can confirm that there were no significant differences between the treatment groups following the second randomisation.

Risk reduction: The ARR for the protocol-specified primary endpoint of MVE was 2.316%; the ARR for the SAP-specified key outcome of MAE was 2.086%.

Patients with other conditions: Patients who had pre-existing CHD, as reflected by a prior MI or coronary revascularisation procedure, were not eligible for randomisation because it was considered likely that a high proportion of such patients would at some future point commence LDL-lowering therapy, which would reduce the power of SHARP.

Lists of studies: The list of studies involving Vytorin is provided (see *Detailed response*, below).

TGA requested changes to the PI: the indication, some of the changes regarding children, more detail for baseline demographic including age ranges, disease characteristics, degree of compliance, primary and revised outcome analysis, risk reductions, plus separate contributions of the components and the effects of other statins, plus update to the current format have been incorporated.

Conclusion

The design of the SHARP trial is consistent with the CHMP guideline to improve the overall benefit risk ratio by mitigating side effects. The results of the trial show that ezetimibe/simvastatin 10/20 mg daily is able to reduce cardiovascular events in CKD, which no other treatment has been shown to do. The positive results of the SHARP study have been acknowledged by the clinical evaluator and the Delegate.

SHARP aimed to meet an unmet medical need for a high-risk population. An indication for the ezetimibe/simvastatin combination in CKD will provide these patients with equitable access to a treatment that will result in preventable major cardiovascular events actually being prevented.

Chronic kidney disease is a common and serious condition and the incidence can be expected to rise substantially in coming years due to an ageing population and an epidemic of type 2 diabetes. Patients with moderate to severe CKD are at high risk of cardiovascular disease, both non-atherosclerotic in causality (for example, heart failure, cardiomyopathy and arrhythmias), as well as cardiovascular disease with atherosclerotic aetiology, including CHD, ischemic stroke, and peripheral artery disease. Despite this large burden of disease, prior to SHARP there have been no treatments that have been clearly shown to reduce cardiovascular risk in CKD patients. The main reason for this is that patients with CKD have typically been excluded from large-scale randomised trials, largely because of concerns about possible adverse effects.

If an indication for the combination is denied because of the inability to separate the effects on outcomes of the components, doctors and patients in Australia will be substantially limited in their ability to access ezetimibe/simvastatin 10/20 mg for use in

34 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.e.10.

CKD patients, with the result that preventable major cardiovascular events in CKD patients will not be prevented. Given that the ezetimibe/simvastatin 10/20 mg combination clearly reduces cardiovascular events in CKD, a benefit that no other lipid-lowering treatment or other treatment of any kind has been shown to provide, the contribution of the components seems less relevant clinically.

A new indication for the reduction of major cardiovascular events in CKD is an important medical advance that can benefit the large numbers of patients with CKD in Australia for whom no other proven therapy exists. In support, the sponsor provided Expert statements from two Australian renal specialists.

Detailed response

Delegate's questions*: The sponsor is asked to address the following major concerns raised by the Delegate in the Risk/Benefit discussion. Can it be entirely certain that the claimed final benefit could not have also been achieved by simply being on simvastatin 20 mg alone for the duration of the study? There is the other issue of the apparent lack of dose-ranging studies. How can it be entirely certain that the same effect could not have also been achieved by being on a fixed-combination dose of ezetimibe 10 mg/Simvastatin 10 mg for the duration of the study?*

Sponsor's response: The rationale in SHARP for use of the fixed dose combination was to achieve a large LDL-C reduction with maximum safety. Careful assessment of a large number of statin trials has unequivocally demonstrated that larger reductions in LDL-C yield larger reductions in major vascular events (MVE)[35,36]. This was the major reason for using Vytorin 10/20 rather than simvastatin 20 mg in SHARP. The latter would have been predicted to produce a reduction in LDL-C of about 0.6 mmol/l on average over the whole trial, and this would only have been predicted to result in about a 12% reduction in MVE.

The addition of ezetimibe 10 mg to statin therapy provides an incremental reduction of LDL-C equivalent to three doublings of the statin dose. The use of ezetimibe in combination with simvastatin thus allowed for a much lower and therefore safer dose of simvastatin, 20 mg, than would otherwise have been required to achieve a large reduction of LDL-C (in fact, a dose higher than the maximal dose of simvastatin, 80 mg daily, would have been necessary in a simvastatin-only regimen of equivalent potency).

Myopathy (including rhabdomyolysis) associated with simvastatin use (as well as other statins) is dose-related, and patients with CKD have an increased risk of myopathy. The use of ezetimibe 10 mg in combination with simvastatin 20 mg yielded a clear safety advantage over high-dose (80 mg) simvastatin monotherapy, as demonstrated by the comparison of the results of SHARP with those of the cardiovascular outcome trial *Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine* (SEARCH)[37]; in SEARCH, 12,000 patients with a history of myocardial infarction were allocated to simvastatin 80 mg or 20 mg with a follow-up period of 6.7 years. Myopathy was reported in 2 patients in the simvastatin 20 mg group, compared to 53 patients in the simvastatin

35 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

36 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

37 SEARCH Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010;376:1658-69.

80 mg group, of whom at least 7 patients had rhabdomyolysis. A later analysis[38] of myopathy in patients in SEARCH allocated to 80 mg showed that the risk of myopathy including "incipient myopathy" was more than doubled in patients with an estimated glomerular filtration rate of 60 mL/min or less, confirming the long-held belief that patients with CKD are more vulnerable to statin-induced myopathy.

Unlike statins, ezetimibe was not believed to cause myopathy based on early findings, subsequently confirmed with greater experience[39]. A pooled meta-analysis of clinical trial data (mostly short-term) demonstrated an incidence of myopathy/rhabdomyolysis of 4/10342 (0.04%) on statin alone versus 3/11514 (0.03%) on ezetimibe/statin[40]. Thus the rationale for using ezetimibe in combination with simvastatin was justified by valid therapeutic principles and complies with regulatory guidelines.

While it cannot be said with absolute certainty that the SHARP result could have been observed with simvastatin 20 mg alone, it is extremely unlikely given the observed reduction in a population that has proved difficult to demonstrate significant benefit at all using statin monotherapy. Similarly, the fact that the LDL-C produced by ezetimibe/simvastatin 10/10 mg would yield somewhat less MVE reduction than 10/20 mg is based on established knowledge, but could never be demonstrated in a feasible clinical trial of CKD patients given the enormous numbers that would be required.

Each component of the fixed combination contributes to LDL-C reduction, and ezetimibe improves the benefit/risk ratio in patients with CKD by avoiding the use of higher doses of simvastatin. For reasons of achieving optimal LDL-C-lowering efficacy and for reasons of safety, no dose of simvastatin alone would have been satisfactory; therefore, the use of the fixed combination product ezetimibe/simvastatin 10/20 mg was appropriate to optimise the benefit/risk ratio of the LDL-C lowering intervention.

Delegate's questions: *The second major concern (and the more important in the view of the Delegate) revolves around the issue of whether the results from SHARP genuinely and robustly support a new, separate indication (one indicative of a benefit which can, without any doubt, be attributed to a special, specific effect of the combination extra to and independent of the already established lipid lowering effects of the combination.). How certain is it that the primary endpoint achieved in the SHARP study is not simply and wholly due to the already approved lipid lowering effects of the combination of ezetimibe and simvastatin? How robustly do the findings of SHARP support the existence of a special, specific effect in those with CKD extra to and independent of the already approved lipid lowering indications of the fixed-dose combination. The Delegate has asked the sponsor to respond to a number of questions on this issue and also to perform a detailed post hoc analysis of the primary efficacy endpoint when the patient population is stratified according to the relative extent of reductions in LDL-C.*

Sponsor's response: Information from the CTT meta-analysis of trials of statin therapy indicate clearly that relative risk reductions for major vascular events correlate strongly with the absolute size of the LDL-C reduction in a given trial or in a given subgroup of patients[41,42].

38 The SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy - A genomewide study. N Eng J Med 2008;359(8):789-99.

39 Davidson MH, Maccubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). Am J Cardiol 2006;97:223-8.

40 Toth PP, Weintraub W, Morrone D, Hanson ME, Lowe RS, Lin J. et al. Safety profile of statins alone or combined with ezetimibe: a pooled analysis of over 21,000 patients [Abstract]. Atheroscler Suppl 2011;12(1):55.

41 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

However patients with CKD are a distinct high-risk population for whom there are currently no licensed treatments for the prevention of cardiovascular disease. Such patients are routinely excluded from trials, chiefly because of concerns about safety, so it is important that they are studied in specific trials to ensure that they are not excluded from receiving effective treatments.

Patients with CKD typically develop hypertriglyceridaemia and low HDL cholesterol, but not typically hypercholesterolaemia, but (as recognised by the recently published ESC/EAS guidelines[43]) CKD is a coronary risk equivalent and the recommendation is a target level of 70mg/dL (or at least a 50% reduction in LDL-C).

The sponsor's concern is that without the new indication, only CKD patients with raised LDL-C (who, paradoxically, are those at lowest risk based on observational data) will be treated and that they will receive low dose statin therapy, consequently deriving little benefit based on the known relationship between absolute LDL-C reduction and MVE reduction and despite the clear evidence of both efficacy and safety provided by SHARP.

Delegate's questions: *The sponsor is asked to address all issues raised by the Delegate including: … to provide baseline distribution of lipid values (such as total cholesterol, LDL-C or triglycerides) by treatment group. As well as mean and range, … baseline lipid data arranged by quartiles for each treatment group.*

Sponsor's response: As requested, the baseline lipid data arranged by quartiles for each treatment group are provided in Table 15, below. The data demonstrate that the two groups are well balanced with respect to baselines lipids, based on the quartile analysis.

42 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

43 Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O. et al. ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769-818.

Table 15. SHARP: Baseline characteristics of randomised patients: All patients randomised to ezetimibe/simvastatin 10/20 mg versus placebo (Number and Percentage or Mean ± SD)

SHARP: Baseline Characteristics of Randomized Patients: All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg versus Placebo (Number and Percentage or Mean ± SD)

Baseline Characteristic	Ezetimibe/simvastatin 10/20 mg (N=4650) n(%)	Placebo (N=4620) n(%)
Total cholesterol (mmol/L)	4.88 ± 1.20	4.90 ± 1.17
<4.1	1165 (25%)	1119 (24%)
≥4.1 <4.8	1072 (23%)	1052 (23%)
≥4.8 <5.6	1174 (25%)	1170 (25%)
≥5.6	1052 (23%)	1089 (24%)
Not available	187 (4%)	190 (4%)
LDL cholesterol (mmol/L)	2.77 ± 0.88	2.78 ± 0.87
<2.2	1188 (26%)	1171 (25%)
≥2.2 <2.7	1005 (22%)	971 (21%)
≥2.7 <3.3	1167 (25%)	1169 (25%)
≥3.3	1102 (24%)	1119 (24%)
Not available	188 (4%)	190 (4%)
HDL cholesterol (mmol/L)	1.12 ± 0.35	1.11 ± 0.34
<0.9	1195 (26%)	1264 (27%)
≥0.9 <1.1	1185 (25%)	1195 (26%)
≥1.1 <1.3	984 (21%)	862 (19%)
≥1.3	1095 (24%)	1109 (24%)
Not available	191 (4%)	190 (4%)
Non-HDL cholesterol (mmol/L)	3.75 ± 1.12	3.79 ± 1.11
<3.0	1103 (24%)	1071 (23%)
≥3.0 <3.7	1181 (25%)	1121 (24%)
≥3.7 <4.4	1069 (23%)	1080 (23%)
≥4.4	1106 (24%)	1158 (25%)
Not available	191 (4%)	190 (4%)
Triglycerides (mmol/L)	2.31 ± 1.76	2.34 ± 1.68
<1.3	1061 (23%)	1030 (22%)
≥1.3 <1.9	1168 (25%)	1158 (25%)
≥1.9 <2.8	1154 (25%)	1104 (24%)
≥2.8	1079 (23%)	1137 (25%)
Not available	188 (4%)	191 (4%)
Apolipoprotein B (mg/dL)	95.91 ± 25.98	96.67 ± 25.53
<78	1121 (24%)	1051 (23%)
≥78 <95	1171 (25%)	1160 (25%)
≥95 <112	1107 (24%)	1097 (24%)
≥112	1068 (23%)	1127 (24%)
Not available	183 (4%)	185 (4%)
Apolipoprotein A1 (mg/dL)	134.51 ± 29.02	133.38 ± 28.46
<115	1149 (25%)	1181 (26%)
≥115 <130	1026 (22%)	1101 (24%)
≥130 <150	1153 (25%)	1087 (24%)
≥150	1143 (25%)	1067 (23%)
Not available	179 (4%)	184 (4%)

Delegate's questions: *The sponsor is requested to clarify the need for the Steering Committee to recommend a change in the key outcome to be measured and also to clarify the precise difference between the parameters MAE and MVE. As part of the latter, the sponsor is requested to define precisely what is meant by the term "non-coronary cardiac death". The sponsor is also requested to provide a detailed discussion of the precise power of the study to achieve each of these endpoints and also to clarify the precise make-up of the populations which were compared in each analysis.*

Sponsor's response: The SHARP study, while funded by Merck & Co., Inc., was independently conducted by the University of Oxford CTSU under the oversight of an independent Steering Committee. The Steering Committee made the decision to change the key outcome to MAE based on findings from other lipid-lowering trials indicating that the event categories of haemorrhagic stroke and non-coronary death would not be substantively influenced by LDL-C-lowering therapy and consequently would only dilute

the treatment effect on the primary endpoint. The rationale behind the SC decision is explained in detail in the publication that was issued prior to unblinding[44].

The adjudication procedures and rules for all outcome events including non-coronary cardiac death are described in detail in the SHARP standard operating procedure for event adjudication in the CSR. In brief, cardiac deaths comprised MI death (when the cause of death met the criteria for death from a MI), CHD death (when the criteria for MI were not met, but the cause of cardiac death was believed to be coronary atherosclerosis) and other cardiac death (when the criteria for MI were not met and the cause of cardiac death was not believed to be due to atherosclerotic heart disease). CHD death (not MI) included death following admission with acute coronary syndrome (ACS)/angina, death from ischemic cardiac myopathy, and death from ischemic heart disease that did not meet the definition for acute MI. Other cardiac deaths included death from nonischemic cardiomyopathy or heart failure, and death from heart disease without evidence of underlying coronary atherosclerosis (for example, sudden cardiac death), death from cardiac arrest, ventricular tachycardia or other arrhythmia with no evidence of underlying coronary disease, and death from other cardiac diseases (for example, valvular heart disease). Thus, non-coronary cardiac deaths consisted of all cardiac deaths that did not meet criteria for CHD death. As noted in the CSR, it must be recognised that despite the detailed criteria for adjudication, it is not always possible to distinguish cardiac from noncardiac deaths and CHD deaths from other cardiac deaths, especially in this population with chronic renal disease.

The following is provided with regard to the request for further discussion of power for the study endpoints and the precise make up of the study populations that were compared in each analysis. The protocol specified primary endpoint was MVE in the population of patients who were initially randomised to either the placebo group (n = 4191) or the ezetimibe/simvastatin group (n = 4193); that is, it excluded those patients initially randomised to the simvastatin monotherapy group (n = 1054). All other analyses of MVE or its components were performed on the entire population randomised at any time to placebo (n = 4620) or ezetimibe/simvastatin (n = 4650). For the SAP key outcome of MAE, the population was specified as the entire cohort randomised at any time to placebo (n = 4620) or ezetimibe/simvastatin (n = 4650), and all analyses of components of that key outcome were also performed on that population. The most precise estimates of power (at 2p = 0.01) to achieve the MVE and MAE outcomes specified in the protocol and the SAP, respectively, are provided in the study design publication, and correspond to 66% (assuming an anticipated proportional event reduction in MVE of 13%) for the original protocol-specified primary endpoint, and 88% (assuming an anticipated proportional event reduction in MAE of 18%) for the SAP-specified key outcome.

Delegate's question: *The sponsor is requested to confirm that there were no significant differences between treatment groups following the second randomisation i.e. at the end of the first year when those patients initially randomised to simvastatin 20mg daily were re-randomised to either ezetimibe 10mg/simvastatin 20mg (Arm 3b) or to placebo (Arm 3a) for the remainder of the trial.*

Sponsor's response: The sponsor confirmed that there were no significant differences between the treatment groups following the second randomisation.

Delegate's questions: *Compared to placebo, ezetimibe/simvastatin 10/20mg reduced the risk of MVE by 16%. The ARR appeared to be in the order of 2.7%. The sponsor is requested to state precisely the value of the ARR demonstrated. In the SAP, the key outcome was the first occurrence of MAE…This outcome occurred in 11.3% vs. 14.5%, a relative risk reduction of*

44 SHARP Collaborative Group. Study of heart and renal protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160(5):785-94.e.10.

17%. The ARR appeared to be of the order of 3.2%. Once again, the sponsor is requested to state precisely the value of the ARR demonstrated.

Sponsor's response: The ARR for the protocol-specified primary endpoint of MVE was 2.316%. The absolute risk reduction for the SAP-specified key outcome of MAE was 2.086%.

Delegate's questions: *There were analyses of the protocol-specified components of the primary MVE outcome in all randomised patients with apparently significant reductions in the rates of total stroke, ischaemic stroke and any revascularisation procedure but not in the rates of major cardiac events, haemorrhagic stroke or stroke of unknown cause. However, it is uncertain whether there was a pre-determined hierarchy of these components. The sponsor is requested to clarify this issue. For both MVE and MAE, the effects on each appeared to be driven by a benefit on ischaemic stroke (not haemorrhagic) and revascularisation procedures.*

Sponsor's response: No pre-determined hierarchy was assigned to the components of the primary endpoint. However, the SAP specified that the Hochberg procedure would be employed for purposes of assessing the impact of multiplicity on the evaluation of separate components of MAE. The observed reduction in stroke, ischemic stroke, and revascularisation remained statistically significant after multiplicity adjustment.

It is correct that the largest differences among the components of the composite endpoints were seen for stroke, ischaemic stroke and revascularisation procedures, and in that sense, it could be said that these components were "drivers" for the overall significance of the composites. However, the other components were all numerically directionally consistent. Based on the size and power of the SHARP trial, statistical significance cannot be expected for all components. Separate analyses showed that the composites remained statistically significant even after revascularisation, strokes, or ischaemic strokes were individually excluded from the analysis, reflecting the contribution of all of the components to the overall primary endpoint results.

Delegate's questions:

- *As noted by the clinical evaluator, after weighting the risk ratios in the efficacy endpoints according to the reductions in LDL-C, the trends for MAE were much reduced and remained only statistically significant (before accounting for multiple testing) only for total cholesterol and waist circumference. For MVE, only the trend by baseline cholesterol remained significant after accounting for LDL-C differences. Thus the clinical evaluator concludes, no particular sub-group in SHARP obtained more or less benefit, other than that variation among sub-groups in the absolute reduction of LDL-C. The Delegate is not entirely certain of the precise meaning of these statements and requests the sponsor to provide some clarification.*
- *Are the benefits demonstrated by SHARP really only conferred by the lipid lowering effects of ezetimibe, effects for which the medicine already has an approved indication? (The fact that there was no significant effect on the risk of progression to ESRD raises the question..). Is there enough evidence to support the existence of a special, specific effect in patients with CKD above and beyond the lipid lowering effect?*

As mentioned by the clinical evaluator, the trends for MAE were much reduced once reductions in LDL-C had been taken in to account. Does this imply no benefit or perhaps only a very small benefit in patients with CKD on top of the already approved lipid lowering effect? Does it imply that a proportion only of the benefit claimed is due to the already approved lipid lowering effect with the remainder of this benefit then and only then able to be ascribed to the specific effect in patients with CKD? Is it possible to determine the exact size of each proportion, i.e. the proportion of the benefit due simply to the lipid lowering effect, and the remainder due to the specific renal effect? Is it possible to see evidence for this

specific effect quite independently of the lipid lowering effect of ezetimibe? Is the benefit evenly distributed across the population, when that population is stratified by the extent to which lipid levels, e.g. those of LDL-C, were reduced? The sponsor is requested to address all of these questions, particularly the last question.

The sponsor is requested to conduct a post hoc analysis which begins by comparing the rate of the primary endpoint in those whose LDL-C was reduced by less than 10% of its baseline value (including those whose LDL-C increased) with those whose LDL-C was reduced by at least 10% of its baseline value and which continues by repeating the analysis by advancing, at each step, the reduction in LDL-C by a further 10%. This means that the second step of the analysis would be to compare the rate of the primary endpoint in those whose LDL-C was reduced by less than 20% of its baseline value (including those whose LDL-C increased) with those whose LDL-C was reduced by at least 20% of its baseline value. The analysis is to be repeated across the entire range possible.

Sponsor's response: With regard to the question of whether the benefit in SHARP is evenly distributed across the population when that population is stratified by the extent to which LDL-C was reduced, information from the CTT meta-analysis of trials of statin therapy indicate clearly that relative risk reductions for major vascular events correlate strongly with the absolute size of the LDL-C reduction in a given trial or in a given subgroup of patients[45,46]. In view of this, the relative risk reductions observed in SHARP subgroups should be interpreted in the light of the size of the LDL-C reductions achieved in each. When this is done, as expected, smaller risk reductions were observed in those subgroups where smaller LDL-C reductions were observed. These include, for example, subgroups of patients with low baseline LDL-C. It is most appropriate to conclude from SHARP, therefore, that the lack of significant reductions in these patients is likely to be attributable to a lack of statistical power. Kidney patients with low LDL-C may be at particularly high risk of vascular events. Consequently, a small relative risk reduction may well translate into large and worthwhile absolute benefits. The sponsor believes, therefore, that SHARP does indeed provide evidence on efficacy for a wide range of patients with CKD, and not a subset of those.

The proposed analysis of looking at event reductions in groups of patients whose LDL-C was reduced by increments of a certain percent (for example, 10%, 20%) would not be statistically valid because it would be a post-randomisation analysis and hence subject to serious bias/confounding. For example, those patients with the largest LDL-C reductions are likely to be those who adhered best to therapy and are also likely to be the less sick patients. For the latter reason, they may be less likely to have certain events. These analyses could only be done among those subjects allocated active therapy, so non-randomised comparisons of people with different lipid responses are being made. Variations in event rates between these groups of people may be explained by things other than their lipid responses, and it is impossible to make adequate adjustment for this. So they are not reliable analyses and should not form part of the assessment of a randomised trial.

The sponsor agreed with the clinical evaluator's assessment that the evidence suggests that no particular sub-group in SHARP obtained more or less benefit other than that variation among sub-groups related to the absolute reduction of LDL-C (which in turn largely reflects compliance, as well as baseline LDL-C). As with any large trial, SHARP of

45 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670 81.

46 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

course did not have the statistical power to provide accurate point estimates of benefit for a variety of subgroups; however, given the absence of evidence of heterogeneity after accounting for absolute differences in LDL-C reduction, the most appropriate conclusion is that the general observation of benefit observed for the full cohort applies similarly to all of the subgroups analysed. This observation is not surprising in light of the fact that the largest meta-analysis of LDL-C lowering trials using patient-level data[47,48] in as many as 170,000 patients also showed evidence of treatment benefit across all subgroups analysed, largely overlapping with the subgroups analysed in SHARP.

In general, the sponsor believes that, based on all that is known about the mechanism of action of both statins and ezetimibe and based on the key meta-analyses of these therapies, their efficacy for reducing cardiovascular risk is primarily attributable to LDL-C reduction *per se* and the magnitude of event reduction is proportional to the absolute magnitude of LDL-C reduction achieved. There is no reason to believe that the reductions in atherosclerotic events observed in SHARP would differ from this relationship.

Delegate's questions: *The data indicated a reduction in major vascular events in patients over 40 years of age with CKD who have had neither a revascularisation procedure nor a myocardial infarction. Given the concerns of the Delegate expressed above, it could be speculated whether exactly the same benefit would have been demonstrated if SHARP had been conducted in a population of patients all with some other condition e.g. osteoarthritis of the hip. The data does not appear to demonstrate a benefit in any particular sub-group, or a benefit on progression to ESRD or any mortality benefit.*

Sponsor's response: Patients who had pre-existing coronary heart disease, as reflected by a prior MI or revascularisation procedure, were excluded from SHARP because, in Merck's view such patients were considered to be already appropriate for LDL-C lowering treatment irrespective of concurrent CKD, based on existing approved indications for certain statin therapies. It would therefore not have been appropriate to randomise them to a study with a 50% chance of going on placebo for the duration of the trial. As noted in the response to the prior question, the treatment effect in SHARP is considered by the sponsor most likely to attributable to the LDL-C lowering achieved with ezetimibe/simvastatin. The point of studying the population of moderate to advanced CKD in SHARP was that the value of LDL-C-lowering therapy had not been demonstrated in these very high-risk patients. SHARP clearly demonstrated that benefit, which had remained unclear despite two other statin trials in dialysis patients which failed to achieve a significant primary endpoint. The fact that the results of SHARP do not point to a particular benefit in any CKD subgroup is a very important finding, as it aligns with the evidence that all CKD patients benefit from the treatment, irrespective of severity of renal insufficiency or other factors.

If ezetimibe/simvastatin were conducted in a population of patients having some other condition (e for example, osteoarthritis of the hip, as the Delegate speculates), Merck would suggest that based on the strong evidence from CTT, benefit would be demonstrated; in fact, it would be expected that the LDL-C reduction would be larger to the extent that such patients had higher baseline LDL cholesterol, consequently the relative risk reduction would be larger. But of course such patients would be at much smaller risk of atherosclerotic cardiovascular events than the CKD SHARP population and consequently it would have required a much larger number of subjects to demonstrate

47 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

48 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

that benefit. The point is really that based on strong clinical trial data highlighted by the CTT meta-analysis, cardiovascular event reduction benefits are expected with LDL-C lowering in populations at risk for atherosclerotic CHD, however for CKD patients such benefit would not be achieved if nephrologists (or other physicians) caring for these patients followed the existing label which does not have an indication for their treatment unless they meet hypercholesterolemia criteria that the majority do not in fact have.

The nature of cardiovascular disease in CKD is such that in addition to atherosclerotic cardiovascular events there are known to be substantial numbers of other cardiac events (for example, arrhythmias, CHF, non-atherosclerotic cardiomyopathies) that would not be predicted to be reduce by LDL-C lowering therapy. Because of the difficulty in discriminating all such events from pre-specified atherosclerotic event endpoints despite rigorous adjudication methodology, there can be expected to be a degree of dilution of the treatment effect that would be observed in a population in which nearly all of the cardiovascular events are atherosclerotic in etiology. This makes it all the more impressive that treatment with ezetimibe/simvastatin in SHARP resulted in MAE and MVE reductions that are quite consistent with statin studies relative to the degree of LDL-C reduction achieved.

It is correct that treatment with ezetimibe/simvastatin did not appear to demonstrate a benefit on progression to ESRD in SHARP. This is not surprising given the advanced degree of CKD in the SHARP population. It does not contradict prior observations that LDL-C lowering therapy appears to have a small effect on slowing decreases in renal function in normal or mild CKD populations.

It is also correct that no all-cause mortality benefit was seen in SHARP, but this is not at all surprising given that any reduction in mortality that might have been associated with the observed reduction in MVE and MAE in SHARP would have to be very small owing to the large majority of deaths being due to non-atherosclerotic disease. SHARP did observe a numerical (7%) reduction in any vascular death, which constituted a little over a third of all deaths. Atherosclerotic deaths known to be reducible by lipid-lowering therapy are limited to deaths caused by CHD and possibly ischaemic stroke, but in SHARP these accounted for only 181 (8%) and 71 (3%) deaths respectively, out of the total of 2,257 deaths. Thus only 11% of all the deaths in SHARP were potentially preventable by ezetimibe/simvastatin. No reductions in mortality due to CHD (or ischaemic stroke) were observed, but the power was low due to small numbers; also, because determination of the cause of cardiac death is often difficult in CKD, some of the deaths adjudicated as CHD deaths might be due to structural heart disease. For illustrative purposes, if it is supposed that ezetimibe/simvastatin could reduce deaths due to CHD by 20% and ischaemic stroke by 10%, the reduction in all-cause mortality would be about 2%. SHARP had virtually no power to detect such a small decrease; about a quarter of a million patients would have been required to reliably detect a 2% risk reduction in all-cause mortality.

Delegate's questions*: The sponsor is requested to provide a list of all ongoing studies involving Vytorin.*

Sponsor's response: See Table 16.

Table 16. Ongoing studies

Drug	Study #	Protocol Title
Vytorin	SP4103	A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs. Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial – IMPROVE IT)
Vytorin	043-10	A Multinational, Observational Follow-Up Study of the Incidence of Cancer and Mortality in Patients from the SEAS Trial
Vytorin	259	A Study to Evaluate Fasting/Postprandial Serum Apolipoprotein B-48 (apoB-48) Levels in Diabetic Participants With Normal to Moderately High Low Density Lipoprotein-C (LDL-C) Levels
Vytorin	406	A Multicenter, Open-Label, 6 week Study to Evaluate the Efficacy and Safety of Algorithm Based Intensive Treatment with Vytorin Versus Standard Treatment of Other Statins in Moderate, Moderately High and High Risk Patients

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's responses to these documents, advised that the efficacy and safety data do not justify the proposed extension of the indication. The ACPM, however, agreed that the Product Information (PI), and as appropriate the Consumer Medicine Information (CMI), should be updated to include the results of the SHARP study. The PI should include a statement that no benefit was found for patients on dialysis.

Outcome

Following receipt of the ACPM advice and notice of the Delegate's intention to reject the proposed additional indication regarding use of Vytorin for *Prevention of Major Cardiovascular Events in Chronic Kidney Disease*, the sponsor notified TGA that it wished to withdraw the part of the application relating to the proposed extension of indications.

The full indications for Vytorin therefore are unchanged:

Primary Hypercholesterolaemia

Vytorin is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and nonfamilial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:

- *Patients not appropriately controlled with a statin or ezetimibe alone*
- *Patients already treated with a statin and ezetimibe.*

Homozygous Familial Hypercholesterolaemia (HoFH)

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

Pursuant to sections 9D(3) and 25 of the Act, the Delegate approved amendments to the Vytorin PI, including changes to the *"Dosage and Administration"* and *Clinical Trials* sections, to take into account the findings of the SHARP study.

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Specific Conditions Applying to these Therapeutic Goods

- The sponsor is to implement the Risk Management Plan version 1.0, dated 14 April 2011 and the Australian Specific Annex dated 18 June 2011, updated as outlined in the sponsor's letter to the TGA of 9 July 2012. The updated RMP and Australian Specific Annex are to be submitted for review as soon as available to the OPR of the TGA. All future amendments of either the RMP or the Australian Specific Annex negotiated with the OPR and agreed to by that office will come into effect immediately with that agreement.
- The sponsor is to lodge with the TGA, as evaluable data within the context of Category 1 applications, the final study reports of all post-authorisation studies mentioned in the RMP evaluation, in particular the final study report of the ongoing Study P04103 - IMPROVE-IT (IMProved Reduction in Outcomes: Vytorin Efficacy International Trial).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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