CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Crestor 5/10/20/40, 5/10/20/40 mg film-coated tablets AstraZeneca B.V., the Netherlands

rosuvastatin calcium

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0343/001- 004/E/001
Registration number in the Netherlands: RVG 30823, 26872-26874

3 February 2011

Pharmacotherapeutic group:	HMG CoA reductase inhibitors
ATC code:	C10AA07
Route of administration:	oral
Therapeutic indication:	Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.
Prescription status:	prescription only
Date of first authorisation in NL:	6 November 2002 (10 mg, 20 mg, 40 mg), 20 July 2004 (5 mg)
Concerned Member States:	Repeat-use procedure with DE, ES, MT, NO and PL
Application type/legal basis:	Directive 2001/83/EC, Article 8(3), full application, repeat-use procedure

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Crestor 5/10/20/40, 5/10/20/40 mg film-coated tablets, from AstraZeneca. The date of authorisation was on 6 November 2002 (10 mg, 20 mg, 40 mg) and on 20 July 2004 (5 mg) in the Netherlands. The product is indicated for treatment of:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.
- homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

A comprehensive description of the indications and posology is given in the SPC.

The data presented in this PAR with regard to Crestor also apply to the dossiers of Cirantan, Provisacor and Rovustatine AstraZeneca (NL/H/0344-0346/001-004/MR).

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

This repeat-use procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinial and clinical data. The application is supported by a full dossier and consists of the initial dossier submitted for the first wave that is updated with post-approval safety and efficacy data from clinical and observational trials and post-marketing data. Furthermore, a Pharmacovigilance System and an Environmental Risk Assessment have been added to the original dossier.

The dossier has been updated with data and changes from both the first round MRP as well as post-approval variations. On pages 15-19 all post-approval variations are summarized. The variations are sorted into three groups: variations <u>after</u> finalisation of the initial MRP procedure but <u>before</u> the repeat-use procedure (10/20/40 mg); variations for 5 mg strength (<u>after</u> MRP, <u>before</u> repeat-use procedure); and variations <u>after</u> finalisation of the repeat-use procedure (for all strengths).

In addition, two annexes are presented:
- Annex I in which type II variation NL/H/343/II/033 is discussed. Through this variation an indication for a subset of the paediatric population was approved and incorporated with the adult indication: “Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholersterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. “
- Annex II includes a discussion of type II variation NL/H/343/II/035. Through this variation an additional indication was approved: “Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (See Section 5.1), as an adjunct to correction of other risk factors’’.

<u>The initial MRP-procedures</u>

10/20/40 mg:
The original MRP procedure for the 10 mg, 20 mg and 40 mg (NL/H/343/001-003/MR) started on 7 December 2002 and ended on 7 March 2003. At day 90 (7 March 2003) the marketing authorisation was mutually recognised by AT, BE, DK, EL, FI, IC, IRL, IT, LU, PT, SE and UK.

By day 50 of that procedure, potential serious health concerns were raised by AT, BE, ES, FR, IRL, IT, NO, SE and UK. The major issues raised by the CMS in their day 50 comments were the starting dose of 5 mg vs. 10 mg, the benefit/risk ratio of the 40 mg dose, the use in patients with renal and liver dysfunction and the pharmacokinetic interactions.
The application for all strengths was withdrawn in Germany, Norway and Spain. In France the application for 40 mg tablets was withdrawn only, because of their concern with the safety of this dose level (renal effects).

5 mg:
The original MRP procedure for the 5 mg strength started on 8 august 2004 and ended on 19 August 2005. At day 90 (2 November 2004) there were potential serious outstanding issues and therefore the application was referred under Article 29 to the CHMP. The List of Questions that was dealt with during the referral concerned clinical efficacy en safety.
During its April 2005 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, was of the opinion that the benefit/risk ratio is favourable for Crestor 5 mg or Crestor 10 mg both as start dose. The choice of start dose in the individual patient should take into account aspects of efficacy and safety, as detailed in the SPC. Changes to SPC section 4.2 (Posology and method of administration) and 4.4 (Special warnings and special precautions for use) arising from the arbitration process were agreed by the CHMP and a positive opinion was adopted on 21 April 2005. The final opinion was converted into a Decision by the European Commission on 9 August 2005.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
Rosuvastatin calcium is a novel active substance. The active substance is a white powder which shows no polymorphism. Detailed information is present regarding nomenclature, structural and molecular formulas and molecular mass.

Manufacture
Synthesis routes for the manufacturing of rosuvastatin calcium are presented. The first steps leads from the starting materials to the intermediate. In subsequent steps the intermediates are obtained and finally the calcium salt. In 2005 the original process has been optimised by reducing the number of overall steps. Adequate descriptions of manufacturing steps, control of critical steps and intermediates, are present.

Quality control of drug substance
Specifications for rosuvastatin calcium comprise testings on identity (IR spectroscopy, chiral HPLC, calcium ion), assay by HPLC and calcium content, related substances, optical purity by HPLC, residual solvents by GC, water content, chloride content and particle size. There are eight stereoisomers due to two chiral centers and a double bond with four different groups; by adequate analytical methods the unwanted stereoisomers are limited. The active substance is an amorphous solid without the occurrence of polymorphs. The specification is adequate to guarantee a satisfactory quality of the active substance. More than twenty possible structures related to the active substance (synthesis related or degradation products) have been identified and are controlled by HPLC to assure acceptable low levels of these impurities in the active substance.

Stability of drug substance

The MAH claimed a re-test period of eighteen months when stored in the proposed packaging at 2-8°C and protected from light. Stability studies have been performed using three pilot-scale and three production-scale batches at 2-8°C and 'accelerated' conditions (25°C/60% RH up to 60°C/80% RH). Photostability studies demonstrated the protective capability of the proposed packaging. Eighteen months results meeting the set specifications confirm the validity of the claimed re-test period and storage condition.

Medicinal Product

Composition
Crestor 5, 5 mg – are round, yellow coloured, film-coated tablets, intagliated with '*ZD4522*' and '*5*' on one side and plain on the reverse.
Crestor 10, 10 mg – are round, pink coloured, film-coated tablets, intagliated with '*ZD4522*' and '*10*' on one side and plain on the reverse.
Crestor 20, 20 mg – are round, pink coloured, film-coated tablets, intagliated with '*ZD4522*' and '*20*' on one side and plain on the reverse.
Crestor 40, 40 mg – are oval, pink coloured, film-coated tablets, intagliated with '*ZD4522*' and '*40*' on one side and plain on the reverse.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, calcium phosphate, crospovidone, magnesium stearate.
Tablet coating - lactose monohydrate, hypromellose, triacetin, titanium dioxide (E171), ferric oxide red (E172) and yellow (only 5 mg).

The tablets are packed in an aluminium laminate / aluminium foil blister packaging or an HDPE container with screw closure.
Both 10 and 20 mg tablets are fully dose proportional. In addition the 5 mg tablet is almost similar to the 10 mg tablet except for the active substance content, the 40 mg tablet is almost similar to the 20 mg tablet except for the active substance content.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The proposed tablet formulation has been derived by improvement and modification of the Phase III tablet formulations in order to improve reproducibility of pharmaceutical processing. Dissolution characteristics of both Phase III tablets and the proposed tablets have been maintained constant by testing with an established dissolution method.

Excipients
In general, compatibility studies between active substance and excipients have been performed. The formulations comprise well-known excipients, all described in pharmacopoeias, and are quite usual for a composition of film-coated tablets. The colourant ferric oxide, red is in accordance with the applicable European Directives (78/25/EEC and 95/45/EC); this is acceptable. For the coating mixtures Opadry (lactose monohydrate, hypromellose, glycerol triacetate, titanium dioxide, ferric oxide, red or yellow) additional adequate specifications are given, this is also acceptable. In the proposed concentrations of the excipients no safety concerns are present.

Manufacturing process
The chosen method of preparation is dry blending. The manufacturing comprises well-known processes like (pre-) blending, compression and film-coating. The four tablet strengths are derived from two formulation blends by variation in compression weight. IPC (In-Process Control) requirements during compression and coating are adequate. Sufficient validation data on production scale batches are available, including content uniformity testing during various stages. The validation data demonstrate satisfactory homogeneity within a batch, satisfactory reproducibility between batches, and sufficient control of the manufacturing process.

Container closure system

1. Aluminum laminate/aluminum foil blisters lidded with aluminium foil, coated with a heat seal lacquer. The laminate consists of polyamide/soft aluminium foil/unplasticised PVC film.
2. In a white HDPE container with screw (child resistant) closure. Induction sealed membranes provide tamper evidence and a hermetic seal. The packs include a desiccant canister to absorb any atmospheric moisture within the pack.

Quality control of drug substance

The main release specifications of the finished product comprise testings on identity of the active substance (HPLC, IR), assay (HPLC), identity of the colourants, related substances, dissolution, content uniformity, water content and microbiological purity. The release specifications are sufficiently adequate. Batch results are present for batches manufactured at three specific manufacturing sites. Found impurity levels are low.

Stability tests on the finished product

A shelf-life of 3 years is claimed if stored in the two proposed packagings, alu-alu blister packaging or HDPE bottles, without specific storage temperature. (Additional label claim for the HDPE bottle product: "*Keep the con-tainer tightly closed*"). The shelf-life claim is well based on 3 years data of numerous batches for each strength from the various sites. In addition to assay, dissolution, water content, hardness and related substances, also X-ray analysis is applied for checking the crystalline hydrate content. The shelf-life specifications for assay (lower limit) and related substances have been widened to some extent; the latter specifications have been qualified. Considering the full dose-proportionality of the 10/20 mg tablets respectively the 40/80 mg tablets, the total number of stability batches is satisfactory.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Magnesium stearate - a statement is present that this excipient is from vegetable origin. *Lactose monohydrate* - a statement is present that this excipient is sourced from healthy animals in the same condition as milk collected for human consumption. Herewith the excipient is in compliance with the *NfG on Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*.

Opadry II coating systems - a statement is present that the (two) mixtures do not contain components belonging to category I, II, III or IV of the *NfG* mentioned above. This statement is not sufficient for the component glycerol triacetate. The triacetin (glycerol triacetate) component of the film coating formulation (Opadry II) is not derived from any animal materials, but rather from vegetable and synthetic sources. A letter from the vendor certifying this information has been submitted. The provided data from the supplier regarding the non-animal origin of excipients in Opadry II 32K14834 is sufficient regarding TSE-safety.

II.2 Non-clinical aspects

Good Laboratory Practice

Pivotal studies conformed to GLP regulations. For a few studies performed in Japan, the English translations of the final reports written in Japanese were submitted. Also, the English translations of statement of GLP compliance were submitted, which notified that the studies were in compliance with GLP regulations. This was accepted.

Some explorative studies were not performed according to GLP regulations. This was accepted because the studies generally were well-designed and generated useful scientific data. However, these studies have limited weight due to the limited number of animals used in these studies.

Although most toxicokinetic studies were not in compliance to GLP regulations, they are sufficiently reliable to conclude on the toxicokinetic profile.

GCP

All clinical studies were performed under GCP.

Pharmacology

The pharmacodynamics were investigated both *in vitro* and *in vivo*. It was shown that rosuvastatin acts as a representative member of the class of statins. Safety pharmacology studies in animals show that there

is minimal potential of extraneous pharmacological effects in humans after oral dosing of rosuvastatin in the therapeutic dose range.

Pharmacokinetics

Rosuvastatin is readily absorbed from the gut but oral bioavailability is low due to extensive biliairy excretion. Animal distribution studies indicate that rosuvastatin is predominantly present in the liver. Distribution to rat foetuses was low and apparently absent in rabbit foetuses, however, rat milk contained rosuvastatin related material. In toxicology species, protein binding was moderate to high. Rosuvastatin is metabolised in the liver but only to a limited extent. The N-desmethyl metabolite is the main metabolite formed. Rosuvastatin is mainly excreted via the faeces.

Toxicology

Acute oral toxicity of rosuvastatin is low.

In repeated-dose toxicology studies, rosuvastatin toxicity consisted mainly of forestomach, liver and gall bladder toxicity in mice; liver and forestomach toxicity in rats; gall bladder and a low incidence of eye and testis toxicity in the dog; kidney, heart, muscle, gallbladder, and liver toxicity in the rabbit; and testis toxicity in the Cynomolgus monkey. The toxicological profile observed for rosuvastatin conforms to the profile known for this class of drugs. In several limited experiments this was confirmed by comparative investigations using besides rosuvastatin other statins (lovastatin, simvastain, fluvastatin or pravastatin). However, for rosuvastatin, the calculated margins of safety are small, notably for liver/gall bladder toxicity and testicular toxicity. For this reason the safety assessment relies largely on the available clinical data.

Reduced pup survival, litter sizes and litter weight were observed in a rat oral pre- and post-natal development study in the presence of maternal toxicity. In other reproductive toxicity studies, no effect on fertility was observed, nor has any teratogenic effect been seen.

Standard genotoxicity studies revealed no evidence for genotoxic potential of rosuvastatin, the impurities and one specific degradation product.

An increase in the number of hepatocellular adenomas and hepatocellular carcinomas was observed at hepatotoxic doses in a mouse carcinogenicity study. This effect is considered to be a rodent specific effect, which raises no concern for carcinogenic effects in man. In rats, rosuvastatin increased the incidence of uterine stromal polyps in female rats at 80 mg/kg/day, however, this finding, even if a consequence of treatment, is not a significant concern for humans.

Rosuvastatin showed no antigenic or sensitising potential.

Rodent dietary studies showed that a high cholesterol content of the diet could enhance rosuvastatin-induced toxicity, likely being the result of amplified inhibition of HMG-CoA reductase. The effect of a high cholesterol intake on the safety of rosuvastatin has not been studied in humans.

Taken together, rosuvastatin seems to fit the pharmacodynamic and safety profile known from other statins. However, safety margins calculated on the basis of the preclinical data are small and incorporate several uncertainties. Therefore, the safety assessment has to be based also on clinical data.

Environmental risk assessment

The MAH has provided an expert report, based on the Environmental Risk Assessment (ERA) guideline (CPMP/SWP/4447/00-final). A toxicity test with a sediment-dwelling organism has been performed. The risk to sediment dwelling organisms is acceptable.

Based on the provided information for rosuvastatine, the environmental risk assessment is finalised. The risk for all compartments is acceptable. There are no outstanding data requirements.

II.3 Clinical aspects

Pharmacokinetics

Absorption

Upon oral administration maximum rosuvastatin plasma levels were generally achieved after 3 to 5 hours, independent of the rosuvastatin dose administered (between 10 and 80 mg). As indicated by the presence of secondary peaks in the individual rosuvastatin plasma concentration-time curves, rosuvastatin may be subject to enterohepatic circulation. Within 10 days after oral administration of rosuvastatin, approximately 10% of the radioactivity was recovered in urine, and approximately 90% in feces. Based on urine and (late) fecal excretion data, at least 30% of the rosuvastatin dose is absorbed. The absolute bioavailability, based on dose-normalized AUC_{0-t}, was 20.1% (90% CI 17.2%-23.4%). Steady state conditions after once daily oral administration of rosuvastatin were generally achieved in 5 days, independent of the dose given. No unexpected accumulation of rosuvastatin was observed upon o.d. multiple dosing. Absorption of rosuvastatin is more rapid under fasting conditions, with C_{max} levels being 20% higher than under fed conditions. Total exposure under fed and fasted conditions is comparable. Oral administration in the morning or evening did not significantly affect the rate and extent of absorption of rosuvastatin. Dose linearity can not be unequivocally demonstrated if all pharmacokinetic data are considered, probably due to variability in the pharmacokinetics caused by the enterohepatic circulation of rosuvastatin. However, no problems with a-linear pharmacokinetics of rosuvastatin are to be expected in the dosing range of 5 to 40 mg. The V_{ss} of rosuvastatin is approximately 134 l.

Protein binding

In vivo plasma protein binding of rosuvastatin is approximately 85%. The major binding protein was albumin.

Metabolism

Rosuvastatin is metabolized, although not efficiently, by human hepatocytes *in vitro*. The main metabolite formed *in vitro* was N-desmethyl rosuvastatin. *In vitro* studies in human hepatocytes, using specific cytochrome P450 isoenzyme inhibitors, indicate that CYP2C9 may be the principle cytochrome P450 isoenzyme responsible for metabolism of rosuvastatin, with CYP2C19, 2D6 and 3A4 being involved to a lesser extent. The inhibiting potential of rosuvastatin for cytochrome P450 isoenzymes *in vitro* was limited, with maximal inhibition of 10% at a 50 µM rosuvastatin concentration. *In vivo*, only two metabolites were observed, i.e. the aforementioned N-desmethyl rosuvastatin (being 50% less active than rosuvastatin) and rosuvastatin-lactone (inactive). These metabolites are both present at levels between 9-26.5% of the levels of rosuvastatin. HMG-CoA reductase inhibition assay results indicated that most of the pharmacological activity in plasma was accounted for by rosuvastatin.

Special patient groups

Dyslipidaemia patients

Limited data on rosuvastatin pharmacokinetics in dyslipidaemia patients combined with pharmacokinetic data in healthy volunteers indicate that rosuvastatin plasma concentrations in these two groups are partly in the same range. However, a significant number of rosuvastatin plasma levels in dyslipidaemia patients are higher, and thus above the range found in healthy volunteers.

Renal impairment

Rosuvastatin AUC and C_{max} were increased three-fold in patients with severe renal impairment (CCr<30 ml/min/1.73m^2). However, in hemodialysis patients (off hemodialysis), rosuvastatin exposure was not significantly different from rosuvastatin exposure in healthy volunteers.

Hepatic impairment

Exposure to rosuvastatin in patients with severe hepatic impairment (Child-Pugh score 8-9) was statistically significant increased by 2- to 4-fold. No effect on rosuvastatin pharmacokinetics was noted in patients with lower levels of hepatic impairment.

Age, race
No clinically significant differences in rosuvastatin pharmacokinetics between young and elderly, as well as between male and female, were observed.
Absolute bioavailability of oral rosuvastatin in Japanese volunteers was higher than in Caucasian volunteers, i.e. 29.0% vs 20.1%. Plasma clearance in Japanese was lower than in Caucasian, whereas renal clearance was similar.
Ethnic differences in pharmacokinetic parameters have been assessed in the variations NL/H/343/001-003/II/006, NL/H/343/001-003/II/014 and NL/H/343/004/II/002 (see addenum IV.14-IV.18 and IV.36-IV.41).

Interaction
Interaction studies indicated that rosuvastatin does not interact (clinically significant) with fluconazole, ketoconazole, itraconazole, fenofibrate, and digoxin. A possible clinically significant interaction occurred between rosuvastatin and erythromycin, yielding reduced exposure to rosuvastatin. Pharmacokinetics of rosuvastatin are markedly affected by co-administration of cyclosporin, resulting in 7- and more than 10-fold increased rosuvastatin AUC and C_{max}, respectively. In the light of *in vitro* studies, this interaction is unlikely to be due to an interaction at the level of CYP3A4, but may be due to the inhibition of transporter proteins in the liver and gastrointestinal tract by cyclosporin. Pharmacokinetics of cyclosporin were not affected in this combination. Based on this pharmacokinetic interaction, cyclosporin co-administration is contra-indicated. Simultaneous combination of rosuvastatin with the antacid co-magaldrex resulted in a statistically significant, 50% reduced rosuvastatin AUC and C_{max}. This interaction was less when co-magaldrex was administered two hours after rosuvastatin. Rosuvastatin increased the anti-coagulant effect of warfarin, as measured by the INR. However, pharmacokinetic parameters for S- and R-warfarin were not significantly affected by the combination. Simultaneous administration of rosuvastatin and oral contraceptives resulted in increased EE, desAc-NGM, and NG AUC and C_{max}, by approximately 20-30%. Gemfibrozil increased the exposure of rosuvastatin approximately 2-fold by influencing the metabolism to the N-desmethyl metabolite. Therefore, the combination of Crestor and gemfibrozil is not recommended. The 40 mg dose is contraindicated with concomitant use of a fibrate.

Clinical efficacy

Hypercholesterolemia, including heterozygous familial hypercholesterolemia (Fredrickson type IIa and IIb dyslipidemia)
In patients with hypercholesterolemia, including heterozygous familial hypercholesterolemia (Fredrickson type IIa and IIb dyslipidemia), the effects of rosuvastatin on LDL-C, TC, TG and other secondary endpoints are qualitatively comparable to the effects of other statins. A lower dose of rosuvastatin is required to achieve a target value for LDL-C compared to other statins. However, the data suggest that the effect of rosuvastatin on HDL-C might be more pronounced as compared to other statins.
A dose response effect was seen in the dose range of 10 – 80 mg, but in patients with mild to moderate hypercholesterolemia levels of LDL-C < 3 mmol/l were reached in most patients following a 10 mg dose, with a further increase after 20 mg. In patients with severe hypercholesterolemia, a dosage of 40 mg can provide additional benefit in obtaining target levels.
At the time of registration no controlled data on clinical endpoints, in particular cardiovascular morbidity and mortality, are available. But other statins (e.g. atorvastatin) have also been approved while no data on clinical endpoints were available at the time of registration, because LDL-cholesterol has been accepted as a surrogate endpoint for cardiovascular morbidity and mortality.

Homozygous familial hypercholesterolemia (Fredrickson type IIa and IIb dyslipidemia)
It has been established that rosuvastatin is effective in this patient population similar to some other statins. The effects seem to be comparable to the effects of other statins in patients with homozygous familial hypercholesterolemia, in particular atorvastatin. Consequently, efficacy was considered acceptable.

Hypertriglyceridemia (Fredrickson type IV dyslipidemia)
The data show that a relatively high dose of rosuvastatin 40 mg o.d. in patients type IV can lead to significant reductions in TG, comparable to niacin and fenofibrate and improvement in HDL-cholesterol, although somewhat less than the reference compounds. As expected the effect on (LDL)-cholesterol is much stronger. Elevated serum triglycerides have shown to be an independent risk factor for CHD but its

relevance as a risk factor depends on the levels of non-HDL-cholesterol levels and/or HDL cholesterol. This will primarily determine the indication for medical therapy. Isolated hypertriglyceridemia (type IV) remains a poorly defined entity. Hypertriglyceridemia (Fredrickson type IV dyslipidemia) was therefore not accepted as a separate indication.

Rosuvastatin 10 mg in patients with chronic symptomatic systolic heart failure
Rosuvastatin 10 mg added to background therapy could not show a significant beneficial effect on a composite of cardiovascular death, non fatal MI or non-fatal stroke in high-risk patients with chronic symptomatic systolic heart failure. Also total mortality was not reduced. However, the safety profile is not considered to be altered based on the study in these patients (see also safety paragraph).

Starting dose of 5 mg
At first, the MEB considered the 10 mg the starting dose of choice, based on a more pronounced effect of the 10 mg dose as compared to the 5 mg dose with a similar safety profile and a simplification of treatment (one dose step suffices for majority of patients to reach target LDL levels) and a reduction in the prevalence of under-treatment. This was however not supported by some other CMS during the initial procedure.
Therefore, an application for the 5 mg strength was made according to Art 8 of Dir 2001/83/EG (art. 4.8 of Dir 65/65/EEC). It concerned a line extension.
The major issue during that procedure was whether the 5 mg strength should be used in a broader population than originally approved by the RMS. Finally, it was agreed that the choice of the starting dose should be dependent on the initial cholesterol level and predisposing factors to adverse events. This is stated in the present wordings of the SPC.

Clinical safety

In the **initial dossier**, the MEB considered the benefit/risk of the 40 mg dose positive. The overall frequency of patients with any adverse event was similar across the 5 mg to 40 mg dose range, while the frequency and severity of these adverse events was greater in patients treated with the 80 mg dose. This was particularly the case for transaminase and CK elevations and patients that reported muscle disorders. Effects up to 40 mg were comparable to other statins, without an additional risk for rhabdomyolysis. There was already a relatively large data set with 2,831 subjects exposed continuously for ≥ 48 weeks: 1,067 subjects at 10 mg, 151 subjects at 20 mg, 140 subjects at 40 mg, and 863 subjects at 80 mg of rosuvastatin.

In addition, the safety profile of rosuvastatin has now been further evaluated in pharmacoepidemiology studies, from **post-marketing experience** (PSURs) and in high-risk patients with chronic symptomatic systolic heart failure. Thirty-two clinical studies have been completed by 16 September 2005. The exposure to rosuvastatin in different dose groups is 1,683, 13,415, 4,555, and 6,017 subject-years at 5, 10, 20, and 40 mg, respectively. And the cumulative worldwide market exposure is calculated to be approximately 11.7 million patients and 9.5 million patient-years (as of October 2007).

A major concern raised by DE, FR, IRL, SE and UK concerned the benefit/risk ratio of the 40 mg dose, mainly with respect to an observed higher incidence of **proteinuria**. Proteinuria, detected by dipstick testing has been observed in approximately 3% of patients treated with 40 mg dose, but no increase in renal dysfunction or myositis. Data from a follow-up study on the occurrence of proteinuria showed a dose-dependent effect, present at the 40 mg and 80 mg dose, with only a minor change at the 20 mg dose. The 80-mg dose was subsequently withdrawn. The RMS considered the 40 mg dose acceptable, as only a minority of patients did show proteinuria, without a significant rise in creatinine, cases of renal failure or haematuria. The benefit/risk of this dose was considered positive however, only in patients with severe hypercholesterolemia who do not achieve their treatment goal on 20 mg. Also, clinical data indicated that proteinuria was generally tubular in origin and that proteinuria decreases in the majority of cases over time and is reversed by lowering the dose. Mandatory monitoring of proteinuria by dipstick was not considered necessary unless new data would necessitate this. *Pharmaco-epidemiology* (post-marketing) study data showed that rosuvastatin use is not associated with an increased incidence of hospitalisations for acute renal failure compared to other statins. Review of post-marketing data show no

evidence of a causal association between rosuvastatin use and renal dysfunction. In aggregate, the renal effects data indicate that there is no evidence to suggest that long-term treatment with rosuvastatin has a detrimental effect on renal function. In addition, the CORONA study in patients with chronic symptomatic systolic heart failure who received a 10 mg OD dose, did not reveal renal safety problems. In particular, death due to renal failure was considered to be a possible safety problem, however, no difference appears between treatment with rosuvastatin or placebo.

Also, the earlier post-marketing surveillance revealing a higher reported rate of **rhabdomyolysis** associated with the inappropriate use of rosuvastatin 40 mg, has led to restrictions to the SPC. In addition, this incidence is not different from other registered statins (at high dose).
The incidence rate for rhabdomyolysis and myopathy in pharmaco-epidemiology studies (was extensively studied) data was 0.1/1000 person-years and 0.2/1000 person-years resp. in the rosuvastatin group (n=11249) and 0.06/1000 person-years for rhabdomyolysis, with no cases of myopathy in the other statin group (n=37282). These differences were not statistically significant. Also in the clinical study dossier for rosuvastatin doses up to and including 40 mg, the frequency of CK elevations >10 x ULN was low (0.2 to 0.6%) and similar to, or lower than, that reported with other marketed statins.

Furthermore, the RMS considers that sufficient **restrictions** have been made to the **SPC** to limit the use of the 40 mg with adequate precautions to avoid adverse events in high risk patients. These restrictions include a limited indication of severe hypercholesterolemia, a contra-indication for patients with active liver disease, Asian patients and patients with predisposing factors for myopathy, and a maximal dose of 10 mg for patients with severe renal dysfunction. Prescription rates in Canada, France, Italy, the Netherlands, UK, and the USA to 6 November 2005 were 3.5% for rosuvastatin 5 mg, **81.4% for** rosuvastatin **10 mg**, 12.7% for rosuvastatin 20 mg, and 2.5% for rosuvastatin 40 mg showing that the 40 mg dose is being used infrequently, consistent with its restricted use to severe cases of patients at high risk who do not achieve their treatment goal.

The RMS considers that the follow-up safety data after approval are reassuring with respect to the safety margin of all rosuvastatin doses and do not give any indication that these considerations need revision. The PSURs do not reveal any unexpected changes to the safety profile of the highest marketed 40 mg dose.

Conclusion
The overall benefit/risk for rosuvastatin across the 5 mg to 40 mg dose range remains positive. Extensive post-marketing data do not reveal unexpected changes to the safety profile, and show a comparable safety profile to other statins. Furthermore these studies show that the restrictions made to the SPC seem to be followed well in clinical practice. The MEB is of the opinion that the 40 mg dose strength could also be approved in other concerned member states with the mentioned provisions in the labeling.

Risk management plan

The MAH submitted a response document and an updated EU Risk Management Plan for Crestor, both dated 10 February 2009. Assessment led to the following conclusions:
- It is accepted that there is no need for further reporting of the LUNAR, ASTRONOMER, CENTAURUS studies in the EU-RMP. Serious adverse events reported from clinical studies, including the ongoing ASTRONOMER study, will be included in PSURs.
- Initially, the MAH stated that the 40 mg dose of rosuvastatin is used substantially less than the comparable high dose usage of other marketed statins. The RMS however raised a concern because this wording is susceptible to misunderstanding (reagarding equipotency between doses). Therefore, the RMS requests the MAH to changes the wording into: '*Currently the average usage of rosuvastatin 40 mg across the EU is 1.2%*.'.
- Submission of JUPITER data along with the Type II variation, see variation NL/H/343/II/035, Annex I.
- The next Updated RMP should be submitted as a type II-variation.

Pharmacovigilance plan

Taking into account the new requirements for an application, the MAH submitted a Pharmacovigilance system. This information had not been submitted before. Member states involved in the repeat-use procedure were given the chance to comment on the PvVig Plan submitted by the MAH during the repeat-use procedure.
Member states in which the product was already registered (at the start of the MRP) could submit their comments during variation (NL/H/343/001-004/II/031) which ran parallel to the repeat-use procedure.

The RMS considered that the Pharmacovigilance system as described by the MAH has the following deficiencies:

1. A statement of the MAH and the qualified person regarding their availability and the means for notification of adverse reactions (including signatures) is missing and should be provided.
2. Under the section 'Qualified Person Responsible for Pharmacovigilance' the following documents are missing and should be provided:
   - Summary Curriculum Vitae
   - Summary job description
3. Under the section 'Organization' the following documents are missing and should be provided:
   - High-level organization chart(s) providing an overview of the global and EEA pharmacovigilance units
   - Flow diagrams indicating the flow of safety reports
4. Under the section 'Procedures in place which are documented in writing' the following topics have not been addressed and the MAA should clearly indicate if the above mentioned topics are covered by written procedures:
   - Reports from different origin.
   - Meeting commitments to Competent Authorities in relation to a marketing authorisation.
5. Under the section 'Procedures in place which are documented in writing' the following topics are 'under consideration' or the concerning SOPs are 'in preparation'. The MAH should resolve these deficiencies before the product is placed on the market:
   - Signal generation and review
   - Benefit/risk assessment
   - Notifying competent authorities and health professionals of changes to the benefit/risk balance of products
   - Global pharmacovigilance activities applying to all products
6. A copy of the registration, of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to the Competent Authorities is missing and should be provided.
7. The MAA has stated that agreements with co-marketing partners are concluded between affiliates and licence partners. According to Volume 9A of the Rules governing medicinal products in the European Union co-licensing and co-marketing arrangements within the EEA should be identified and the distribution of major responsibilities between the parties made clear.
8. Under the section 'Training' the MAA should provide a brief description of where the CVs and job descriptions can be found.
9. Under the section 'Quality Management System' the MAA should provide a brief description of the responsibilities for quality assurance auditing of sub-contractors.

These deficiencies were resolved upon completion of the repeat-use procedure and variation II/031; the MAH committed to submit an updated version of Pharmacovigilance systems (Module 1.8.1) including the additional information requested as a follow-up measure.

Product information

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The test consisted of two rounds. Both rounds were performed with 10 participants. Several changes in the PL were made between the rounds. After the second round it was recommended that the duplicated information around the 40 mg was causing problems and needed to be restructured. The MAH adapted the section '*Take special care*'.

There were sufficient questions about the critical items like the 40 mg strength, skeletal muscle effects and certain patient populations (Asian origin, age > 70 years, patients with kidney or liver problems).
The conclusions are clear, concise and clearly presented.
The patient information leaflet has been adapted sufficiently taking into account the results of the tests.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB, on the basis of the data submitted, considered that Crestor 5/10/20/40, 5/10/20/40 mg film-coated tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. The other member states mutually recognised the Dutch marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. There are some outstanding issues regarding the pharmacovigilance plan, see page 11 of this report.

For this repeat-use procedure, there was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The SPC, package leaflet and labelling are in the agreed templates.

A European harmonised birth date has been allocated (6 November 2002) and subsequently the first data lock point for rosuvastatin is November 2010. The first PSUR following the completion of the repeat-use procedure covers the period from 7 November 2007 to 6 November 2008, after which the PSUR submission cycle is 1 year.

The first renewal was positively concluded on 30 November 2007. The date for the next renewal is 6 November 2012.

The following post-approval commitments have been made during the procedure:

- The MAH committed to present data on renal effects from the ASTEROID study. This should be addressed in the updated version of the RMP. This commitment has been fulfilled.
- The MAH committed to provide stability for batches of 5-10-40 mg Crestor film-coated tablets using drug substance manufactured with process 2. This commitment has been fulfilled.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
IPC	In Process Controls
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

I Variations after finalisation of the initial MRP procedure but before the repeat-use procedure (10/20/40 mg)

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
SPC change - Ethnic susceptibility.	NL/H/343/ 001-003/ W001	W	12-8-2003	19-11-2003	Approval	N
CMC change - Increase in Batch Size of Rosuvastatin.	NL/H/343/ 001-003/ V001	V	16-9-2003	16-10-2003	Approval	N
SPC change – Rhabdomyolysis.	NL/H/343/ 001-003/II/ 003	II	23-12-2003	20-1-2004	Approval	N
CMC change - Specification of 75ml bottle/closure system.	NL/H/343/ 001-003/IA/ 004	IA	8-3-2004	22-3-2004	Approval	N
SPC change – USR.	NL/H/343/ 001-003/II/ 005	II	22-6-2004	13-7-2004	Approval	N
SPC change - Ethnic differences.	NL/H/343/ 001-003/II/ 006	II	29-6-2004	19-12-2004	Approval	N
Update Section 4.8 of the SPC. Hepatobiliary disorders.	NL/H/343/ 001-003/II/ 007	II	8-10-2004	19-12-2004	Approval	N
SPC change – Polyneuropathy.	NL/H/343/ 001-003/II/ 008	II	22-12-2004	18-2-2005	Approval	N
CMC change - HPLC Methodology.	NL/H/343/ 001-003/IB/ 009	IB	22-3-2005	21-4-2005	Approval	N
Change in the name of a manufacturer of the active substance.	NL/H/343/ 001-003/IA/ 010	IA	22-3-2005	8-4-2005	Approval	N
Minor change in the manufacturing process of the active substance.	NL/H/343/ 001-003/IB/ 011	IB	22-3-2005	21-4-2005	Approval	N
SPC change – Post PSUR 4 - Ezetimibe interaction.	NL/H/343/ 001-003/II/ 012	II	28-6-2005	3-2-2006	Approval	N
SPC change - Integrate 5mg utilisation into 10-40mg SPC.	NL/H/343/ 001-003/II/ 013	II	16-9-2005	10-10-2005	Approval	N
SPC change - Asian PK.	NL/H/343/ 001-003/II/ 014	II	16-9-2005	3-2-2006	Approval	N
CMC change - Telescope process.	NL/H/343/ 001-003/II/ 015	II	2-12-2005	7-4-2006	Approval	N
PIL Harmonisation.	NL/H/343/ 001-003/II/ 016	II	2-12-2005	7-7-2006	Approval	N
SPC change - 90 blister pack.	NL/H/343/ 001-003/IA/ 017	IA	4-5-2005	16-11-2005	Non-Approval	N
SPC change – Pancreatitis.	NL/H/343/ 001-003/II/ 018	II	2-12-2005	31-1-2006	Approval	N
SPC change - 90 blister pack.	NL/H/343/ 001-003/IA/ 019	IA	23-11-2005	7-12-2005	Approval	N
Packaging Harmonisation.	NL/H/343/ 001-003/II/ 020	II	28-8-2006	8-12-2006	Approval	N

CMC change - Batch Size.	NL/H/343/ 001-003/IA/ 021	IA	12-12-2006	2-1-2007	Approval	N
CMC change - Blender change.	NL/H/343/ 001-003/IB/ 022	IB	6-2-2007	8-3-2007	Approval	N
CMC change - Bottle Spec.	NL/H/343/ 001-003/IA/ 023	IA	12-12-2006	2-1-2007	Approval	N
CMC change - Automated Procedures.	NL/H/343/ 001-003/IB/ 024	IB	6-2-2007	8-3-2007	Approval	N
CMC change - Opadry Residue.	NL/H/343/ 001-003/IA/ 025	IA	12-12-2006	2-1-2007	Approval	N
SPC change - Memory Loss.	NL/H/343/ 001-003/II/ 026	II	22-1-2007	6-7-2007	Approval	N
SPC change – Atherosclerosis. Indication not approved, but positive outcome for a trial description in Section 5.1.	NL/H/343/ 001-003/II/ 027	II	22-1-2007	6-7-2007	Approval	N
Renewal of the marketing authorisation.	NL/H/343/ 001-004/R/ 001	R	7-7-2007	30-11-2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/343/ 001-003/IA/ 028	IA	19-3-2008	2-4-2008	Approval	N
Replacement or addition of a mnufacturer responsible for batch release, including batch control/testing.	NL/H/343/ 001-003/IA/ 029	IA	19-3-2008	2-4-2008	Approval	N
The addition of requested undesirable effects under Section 4.8 in Summary of Product Characteristics and wording in Patient Information Leaflet. An administrative correction is proposed to Section 4.2, Dosage in Patients with renal insufficiency.	NL/H/343/ 001-003/II/ 030	II	26-5-2008	25-6-2008	Approval	N

II Variations for 5 mg strength (<u>after</u> MRP, <u>before</u> repeat-use procedure)

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Addition of 5 mg strength (tablet). (line extension)	NL/H/343/ 004/MR	MR	4-8-2004	19-8-2005	Approval	N
SPC change - Integrate 10-40mg variations 006/7/8 into 5mg SPC.	NL/H/343/ 004/II/ 001	II	16-9-2005	10-10-2005	Approval	N
SPC change - Asian PK.	NL/H/343/ 004/II/ 002	II	16-9-2005	3-2-2006	Approval	N
CMC change - HPLC methodology.	NL/H/343/ 004/IB/ 003	IB	20-9-2005	20-10-2005	Approval	N
Change in the name of a manufacturer of the active substance.	NL/H/343/ 004/IA/ 004	IA	13-9-2005	27-9-2005	Approval	N
Minor change in the manufacturing process of the active substance.	NL/H/343/ 004/IB/ 005	IB	20-9-2005	20-10-2005	Approval	N
SPC change – Post PSUR 4 – Ezetimibe.	NL/H/343/ 004/II/ 006	II	4-1-2006	3-2-2006	Approval	N
CMC change - Telescope process.	NL/H/343/	II	2-12-2005	7-4-2006	Approval	N

	004/II/ 007					
PIL Harmonisation.	NL/H/343/ 004/II/ 008	II	2-12-2005	7-7-2006	Approval	N
SPC change - 90 blister pack.	NL/H/343/ 004/IA/ 009	IA	4-11-2005	16-11-2005	Non-Approval	N
SPC change – Pancreatitis.	NL/H/343/ 004/II/ 010	II	2-12-2005	31-1-2006	Approval	N
SPC change - 90 blister pack.	NL/H/343/ 004/IA/ 011	IA	23-11-2005	7-12-2005	Approval	N
Packaging Harmonisation.	NL/H/343/ 004/II/ 020	II	28-8-2006	8-12-2006	Approval	N
CMC change - Batch Size.	NL/H/343/ 004/IA/ 021	IA	12-12-2006	2-1-2007	Approval	N
CMC change - Blender change.	NL/H/343/ 004/IB/ 022	IB	6-2-2007	8-3-2007	Approval	N
CMC change - Bottle Spec.	NL/H/343/ 004/IA/ 023	IA	12-12-2006	2-1-2007	Approval	N
CMC change - Automated Procedures.	NL/H/343/ 004/IB/ 024	IB	6-2-2007	8-3-2007	Approval	N
CMC change - Opadry Residue.	NL/H/343/ 004/IA/ 025	IA	12-12-2006	2-1-2007	Approval	N
SPC change - Memory Loss.	NL/H/343/ 004/II/ 026	II	22-1-2007	6-7-2007	Approval	N
SPC change – Atherosclerosis. **Indication not approved, but positive outcome for a trial description in Section 5.1**.	NL/H/343/ 004/II/ 027	II	22-1-2007	6-7-2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product.	NL/H/343/ 004/IA/ 028	IA	19-3-2008	2-4-2008	Approval	N
Replacement or addition of a mnufacturer responsible for batch release, including batch control/testing.	NL/H/343/ 004/IA/ 029	IA	19-3-2008	2-4-2008	Approval	N
The addition of requested undesirable effects under Section 4.8 in Summary of Product Characteristics and wording in Patient Information Leaflet. An administrative correction is proposed to Section 4.2, Dosage in Patients with renal insufficiency.	NL/H/343/ 004/II/ 030	II	26-5-2008	25-6-2008	Approval	N

III Variations <u>after</u> finalisation of the repeat-use procedure (for all strengths)

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Addition of Ph.Vig. system, Environmental Risk Assessment and Clinical study which are included in the documentation for the repeat-use procedure E/01	NL/H/343/ 001-004/II/ 031	II	7-8-2008	7-10-2008	Approval	N
This variation relates to both administrative corrections and post approval commitments made for the Repeat Use Mutual Recognition	NL/H/343/ 001-004/II/ 032	II	10-12-2008	18-3-2009	Approval	N

(rMR) procedure. The variation includes the following changes: 1. Summary of Product Characteristics (SPC), addition of requested wording under Section 4.4 2. SPC, as per request revised wording of Section 5.3 3. Patient Information Leaflet (PIL), administrative update of Section 6						
Extension of the current approved indication with children and adolescents 10-17 years of age.	NL/H/343/ 001-004/II/ 033	II	21-6-2009	26-3-2010	Approval	Y, Annex I
Update Pharmacovigilance System.	NL/H/343/ 001-004/II/ 034	II	11-5-2009	10-7-2009	Approval	N
This variation relates to new indication for the use of rosuvastatin tablets for the prevention of major cardiovascular events in adult patients. This involves changes to SPC and PIL in the following sections: SPC sections 4.1, 4.2 and 5.1; PIL section 1.	NL/H/343/ 001-004/II/ 035	II	21-6-2009	24-3-2010	Approval	Y, Annex II
Updated Pharmacovigilance System, version 10 dated 26 August 2009 will replace the previous version 9, dated 2 February 2009.	NL/H/343/ 001-004/II/ 036	II	2-12-2009	31-1-2010	Approval	N
The addition of a requested warning within the Summary of Product Characteristics (SPC), Section 4.4 and undesirable effects within Section 4.8, together with the corresponding changes to the Patient Information Leaflet (PIL). Implementation of the agreed Core Safety Profile (CSP).	NL/H/343/ 001-004/II/ 037	II	21-1-2010	22-3-2010	Approval	N
To introduce tamper evident security seals of the secondary packaging (carton).	NL/H/343/ 001-004/II/ 038	II	21-1-2010	22-3-2010	Approval	N
Deletion of manufacturing sites, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier).	NL/H/343/ 001-004/IA/ 039/G	IA/G	1-4-2010	1-5-2010	Approval	N
1) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site. Replacement or addition of a manufacturer responsible for batch release, Not including batch control/testing. 2) Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site	NL/H/343/ 001-004/IA/ 040/G	IA/G	18-8-2010	17-9-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the DDPS. Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of	NL/H/343/ 001-004/IA/ 041/G	IA/G	17-12-2010	19-1-2011	Approval	N

pharmacovigilance obligations and described in the DDPS, in particular where the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted.						
Update EU-RMP as asked in the AR of the PSUR workshare (NL/H/PSUR/0019/002).	NL/H/343/ 001-004/ WS/042	WS	26-1-2011	27-3-2011	Approval	N
Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier.	NL/H/343/ 001-004/IB/ 043	IB	13-5-2011	12-6-2011	Approval	N

ANNEX I – Extension of the indication, inclusion of paediatric data in the SPC (Type II variation NL/H/343/001-004/II/033)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variation application NL/H/0343/001/II/033 for Crestor® for the extension of the indication to include adolescents and children aged 10 years or older, is approvable. Paediatric data have been included in the SPC, as indicated in section IV.1.

Major objections have been solved and the SPC has been amended accordingly.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

The MAH submitted a type II variation for Crestor tablets for paediatric patients via the Mutual Recognition Procedure. The application concerns changes proposed to the SPC in section 4.1, 4.2, 4.4, 5.1 and 5.2, to extend the information for treatment of hypercholesterolaemia to a paediatric patient population. To support these changes, one pharmacokinetic study and one pivotal efficacy/safety study were submitted. The pivotal study included children aged 10 to 17 years with heterozygous familial hypercholesterolaemia. Experience in children younger than 10 years is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia.

The objectives and design of the pivotal study were discussed in CHMP scientific advice and agreed upon with the Paediatric Committee (PDCO) in the Paediatric Investigational Plan (Decision adopted 12 June 2009). The other pharmacokinetic study was not included in the Paediatric Investigation Plan.
In addition to these studies, the MAH should further study paediatric safety for the age group of 6 to 18 years of age. In addition, an efficacy and safety study in children from 6 years of age to less than Tanner stage II including assessment of vascular changes is part of the PIP. Further, a multidose pharmacokinetic study in children from 6 years to 14 years of age should be conducted. This study is part of the Paediatric Investigation Plan for Crestor which has been agreed with the EMA (see doc. EMA/714398/2010, available on http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500017287.pdf). The PIP should be completed by April 2014.

Rosuvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and a member of the statin class of lipid-lowering agents. It was first approved for marketing in the Netherlands on 6 November 2002 and was first launched on 19 February 2003, in Canada. It is indicated for the treatment of primary hypercholesterolaemia, mixed dyslipidaemia, and homozygous familial hypercholesterolaemia.

N.B.: At the same time a variation was pending (NL/H/343/001-004/II/035) to include the indication 'Prevention of major cardiovascular events in adult patients'.

II.2 Supplementary paragraph

The major effect of the statins is to lower LDL-cholesterol levels through inhibition of the enzyme HMG-CoA reductase. Studies using statins have reported 20 to 60 percent lower LDL-cholesterol levels in patients on these drugs. Statins also reduce elevated triglyceride levels and produce a modest increase in HDL-cholesterol. Statins are used for treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. For simvastatin, atorvastatin and pravastatin, studies have shown a beneficial effect in reduction of cardiovascular mortality and morbidity as a primary and/or secondary prevention.

Simvastatin, lovastatin, fluvastatin, and pravastatin have also demonstrated efficacy in the treatment of children and adolescents with HeFH between the ages of 10 and 17 years (8 to 17 years for pravastatin and 9 to 16 years for fluvastatin) based on clinical trials showing LDL-C-lowering efficacy and an acceptable safety profile (Pfizer 2007; Merck 2008; Merck 2007; Bristol-Myers Squibb 2007; Novartis 2006). Long-term trials with pravastatin have demonstrated a reduction in carotid intima medial thickness (IMT) progression versus placebo in paediatric familial hypercholesterolemia (FH) (Wiegman et al 2004). The highest doses tested in clinical trials of paediatric patients with FH or severe hypercholesterolemia resulted in mean LDL-C reductions of -27% for lovastatin (Stein et al 1999), -41% for simvastatin (de Jongh et al -24% for pravastatin (Wiegman et al 2004), -34% for fluvastatin (Van der Graaf et al 2006), and -40% for atorvastatin (McCrindle et al 2003). For atorvastatin-treated children, treatment with 10 or 20 mg resulted in 44% of patients attaining an LDL-C target of <130 mg/dL (3.4 mmol/L) after 52 weeks of treatment. Because the emphasis on a more ambitious LDL-C target goal of <110 mg/dL (2.8 mmol/L) is relatively recent, historical data evaluating statins against this more stringent benchmark are lacking. Not all paediatric data presented above are reflected in current SPCs across Europe.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A.

III.2 Non-clinical aspects

No new data have been submitted.

Environmental Risk Assessment

The MAH has provided an expert report, based on the Environmental Risk Assessment (ERA) guideline (CHMP/SWP/4447/00-final).

The ERA submitted for the current procedure is identical to that submitted in the registration procedure of Crestor. The previous ERA resulted in the conclusion that the risk for all compartments was acceptable.

In both the previous and the current ERA, the MAH has used an F_{pen} of 0.021 to calculate $PEC_{surface\ water}$. Since the F_{pen} is higher than the default F_{pen} of 0.01 (which is allowed as maximum F_{pen} according to the EMA guideline), a further refinement of F_{pen} as a result of expected increased use is not necessary.

III.3 Clinical aspects

Two studies are part of the submission supporting a paediatric indication; one PK study and one efficacy study.

III.3.1 CLINICAL PHARMACOLOGY

Pharmacokinetics

Aim of the study

The primary objective of this study was to determine the pharmacokinetics of single oral doses of 10, 40, and 80 mg rosuvastatin and the pharmacokinetics of multiple doses of 80 mg rosuvastatin given over a 7-day period.

The secondary objective was to assess the safety and tolerability of single 10-, 40-, and 80-mg doses and of repeat 80 mg doses for 7 days.

Assessor's comments:

The aim of the study is considered appropriate.

Patients

Paediatric subjects were included if aged 10 to 17 years, weighing at least 35 kilograms and a LDL-C of at least 190 mg/dL, or LDL-C at least 160 mg/dL and at least 1 first-degree family member or grandparent with a history of premature coronary artery disease.

Exclusion criteria were acute illness within 2 weeks prior to taking trial treatment; clinically significant abnormalities in clinical chemistry, hematology, or urine parameters; history or presence of gastrointestinal, hepatic, or renal condition known to interfere with absorption, distribution, metabolism, or excretion of drugs; history of Gilberts syndrome; treatment within 3 months of trial treatment with any drug known to have a well-defined potential for hepatotoxicity; treatment with any lipid lowering medications within 2 weeks before the first day of the administration of trial treatment; cigarette smoking.

Assessor's comments:
Inclusion and exclusion criteria are considered appropriate. Age is limited to patients from 10 to 17 years of age.

Design

This was an open-label, nonrandomized, parallel group trial conducted at a single centre. Serial blood samples and a 24-hour urine specimen were obtained after ascending single-dose administrations of rosuvastatin 10, 40, and 80 mg in 3 groups of subjects. Subjects receiving the 80 mg dose then received rosuvastatin 80 mg once daily for 7 days after a 4 to 10 day wash-out period; serial blood samples and a 24-hour urine specimen were obtained on Day 7. The first group of subjects received rosuvastatin 10 mg once daily orally with 240 mL of water under fasting conditions on the morning of Day 1. If the trial treatment was well tolerated in 6 evaluable subjects, the second group received rosuvastatin 40 in like fashion. If the trial treatment was well tolerated in 6 evaluable subjects, the third group then received rosuvastatin 80 mg in like fashion. If the first dose of rosuvastatin 80 mg was well tolerated, the third group of subjects received rosuvastatin 80 mg once daily for 7 days beginning after a 4 to 10 day wash-out period.

Assessor's comments
The design is considered acceptable to evaluate rosuvastatin exposure after single and multiple dosing. The washout period between single and multiple dose is considered acceptable. The conduction of the trial is in line whith what is acceptable for conducting a pharmacokinetic trial. Careful progression to high dose rosuvastatin administration in this paediatric patient population based on tolerability is acknowledged.

Measuring efficacy

Blood specimens were collected for the determination of plasma concentrations of rosuvastatin and N-desmethyl rosuvastatin at predose and after the first dose of trial treatment at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 48, 72, and 96 hours; and from subjects receiving rosuvastatin 80 mg at Day 7 predose and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, and 24 hours after the administration on Day 7 in order to determine the following pharmacokinetic parameters for rosuvastatin and its N-desmethyl metabolite: Cmax, the time of the maximum plasma concentration (tmax), the terminal elimination rate constant (□z) and half-life (t1/2), AUC(0-t), the area under the plasma concentration-versus-time curve from time 0 to infinity (AUC), and, for single administrations of trial treatment, the apparent oral clearance (CL/f) and apparent volume of distribution (Vz/f). Additionally, the accumulation ratios were calculated and time-dependent changes in pharmacokinetics were evaluated for rosuvastatin and the N-desmethyl metabolite.

Urine specimens were collected from 0 to 6 hours, 6 to 12 hours, and from 12 to 24 hours after administration of trial treatment on Day 1 and, for subjects receiving a 7-day course, on Day 7 in order to determine the renal clearance (CLR) of rosuvastatin and its N-desmethyl metabolite and the fraction of unchanged rosuvastatin in urine (Fe).

Assessor's comments
Sufficient number of blood samples were taken to accurately assess the most appropriate pharmacokinetic parameters. Sampling is more than 3 times the half life of rosuvastatin and more than

covers the absorption phase of rosuvastatin. Suffcient number of blood samples were taken around the expected t_{max}. The most important pharmacokinetic parameters were assessed.

Efficacy assessment

Primary endpoint: The maximum plasma concentration (Cmax) and the areas under the plasma concentration-versus-time curves from time 0 to 24 hours (AUC(0-24)) and from time 0 to the last observable plasma concentration for rosuvastatin (AUC(0-t)),

Secondary endpoints: Assessment of tmax, t1/2, CL/f, and Vz/f for rosuvastatin; rosuvastatin accumulation ratio and, for multiple dosing of rosuvastatin 80 mg only, temporal changes in the pharmacokinetics on multiple dosing; renal clearance and urinary excretion of rosuvastatin; for the 80 mg treatment group only, AUC(0-24), AUC(0-t), AUC, Cmax, accumulation ratio, temporal change ratio, renal clearance, and urinary excretion for N-desmethyl rosuvastatin

Assessor's comments

The primary endpoint is relevant for assessing the pharmacokinetic profile of rosuvastatin and its metabolite in this pedriatic population.

Patient demographics at baseline

Patient disposition

All subjects completed the trial. All subjects were evaluable for pharmacokinetic analysis and safety.

Baseline characteristics

The 18 subjects included 9 boys (8 Caucasian, 1 Black) and 9 girls (6 Caucasian, 3 Black), with mean age, height, weight, and body mass index of 14 years (range 10 to 17 years), 167 cm (range 142 to 180 cm), 67 kg (range 32 to 116 kg), and 24 (range 16 to 44), respectively.

Table 1: Baseline characteristics

Parameter	Summary statistic	10 mg N = 6	40 mg N = 6	80 mg N = 6	Total N = 18
Sex					
Male	n (%)	3 (50)	3 (50)	3 (50)	9 (50)
Female	n (%)	3 (50)	3 (50)	3 (50)	9 (50)
Age, y					
10 to 13	n (%)	2 (33)	3 (50)	2 (33)	7 (39)
14 to 17	n (%)	4 (67)	3 (50)	4 (67)	11 (61)
	mean (SD)	14 (2.3)	14 (0.6)	15 (1.7)	14 (1.7)
	range	10 to 16	13 to 14	13 to 17	10 to 17
Height, cm	mean (SD)	164 (15.0)	169 (6.0)	167 (4.7)	167 (9.4)
	range	142 to 180	161 to 177	160 to 173	142 to 180
Weight, kg	mean (SD)	56 (12.2)	79 (25.1)	67 (9.4)	67 (19)
	range	32 to 66	57 to 116	56 to 80	32 to 116
Body mass	mean (SD)	21 (3.4)	28 (9.8)	24 (2.5)	24 (6.6)
index	range	16 to 26	20 to 44	21 to 27	16 to 44
Race					
Caucasian	n (%)	4 (67)	4 (67)	6 (100)	14 (78)
Black	n (%)	2 (33)	2 (33)	0	4 (22)

Assessor's comments
Some differences can be observed between the different dose groups. This is not suprising with these low numbers of patients.

Statistical analysis
Descriptive statistics were used as the primary method of data analysis. Corresponding graphs were also to be presented for each subject. Plots of individual and gmean plasma concentrations of rosuvastatin and N-desmethyl rosuvastatin were to be presented on a linear scale and, if a difference in rate of elimination between dose levels was suspected, on a log-linear scale.

Assessor's comments
Statistical analyses can be considered appropriate.

Efficacy results

Table 2: Pharmacokinetic parameters in the primary and secondary endpoints

Parameter	Summary statistic	Single-dose			Multiple-dose
		10 mg N = 6	40 mg N = 6	80 mg N = 6	80 mg N = 6
Primary endpoints					
C_{max}, ng/mL	gmean (CV)	6.3 (58.1)	23.5 (79.6)	42.6 (46.8)	50.6 (43.4)
	range[a]	2.6, 12.7	7.3, 56.6	20.5, 68.3	33.3, 89.5
	n	6	6	6	6
$AUC_{(0-24)}$, ng·h/mL	gmean (CV)	48.7 (48.3)	234 (62.9)	313 (37.1)	467 (35.3)
	range[a]	21.3, 79.9	86.0, 432	177, 493	293, 723
	n	6	6	6	6
$AUC_{(0-t)}$,[b] ng·h/mL	gmean (CV)	52.2 (52.3)	288 (65.2)	361 (35.2)	467 (35.3)
	range[a]	21.3, 79.9	101, 478	225, 560	293, 723
	n	6	6	6	6
AUC, ng·h/mL	gmean (CV)	47.6 (71.6)	299 (63.5)	371 (35.6)	NC
	range[a]	23.9, 85.5	105, 485	230, 578	NC
	n	3	6	6	NA
Secondary endpoints					
t_{max}, h	median	2.5	3.0	4.5	5.0
	range[a]	0.5, 5.0	2.0, 6.0	1.0, 5.0	3.0, 5.0
	n	6	6	6	6
$t_{1/2}$, h	mean[a] (SD[a])	8.6 (1.4)	14.8 (4.9)	20.0 (10.7)	NC
	range[a]	7.0, 9.7	8.3, 21.0	9.9, 34.7	NC
	n	3	6	6	NC
CL/f, L/h	gmean (CV)	210 (71.5)	134 (63.5)	215 (35.7)	NC
	range[a]	117, 418	82.4, 381	138, 348	NC
	n	3	6	6	NA
CL_R, L/h	gmean (CV)	6.0 (40)	9.3 (17)	12.9 (28)	5.6 (30)
	range[a]	4.1, 10.0	8.0, 11.7	8.6, 18.1	3.8, 8.4
	n	6	6	5	6
Fe, %	gmean (CV)	2.9 (45)	5.5 (53)	5.2 (41)	3.3 (24)
	range[a]	1.9, 6.1	2.5, 8.8	3.0, 7.2	2.2, 4.2
	n	6	6	5	6
X_{tu}, µg	gmean (CV)	294 (45)	2180 (53)	4150 (41)	2630 (24)
	range[a]	187, 609	1010, 3520	2400, 5740	1740, 3390
	n	6	6	5	6

Primary endpoint

Systemic exposure of rosuvastatin increased with single administrations of rosuvastatin 10 to 40 to 80 mg in children and adolescents with heterozygous familial hypercholesterolemia. For subjects receiving multiple doses of rosuvastatin 80 mg, Cmax and AUC(0-24) were approximately 19% and 49% greater, respectively, than the corresponding values after single-dose administrations. Pre-dose and 24-hour trough concentrations of rosuvastatin in plasma were comparable by inspection, suggesting that steady state was achieved by Day 7. The accumulation ratio of rosuvastatin was 1.5. No important time-dependent changes were observed when comparing the pharmacokinetics on Day 7 with Day 1. The apparent oral clearance of rosuvastatin appeared independent of dose. The maximum gmean renal excretion of rosuvastatin at any dose level was 5.5%. The exposure to N-desmethyl rosuvastatin, a metabolite of rosuvastatin, did not appear to increase with multiple administrations of rosuvastatin; mean first-dose and steady-state values of Cmax were 8.0 and 6.5 ng/mL, AUC(0-t) values were 45.4 and 45.7 ng.h/mL. The metabolite was rapidly formed and plasma concentrations quickly fell below the limit of quantification; it was not possible to determine t1/2 or renal clearance of the metabolite.

Secondary endpoints
Secondary endpoints are provided in table 2.

Assessor's comments
In the first round the following was concluded: Key pharmacokinetic parameters increased in general with higher administered doses. At 40 mg a somewhat higher than dose proportional increase after single dose is observed. The increase is however proportional again at 80 mg. Below the PK data are presented corrected for the administered dose. The relevance of the observed deviations from dose proportionality should be discussed in relation to that observed in adults.
On the issue of dose proportionality in paediatric patients, the answer of MAH was considered resolved. It is clear from the discussion that in healthy volunteers the exposure is linear related to the dose, but if this is the case in patients is still open for discussion. However, the results from the study in paediatric patients do not directly indicate that there will be a large deviation from dose proportionality in this group of patients.
However, there might be a trend in exposure as function of age. But the inter-subject-variability is high and the number of exposed subjects too low, therefore the presented data do not allow for firm conclusion on the exposure according to age.
However, the results seem to indicate that there is no clinical significant difference between the age groups, but for an adequate assessment of the relationship between age and exposure a study with more patients would be necessary. This is currently reflected in the amended PIP. The study provides the opportunity to explore the effect of age on rosuvastatin PK, both as a continuous and categorical variable and to compare the rosuvastatin PK in children and adolescents with hypercholesterolaemia to adult patients with hypercholesterolaemia.

III.3.2 CLINICAL EFFICACY

Main Study

III.3.2.1 PLUTO trial

Aim of the study
The primary objective of this study was to determine the efficacy of once-daily rosuvastatin in reducing low-density lipoprotein cholesterol (LDL-C) in children and adolescents aged 10 to 17 years with heterozygous familial hypercholesterolemia (HeFH) from baseline to the end of the 12-week, double-blind treatment period.

Patients
The patient population included was male or female children and adolescents (Tanner stages II to V, at least 1 year post-menarche) aged 10 to 17 years with HeFH and at least 1 of the following criteria:
- fasting LDL-C ≥190 mg/dL (4.9 mmol/L) at visit 2 (prior to the randomization visit) or

- fasting LDL-C >160 mg/dL (4.1 mmol/L) at Visit 2 and either 1) a family history of premature cardiovascular disease (CVD) defined as onset of clinical atherosclerotic disease before age 55 in males or age 65 in females; or 2) 2 or more other CVD risk factors (HDL-C <35 mg/dL [0.91 mmol/L], hypertension, cigarette smoking, severe obesity, diabetes mellitus, physical inactivity) present after vigorous attempts were made to control these risk factors during 6 weeks of dietary lead-in.

Patients were excluded if they had a history of statin-induced myopathy or serious hypersensitivity reaction to statins, a fasting TG ≥250 mg/dL (2.87 mmol/L), a fasting serum glucose of >180 mg/dL (9.99 mmol/L) or HbA1c >9% or patients with a history of diabetic ketoacidosis within the past 1 year, uncontrolled hypothyroidism, use of specified disallowed concomitant medications (lipid lowering agents, immunosuppressants, antifungal agents, erythromycin), history of alcohol abuse and/or drug abuse, liver disease or hepatic dysfunction, serum creatine kinase (CK) ≥3 × the ULN, eGFR <50 mL, ≥2+ proteinuria on urine dipstick, stage 2 hypertension, history of organ transplantation, documented history of malignancy with the exception of basal or squamous cell carcinoma of the skin, Tanner stage I patients, boys >12 years of age with testicular volume <3 mL, patients with height <3rd percentile for age and sex.

Assessor's comments
The inclusion criteria are considered appropriate. However, the exclusion criteria are comparable with the contra-indicated in the SPC for adults.

Design
This was a 12-week, double-blind, randomized, multicenter, placebo-controlled, Phase IIIb, efficacy, and safety study of rosuvastatin 5 mg, 10 mg, or 20 mg, or matching placebo in paediatric patients (aged 10 to 17 years) with HeFH. At week 12, all eligible patients entered a 40-week, open-label, titration-to-goal period during which the dose of rosuvastatin could be up-titrated (to the maximum daily dose of 20 mg) to achieve the LDL-C target goal of <110 mg/dL (2.8 mmol/L). Patients with an LDL-C of ≥110 mg/dL at week 12 who received double-blind treatment with rosuvastatin 10 mg or 20 mg continued on that same dose at the start of the open-label period. For all other patients (including those in the placebo group), the starting open-label dose of rosuvastatin was 5 mg.
Safety assessments were conducted throughout all treatment periods. In addition, the effects on growth and secondary characteristics of sexual maturation were assessed at the end of the study (i.e., changes from study entry to week 52 in height and Tanner staging).
Enrolment in the study was actively managed to achieve a reasonable demographic distribution of patients by age, sex, and Tanner stage. This distribution included a minimum of approximately 10% for each Tanner stage II through V (at least 1 year post-menarche) and a minimum of approximately 30% of patients younger than 14 years of age. Five weeks after dietary modification and withdrawal of any current lipid therapy, patients qualified for the study by LDL criteria at week -1.

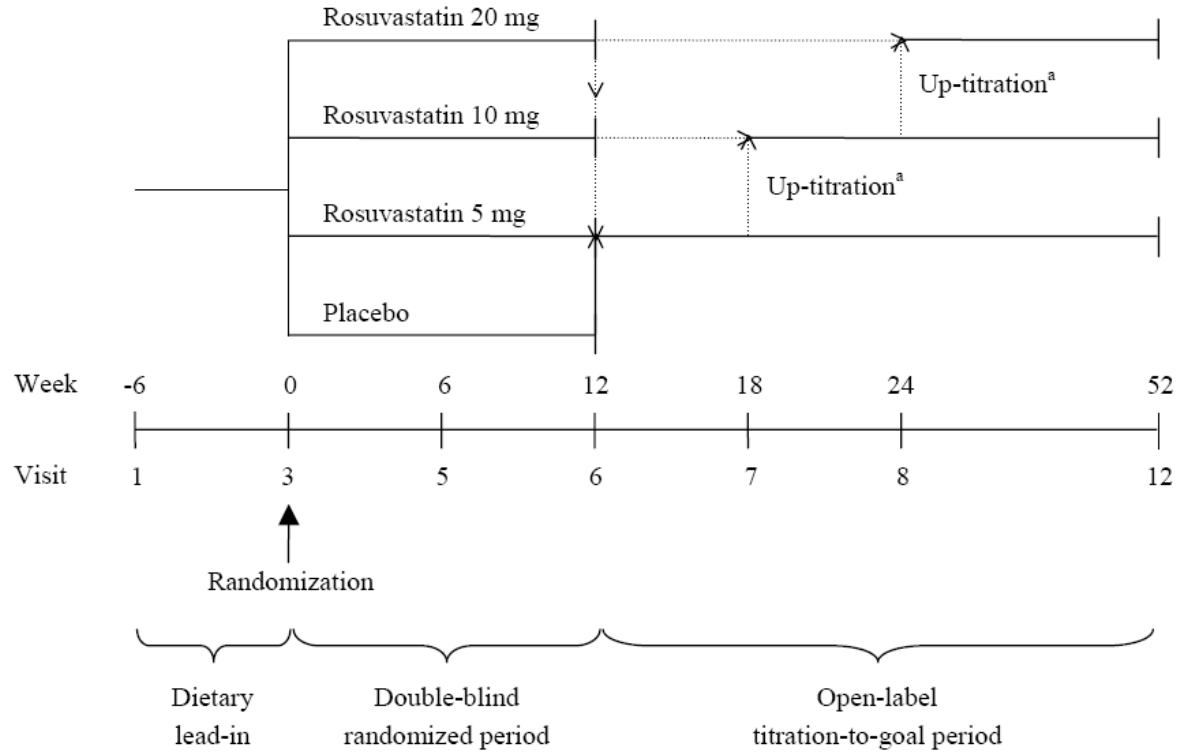


Figure 1.

Assessor's comments
The design is considered appropriate for assessing LDL-efficacy for the different doses of rosuvastatin. Placebo controlled treatment period is of sufficient duration. The open-label treatment period provides additional safety information as well as data relevant to support a step wise up-titration in daily clinical practice.

Measuring efficacy
Lipids and lipoproteins, as well as hsCRP (an inflammatory marker), were assessed from laboratory data. The results were blinded during the double-blind period of the study. The concentration of fasting LDL-C was determined for all relevant visits by the Friedewald Equation (LDL-C= Total cholesterol - {HDL-C + TG/2.2}), with the exception of those visits in which the TG level was >400 mg/dL (4.52 mmol/L)

Assessor's comments
The method of measuring efficacy is sufficiently assured. Using Friedewald equation is a generally accepted method for assessing LDL-C.

Efficacy assessment
Primary endpoint: The percent change in LDL-C from baseline (week 0) to week 12 (end of the 12-week, double-blind treatment period). The concentration of fasting LDL-C was determined for all relevant visits by the Friedewald equation, with the exception of those visits when the TG level was >400 mg/dL (4.52 mmol/L), in which case a β-quantification measurement of LDL-C was used.

Secondary endpoints: were percent change in LDL-C from baseline to week 6; percent change in HDL-C, TC, TG, non–HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, non–HDL-C/HDL-C ratio, ApoB, ApoA-1, and ApoB/ApoA-1 ratio from baseline to week 6, and to week 12; percentage of patients who achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L) (percent response rate) after 12 weeks of double-blind treatment

and after an additional 40 weeks of open-label titration-to-goal dosing up to a maximum rosuvastatin dose of 20 mg once daily.
An additional exploratory efficacy variable was the change in hsCRP from baseline to week 6, and to week 12.
Safety assessment: general, renal parameters, and growth/maturation and preferred terms for hepatic, muscle and renal system.

Assessor's comments
The chosen primary endpoint is considered appropriate for assessing efficacy of a statin. The secondary endpoints can be supportive to establish the effect of rosuvastatin on the total lipid spectrum and onset of action (change in LDL-C at 6 weeks). In addition, the percentage response rate is considered important supportive data.

Patient demographics at baseline

Patient disposition
A total of 222 patients entered the screening period. Of these, 177 patients were assigned to randomized treatment (42 patients to rosuvastatin 5 mg, 44 patients to rosuvastatin 10 mg, 45 patients to rosuvastatin 20 mg, and 46 patients to placebo). Of these, 176 patients received study drug;

- 1 patient in the rosuvastatin 20 mg group was randomized in error and did not receive study drug.
- 2 patients discontinued from the study during the double-blind period due to AEs.
- One additional patient completed double-blind treatment and chose not to continue study participation in the open-label period.

Overall, 173 (98.3%) patients completed the 12-week, double-blind period and entered the open-label treatment period. Nine patients discontinued from the study during the open-label period (4 due to AEs, 1 due to protocol non-compliance, 3 who withdrew consent, and 1 other) and 164 of 173 (94.8%) patients completed the 40-week, open-label period (see also figure 2).

Entered 6-week dietary lead-in period	222
Withdrawn during dietary lead-in period	45
Adverse event	1
Incorrect enrollment	38
Voluntary discontinuation by patient	6
Randomized	177

	Rosuvastatin			
	5 mg	10 mg	20 mg	Placebo
Randomized, n	42	44	45	46
Not treated	0	0	1	0
Received drug	42	44	44	46
Discontinued during 12-week, double-blind period[a], n (%)	1 (2.4)	0	0	1 (2.2)
Adverse event	1 (2.4)	0	0	1 (2.2)
Completed 12-week, double-blind period, n (%)	41 (97.6)	44 (100)[b]	44 (100)	45 (97.8)
	All patients (rosuvastatin 5 mg, 10 mg, or 20 mg)			
Patients entering open-label period	173[b]			
Discontinued during 40-week, open-label period[a], n (%)	9 (5.2)			
Adverse event	4 (2.3)			
Protocol non-compliance or deviation	1 (0.6)			
Patient withdrew consent	3 (1.7)			
Other	1 (0.6)			
Completed 40-week, open-label period, n (%)	164 (94.8)			

Figure 2: Patient disposition.

Major protocol violations were 5 (11.9%), 6 (13.6%), 5 (11.1%) and 10 (21.7%) for respectively 5 mg, 10 mg, 20 mg and placebo. This was almost entirely attributable to treatment non-compliance.

Table 3: Baseline characteristics

Characteristic*	Treatment assigned during double-blind period					
	Rosuvastatin					
	5 mg (N=42)	10 mg (N=44)	20 mg (N=45)	Total (N=131)	Placebo (N=46)	Overall total (N=177)
Sex, n (%)						
Male	26 (61.9)	25 (56.8)	22 (48.9)	73 (55.7)	24 (52.2)	97 (54.8)
Female	16 (38.1)	19 (43.2)	23 (51.1)	58 (44.3)	22 (47.8)	80 (45.2)
Age, years						
Male						
Mean (SD)	13.9 (1.9)	14.0 (1.5)	13.6 (1.8)	13.8 (1.7)	13.9 (1.5)	13.9 (1.7)
Range	10 to 17	11 to 17	11 to 17	10 to 17	11 to 16	10 to 17
Female						
Mean (SD)	14.4 (2.0)	15.2 (1.2)	14.8 (1.6)	14.8 (1.6)	14.8 (1.7)	14.8 (1.6)
Range	10 to 17	13 to 17	12 to 17	10 to 17	10 to 17	10 to 17
Race, n (%)						
Caucasian	39 (92.9)	42 (95.5)	43 (95.6)	124 (94.7)	41 (89.1)	165 (93.2)
Black	0	2 (4.5)	0	2 (1.5)	1 (2.2)	3 (1.7)
Asian	2 (4.8)	0	0	2 (1.5)	3 (6.5)	5 (2.8)
Hispanic	1 (2.4)	0	1 (2.2)	2 (1.5)	1 (2.2)	3 (1.7)
Other	0	0	1 (2.2)	1 (0.8)	0	1 (0.6)
Tanner stage, n (%)						
II	6 (14.3)	7 (15.9)	9 (20.0)	22 (16.8)	8 (17.4)	30 (16.9)
III	14 (33.3)	4 (9.1)	5 (11.1)	23 (17.6)	8 (17.4)	31 (17.5)
IV	11 (26.2)	20 (45.5)	20 (44.4)	51 (38.9)	20 (43.5)	71 (40.1)
V	11 (26.2)	13 (29.5)	11 (24.4)	35 (26.7)	10 (21.7)	45 (25.4)
Current smoker (habitual), n (%)	0	6 (13.6)	2 (4.4)	8 (6.1)	2 (4.3)	10 (5.6)
Height						
Mean (SD), cm	165.2 (11.5)	167.0 (10.3)	163.3 (10.9)	165.2 (10.9)	163.3 (8.6)	164.7 (10.4)
Mean, z-score (SD)	0.4 (1.1)	0.5 (1.1)	0.3 (1.0)	0.4 (1.1)	0.1 (0.8)	0.3 (1.0)
Range, z-score	-1.9 to 2.0	-2.0 to 2.8	-1.7 to 2.6	-2.0 to 2.8	-1.6 to 1.9	-2.0 to 2.8
Weight						
Mean (SD), kg	56.6 (13.0)	60.8 (13.7)	59.0 (12.6)	58.9 (13.1)	58.0 (13.4)	58.6 (13.1)
Mean, z-score (SD)	0.3 (1.0)	0.5 (1.1)	0.6 (0.8)	0.5 (1.0)	0.4 (0.9)	0.4 (1.0)
Range, z-score	-2.6 to 1.7	-3.0 to 2.4	-1.6 to 2.0	-3.0 to 2.4	-1.8 to 2.1	-3.0 to 2.4
BMI						
Mean (SD), kg/m^2	20.6 (3.7)	21.7 (4.1)	22.0 (3.5)	21.4 (3.8)	21.6 (4.0)	21.5 (3.8)
Mean, z-score (SD)	0.1 (1.2)	0.3 (1.1)	0.5 (0.8)	0.3 (1.1)	0.4 (0.9)	0.3 (1.0)
Range, z-score	-3.9 to 1.9	-2.5 to 2.3	-1.5 to 1.8	-3.9 to 2.3	-1.3 to 2.0	-3.9 to 2.3

Criteria, n (%)	Treatment assigned during double-blind period: Rosuvastatin 5 mg (N=42)	Rosuvastatin 10 mg (N=44)	Rosuvastatin 20 mg (N=45)	Rosuvastatin Total (N=131)	Placebo (N=46)	Overall total (N=177)
LDL-C criteria[a]						
LDL-C ≥190 mg/dL (4.9 mmol/L)	37 (88)	35 (80)	37 (82)	109 (83)	40 (87)	149 (84)
LDL-C >160 mg/dL (4.1 mmol/L) and <190 mg/dL (4.9 mmol/L) with family history of premature CVD[b]	5 (12)	7 (16)	7 (16)	19 (15)	5 (11)	24 (14)
LDL-C >160 mg/dL (4.1 mmol/L) and <190 mg/dL (4.9 mmol/L) with ≥2 CVD risk factors[c]	0	1 (2)	1 (2)	2 (2)	1 (2)	3 (2)
Did not meet eligibility criteria[d]	0	1 (2)	0	1 (1)	0	1 (1)
HeFH criteria						
FH in first-degree adult relative[e]	33 (79)	40 (91)	38 (84)	111 (85)	36 (78)	147 (83)
FH in first-degree relative <18 years of age[e]	14 (33)	12 (27)	13 (29)	39 (30)	18 (39)	57 (32)

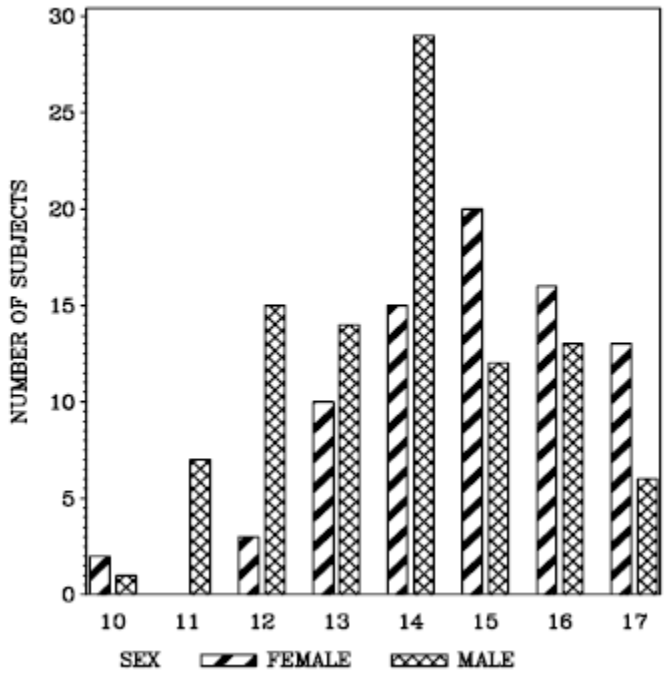


Figure 3: Age distribution

Most (84%) patients were included in the study based on an LDL_C ≥190 mg/dL. Approximately 10% of the patients had a LDL_C ≥160 mg/dL and additional family history of CV risk. Only a few patients met the inclusion criterion of LDL_C ≥160 mg/dL and additional ≥2 CVD risk factors.
Randomisation was less successful for gender, age between both genders, Tanner stage, and race.

Assessor's comments
In the first round it was observed that treatment non-compliance was twice as common in the placebo group as in the active treatment groups. However, it is agreed that as fewer patients took <80% of study drug in the rosuvastatin arm than in the placebo arm this indicates that tolerability does not seem the issue for patients being non-compliant. Furthermore, efficacy of rosuvastatin is not diminished due to non-compliance because of similar efficacy in the PP analysis
Randomisation was not totally successful for all subgroups. Active enrolment control for sex and Tanner stage was only partly successful. However, due to the limited number of patients included in the trial and thus small subgroups this was to be expected and had the largest impact on multiple category Tanner stage and race subgroups. In the first round it was commented that only small numbers of patients under the age of 13 were included in the trial, and that no further differentiation according to gender has been made for growth and sexual maturation follow-up. However, in accordance with PIP agreements the MAH is planning to conduct a trial where more patients between 10 and 13 years are included and where more specific follow-up according to gender is planned. Therefore, this is not considered a major hurdle to also approve rosuvastatin for the patients between 10 and 14 years of age.

Statistical analysis
The primary efficacy analysis was based on the intention-to-treat (ITT) analysis set (defined as patients who had taken at least 1 dose of study medication and who had both a baseline reading and at least 1 post-baseline reading for LDL-C). The primary analysis of the change in LDL-C from randomization to week 12 (using the last [valid] observation carried forward [LOCF] principle for missing data) tested the superiority of each rosuvastatin dose group using an analysis of covariance (ANCOVA) model with the baseline LDL-C as the covariate and including treatment as a fixed effect.
Each of the secondary efficacy lipid and lipoprotein variables was analyzed and summarized for the ITT analysis set in the same manner as the primary LDL-C efficacy variable.
For the exploratory variable, hsCRP, the log-transformed change from baseline was analyzed using an ANCOVA model with the baseline LDL-C as the covariate and including treatment as a fixed effect to compare each rosuvastatin dose group to the placebo group.

Assessor's comments
The proposed and conducted statistical methods are considered adequate for calculating treatment effects of rosuvastatin based on LDL-C difference from baseline.

Efficacy results

Primary endpoint
The percent change in LDL-C after 12 weeks of double-blind treatment was significantly greater in the rosuvastatin 5-mg, 10-mg, and 20-mg groups compared with placebo. The (LS) mean percent reduction in LDL-C at week 12 was -38.3% in the rosuvastatin 5 mg group; -44.6% in the rosuvastatin 10 mg group; and -50.0% in the rosuvastatin 20 mg group; compared with -0.7% in the placebo group ($p<0.001$ for all 3 rosuvastatin doses compared with placebo) (see table 2).
A similar treatment effect of rosuvastatin to that seen in the overall population was observed in patients with TG levels that were above normal at baseline (n=25); mean percent reductions were -51.3%, -35.0%, -52.0% for rosuvastatin 5, 10, and 20 mg, respectively, compared with -1.8 for placebo; $p<0.001$.

Table 4: LDL-C percent change from baseline to week 12 during the double-blind period (LOCF, ITT analysis set)

LDL-C[a]	Rosuvastatin 5 mg (N=42)	Rosuvastatin 10 mg (N=44)	Rosuvastatin 20 mg (N=44)	Placebo (N=46)
Baseline[b]				
n	42	44	44	46
Mean (SD) (mg/dL)	237.7 (55.06)	229.1 (44.70)	237.4 (47.84)	229.0 (43.13)
Median	223.5	229.5	245.5	223.5
Range	149 to 394	154 to 325	129 to 399	168 to 344
Mean (SD) (mmol/L)	6.2 (1.42)	5.9 (1.16)	6.1 (1.24)	5.9 (1.12)
Week 12				
n	42	44	44	46
Mean (SD) (mg/dL)	143.1 (31.15)	127.8 (39.89)	117.1 (33.19)	227.1 (48.76)
Median	138.0	118.0	113.5	217.5
Range	102 to 252	69 to 249	53 to 217	123 to 387
Mean (SD) (mmol/L)	3.7 (0.81)	3.3 (1.03)	3.0 (0.86)	5.9 (1.26)
% Change from baseline to Week 12[c]				
n	42	44	44	46
Mean (SD)	-38.5 (11.38)	-44.4 (12.15)	-50.2 (13.30)	-0.5 (13.18)
Median	-39.5	-47.2	-51.9	0.5
Range	-66.5 to -15.5	-61.8 to -0.8	-70.0 to 1.4	-30.1 to 46.3
ANCOVA analysis				
n	42	44	44	46
LS mean % change from baseline	-38.3	-44.6	-50.0	-0.7
Rosuvastatin difference vs placebo				
LS mean difference vs placebo in % change from baseline[d]	-37.5	-43.9	-49.2	NA
LCL to UCL[e]	-42.8 to -32.3	-49.1 to -38.8	-54.4 to -44.1	NA
p-value	<0.001	<0.001	<0.001	NA

Secondary endpoints

No significant differences were observed at week 12 between placebo and any dose of rosuvastatin for the following secondary lipid measurements: HDL-C (10.1% and 8.9% for 10 and 20 mg doses, respectively) and ApoA-1 and TG (-14.2% and -7.9% for 10 and 20 mg doses, respectively). TG was only significantly reduced with the 10 mg dose (p=0.048) at week 12. Significantly greater mean changes for non–HDL-C, TC, ApoB, ApoB/ApoA-1, LDL-C/HDL-C ratio, TC/HDL-C, non–HDL-C/HDL-C (p<0.001 for all rosuvastatin doses vs placebo) were observed at both week 6 and 12.

Table 5: Patients who achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L)

	Rosuvastatin				
	5 mg (N=42)	**10 mg (N=44)**	**20 mg (N=44)**	**Total**	**Placebo (N=46)**
Week 12					
Yes	5 (11.9)	18 (40.9)	18 (40.9)	NA	0
No	37 (88.1)	26 (59.1)	26 (59.1)	NA	46 (100.0)
Total	42 (100.0)	44 (100.0)	44 (100.0)	NA	46 (100.0)
Week 52[a]	**(N=26)**	**(N=25)**	**(N=122)**	**(N=173)**	
Yes	17 (65.4)	14 (56.0)	39 (32.0)	70 (40.5)	NA
No	9 (34.6)	11 (44.0)	83 (68.0)	103 (59.5)	NA
Total	26 (100.0)	25 (100.0)	122 (100.0)	173 (100.0)	NA

Legend: a= after uptitration

At week 12, 5 of 42 (11.9%), 18 of 44 (40.9%), and 18 of 44 (40.9%) patients treated with rosuvastatin 5, 10, and 20 mg, respectively, achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L), compared with none of the placebo patients (see table 3). Patients achieving the LDL-C target goal of <130 mg/dL (3.4 mmol/L) were 33.3%, 63.6%, and 68.2% for rosuvastatin 5, 10, and 20 mg, respectively, compared with 1 (2.2%) patient treated with placebo. At week 52, 70 of 173 rosuvastatin-treated patients (40.5%) had achieved the LDL-C goal of <110 mg/dL (2.8 mmol/L). the distribution of patients by rosuvastatin dosage was 26 patients at 5 mg, 25 patients at 10 mg, and 122 patients at 20 mg. As of week 52, the distribution of patients by rosuvastatin dose was 26 patients at 5 mg, 25 patients at 10 mg, and 122 patients at 20 mg.

hsCRP

At baseline, mean hsCRP values were low and similar across the 4 treatment groups (0.14, 0.23, 0.19, and 0.20 mg/L in the rosuvastatin 5 mg, rosuvastatin 10 mg, rosuvastatin 20 mg, and placebo groups, respectively) Changes from baseline to week 6 and to week 12 in hsCRP levels were small and did not differ significantly between the rosuvastatin and placebo treatment groups (LS mean percent changes from baseline to week 12 were -0.45%, -6.55%, and -31.5% for rosuvastatin 5, 10, and 20 mg, respectively, compared with -3.96% for placebo; p=0.885, 0.914, and 0.179, respectively).

Assessor's comments

Treatment with rosuvastatin demonstrated a clear reduction in LDL-C, with a dose related difference in effect size. The proportion of patients achieving LDL-C of less than 110 mg/dL was sufficient at 10 and 20 mg dose levels. This when considering that these are heFH patients of whom approximately 90% had LDL-C levels of more than 190 mg/dL at baseline. The secondary endpoints show changes in the expected (beneficial) direction known from rosuvastatin use in adults, but without reaching statistical significance. Only TG is statistically significantly reduced at a 10 mg rosuvastatin dose.

Results from the open label period demonstrate that most patients are uptitrated to the 20 mg dose. The goal of less than 110 mg/dL for LDL-C seems too optimistic as only approximately 40% of the patients reached this goal. For the 130 mg/dL goal, 33.3%, 63.6%, and 68.2% reached goal for 5, 10 and 20 mg, which is considered a more acceptable result.

No relevant changes in hsCRP levels are observed.

Subgroup analyses

No subgroup analyses were performed.

Assessor's comments
Analyses according to subgroups will not provide any extra information due to too limited numbers according to subgroup.

Supportive studies
N/A

Clinical studies in special populations
No submitted data.

Analysis performed across trials (pooled analyses and meta-analysis)
No submitted data.

III.3.3 CLINICAL SAFETY

III.3.3.1 Patient exposure

The safety population included all subjects who were randomized and who started treatment. There were 176 subjects in the safety population (see table 6).

Table 6: Overview of exposure

	Rosuvastatin				
Duration of treatment (days)[a]	**5 mg**	**10 mg**	**20 mg**	**Total**	**Placebo**
12-week, double-blind period					
N	42	44	44	130	46
Mean (SD)	83.9 (7.2)	84.4 (4.3)	84.3 (4.2)	84.2 (5.4)	83.2 (13.1)
Median	84	84	84	84	84
Range	45 to 103	76 to 103	70 to 97	45 to 103	1 to 96
40-week, open-label period					
N	129	123	123	173	NA
Mean (SD)	93.0 (85.2)	86.3 (64.7)	190.3 (62.7)	266.1 (41.0)	NA
Median	48	52	194	277	NA
Range	7 to 300	1 to 255	11 to 285	54 to 302	NA

The extent of exposure was similar among the treatment groups during the randomized treatment period.

Assessor's comments
Exposure to treatment assignment was approximately similar across the different dose groups.

III.3.3.2 Adverse events

Safety in the pharmacokinetic trial
There were no withdrawals from the trial, no serious adverse events, and no deaths during the trial (see table 7). The most frequent adverse events were headache (1 subject on 10 mg, 2 subjects on 40 mg, and 1 subject on 80 mg in the multiple-dose phase), and abdominal pain and nausea (2 subjects each on 40 mg and 1 subject on 80 mg in the multiple-dose phase). One subject had an adverse event attributed by the investigator to rosuvastatin, a mild elevation of ALT on Day 13 (rosuvastatin 80 mg multiple dose), 6 days following the last dose, that resolved without treatment.

Table 7: Adverse events during the pharmacokinetic trial

Category[a]	Number of subjects			
	Single-dose			Multiple-dose
	Rosuvastatin 10 mg N = 6	Rosuvastatin 40 mg N = 6	Rosuvastatin 80 mg N = 6	Rosuvastatin 80 mg N = 6
Number of subjects with at least 1 adverse event	2	3	1	2
Number of adverse events	2	8	1	5
Deaths	0	0	0	0
Withdrawals	0	0	0	0
Serious adverse events	0	0	0	0

General adverse events in the efficacy trial

Table 8: General numbers of adverse events

Category of adverse event[a]	Rosuvastatin 5 mg (N=42)	Rosuvastatin 10 mg (N=44)	Rosuvastatin 20 mg (N=44)	Rosuvastatin Total (N=130)	Placebo (N=46)
Number (%) of patients who had an AE in each category[b]					
Any AE	21 (50.0)	28 (63.6)	24 (54.5)	73 (56.2)	25 (54.3)
SAE	0	0	0	0	1 (2.2)
SAE leading to death	0	0	0	0	0
SAE not leading to death	0	0	0	0	1 (2.2)
AE leading to discontinuation of study treatment	1 (2.4)	0	0	1 (0.8)	1 (2.2)
Treatment-related AE	1 (2.4)	3 (6.8)	3 (6.8)	7 (5.4)	3 (6.5)
Treatment-related SAE leading to death	0	0	0	0	0
Treatment-related SAE not leading to death	0	0	0	0	1 (2.2)
Treatment-related AE leading to discontinuation of study treatment	0	0	0	0	1 (2.2)

Table 9: Adverse events according to SOC in the placebo-controlled study phase

	Rosuvastatin				
SOC[a,b]	**5 mg (N=42)**	**10 mg (N=44)**	**20 mg (N=44)**	**Total (N=130)**	**Placebo (N=46)**
Infections and infestations	8 (19.0)	12 (27.3)	14 (31.8)	34 (26.2)	17 (37.0)
Nervous system disorders	7 (16.7)	8 (18.2)	9 (20.5)	24 (18.5)	10 (21.7)
Gastrointestinal disorders	5 (11.9)	3 (6.8)	5 (11.4)	13 (10.0)	4 (8.7)
Musculoskeletal and connective tissue disorders	3 (7.1)	5 (11.4)	4 (9.1)	12 (9.2)	3 (6.5)
Respiratory, thoracic and mediastinal disorders	3 (7.1)	3 (6.8)	2 (4.5)	8 (6.2)	2 (4.3)
General disorders and administration site conditions	3 (7.1)	2 (4.5)	2 (4.5)	7 (5.4)	1 (2.2)
Reproductive system and breast disorders	1 (2.4)	3 (6.8)	0	4 (3.1)	0
Skin and subcutaneous tissue disorders	1 (2.4)	1 (2.3)	2 (4.5)	4 (3.1)	1 (2.2)
Injury, poisoning and procedural complications	0	2 (4.5)	1 (2.3)	3 (2.3)	1 (2.2)
Immune system disorders	1 (2.4)	1 (2.3)	0	2 (1.5)	0
Investigations	0	1 (2.3)	1 (2.3)	2 (1.5)	1 (2.2)

The most common AEs for all rosuvastatin groups were headache (16.9%) and nasopharyngitis (13.1%). The most common AEs assessed by the investigator to be related to treatment with rosuvastatin were nausea (2 of 130 (1.5%)) and headache (2 of 130 (1.5%)). During the 40 weeks open-label period, the most common AEs for total rosuvastatin were nasopharyngitis (20.8%), headache (16.8%), influenza (8.1%), nausea (5.8%), and fatigue (5.2%). Of 173 patients treated during the open-label period, 21 (12.1%) of patients had treatment-emergent AEs considered by the investigator to be related to treatment with rosuvastatin. The most common were headache (3.5%), nausea (2.3%), and fatigue (1.7%)

Table 10: Most commonly reported adverse events (SOC terms) in the 40 week open-label period.

SOC[a,b]	All patients (Rosuvastatin 5 mg, 10 mg, or 20 mg) (N=173)
Infections and infestations	74 (42.8)
Nervous system disorders	36 (20.8)
Gastrointestinal disorders	35 (20.2)
Injury, poisoning and procedural complications	24 (13.9)
General disorders and administration site conditions	15 (8.7)
Musculoskeletal and connective tissue disorders	15 (8.7)
Skin and subcutaneous tissue disorders	14 (8.1)
Respiratory, thoracic and mediastinal disorders	11 (6.4)
Investigations	9 (5.2)
Immune system disorders	4 (2.3)
Reproductive system and breast disorders	4 (2.3)
Eye disorders	3 (1.7)
Ear and labyrinth disorders	2 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2)
Psychiatric disorders	2 (1.2)
Renal and urinary disorders	2 (1.2)

Discontinuation due to adverse events

There were 2 patients who discontinued study treatment during the 12-week, randomized, double-blind period due to an AE: 1 treated with rosuvastatin 5 mg (menorrhagia) and 1 treated with placebo (vision blurred). Four (2.3%) patients discontinued study treatment (all rosuvastatin) due to AE during the open-label period (nausea (2), fatigue, vesicular skin eruption). One of these events was not considered to be treatment-emergent (fatigue) because the patient had experienced a previous AE of fatigue while taking rosuvastatin.

Assessor's comments

Rosuvastatin was well tolerated at each dose (5 to 20 mg) during the placebo controlled period. The adverse event profile of rosuvastatin is generally similar for a clinical trial paediatric population compared to an adult population. Muscle symptoms seem to be slightly higher than for adults, however this is based on limited numbers. Exposure to doses above 20 mg is very limited, only 12 patients in total with 6 receiving more than a single dose. The number of discontinuations due to adverse events was too small to draw any conclusions.

As agreed in the PIP, a long-term safety trial will be conducted as a post-approval commitment to provide additional safety information.

III.3.3.3 Serious adverse events and deaths

Deaths
No deaths occurred in this study.

Serious adverse events
There were 3 SAEs during this study: blurred vision (placebo, treatment-related), acute appendicitis (10 and 20 mg rosuvastatin open-label period, not treatment-related) , and vesicular rash (20 mg rosuvastatin open-label period, treatment-related).

Assessor's comments
A low number of severe adverse events were observed. No worrying results appeared related to deaths and severe adverse events.

III.3.3.4 Specific adverse events

Hepatic AEs

Table 11: Hepatic AEs

	Rosuvastatin				
MedDRA preferred term	**5 mg**	**10 mg**	**20 mg**	**Total**	**Placebo**
12-week, double-blind period	**(N=42)**	**(N=44)**	**(N=44)**	**(N=130)**	**(N=46)**
Aspartate aminotransferase (AST) increased	0	0	1 (2.3)[a]	1 (0.8)	0
40-week, open-label period	**(N=129)**	**(N=123)**	**(N=123)**	**(N=173)**	
Alanine aminotransferase (ALT) increased	0	0	1 (0.8)[b]	1 (0.6)	NA
Liver function test abnormal	1 (0.8)[c]	0	0	1 (0.6)	

There was no evidence of an excess of AEs related to the liver in any treatment group during either the randomized or open-label treatment period.

Muscle related Aes

Table 12: Mucle related AE's

	Rosuvastatin				
MedDRA preferred term	**5 mg**	**10 mg**	**20 mg**	**Total**	**Placebo**
12-week, double-blind period	**(N=42)**	**(N=44)**	**(N=44)**	**(N=130)**	**(N=46)**
Blood creatine phosphokinase increased	0	0	0	0	1 (2.2)
Musculoskeletal chest pain	1 (2.4)	0	0	1 (0.8)	1 (2.2)
Musculoskeletal pain	0	0	1 (2.3)	1 (0.8)	0
Myalgia	1 (2.4)	1 (2.3)	2 (4.5)	4 (3.1)	0
Myopathy	0	1 (2.3)	1 (2.3)	2 (1.5)	0
40-week, open-label period	**(N=129)**	**(N=123)**	**(N=123)**	**(N=173)**	
Blood creatine phosphokinase increased	1 (0.8)	1 (0.8)	1 (0.8)	3 (1.7)	NA
Muscle spasms	2 (1.6)	1 (0.8)	0	3 (1.7)	NA
Muscular weakness	0	0	1 (0.8)	1 (0.6)	NA
Musculoskeletal chest pain	0	0	1 (0.8)	1 (0.6)	NA
Musculoskeletal pain	1 (0.8)	0	0	1 (0.6)	NA
Myalgia	1 (0.8)	3 (2.4)	2 (1.6)	5 (2.9)	NA

Renal AEs

Table 13: Renal AE's

	Rosuvastatin				
MedDRA preferred term	**5 mg**	**10 mg**	**20 mg**	**Total**	**Placebo**
12-week, double-blind period	**(N=42)**	**(N=44)**	**(N=44)**	**(N=130)**	**(N=46)**
None					
40-week, open-label period	**(N=129)**	**(N=123)**	**(N=123)**	**(N=173)**	
Chromaturia	1 (0.8)[a]	0	0	1 (0.6)	NA
Dysuria	0	0	1 (0.8)[b]	1 (0.6)	NA

Vital signs

There were no notable changes from study entry (Week -6) to Week 52 in mean systolic and diastolic BP. There was no notable impact of treatment on growth from study entry (Week -6) to Week 52 as assessed by height, weight, or BMI based on mean values or on z-scores.

Assessor's comments

These adverse events are in line with the known safety profile of rosuvastatin for adults. It is acknowledged that CK related AEs are more frequent at higher doses of rosuvastatin. Back titration should be always considered in clinical decision making. Information on back-titrating could have helped to evaluate AEs in relation to dose. This is further evaluated according to PIP agreement in the next study. The AE data do not warrant SPC/label changes.

III.3.3.4 Laboratory findings

Hepatic enzyme elevation
No patient in any treatment group experienced ALT elevations >3 × the ULN at any treatment visit during the double-blind period, and one patient experienced an ALT elevation >3 × the ULN on 1 occasion during the open-label period.
A total of 3 patients (rosuvastatin 10 mg, 20 mg, and 20 mg, respectively) experienced AST elevations >3 × the ULN during the double-blind period. Each of these was associated with marked concurrent CK elevations. One of 20 mg patients also experienced an adverse event of myopathy. No patients experienced AST elevations >3 × the ULN during the open-label period.

CK elevation (skeletal muscle)
Overall, 3.1% (n=4) of patients treated with rosuvastatin and 0% of patients in the placebo group experienced elevations in CK of >10 × the ULN at any visit during the double-blind treatment period. During the open-label period, elevations in CK of >10 × the ULN at any visit occurred in 2.3% of patients treated with rosuvastatin. No patients had elevations in CK of >10 × the ULN at 2 consecutive visits during the open-label period.

Serum creatinine elevation (renal)
No patients in the study had a >50% increase in serum creatinine from baseline (considered clinically important) during the double-blind period and 1 rosuvastatin-treated patient had >50% increase from baseline during the open-label period.

Blood cells (haematology)
The mean platelet count decreased slightly from baseline to final visit in both the rosuvastatin and placebo treatment groups. There were no appreciable changes in red blood cell counts or white blood cell counts from baseline to the final visit.

Assessor's comments
Laboratory markers for possible damage to specific areas as liver, muscle and kidney were followed. An increased rate of >10 × the ULN could be observed to be higher than for adults. Numbers of patients with laboratory elevations in these areas were too small to draw any conclusions.

III.3.3.5 Safety in special populations

No analyses in special populations were provided.

III.3.4 PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

Amongst others, a detailed description of the pharmacovigilance system (PVS) (version 8.0, dated 25 February 2008, and signed) and a Risk Management Plan (dated 24 March 2009) were submitted.

Assessor's comment:
It is noted that the MAH's PVS version 8.0 has been superseded by PVS version 9.0, dated 2 February 2009, and signed. This updated PVS has been assessed in procedure NL/H/0343/001/II/034. In this report, the RMS assessed the PVS version 9.0 that is currently in force.

III.3.4.1 Assessment of the Pharmacovigilance System

In procedure NL/H/0343/001/II/034, the MAH has provided documents that set out a detailed description of the system of pharmacovigilance (version 9.0, dated 2 February 2009, and signed). The RMS considered that the Pharmacovigilance system as described by the MAH had a few deficiencies.
In the context of procedure NL/H/0343/001/II/034, the MAH responded to these RMS comments. In the response document the location of the database and the responsibilities for ensuring corrective and preventive action were made clear. The MAH committed to add this information to the next version of the PVS.

Assessor's comment:
Following the assessment of the MAH's PVS version 9.0, dated 2 February 2009, and the related response document of the MAH, the RMS concludes that the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

III.3.4.2 Assessment of the Risk Management Plan

The RMP submitted supersedes the previous RMP (dated 16 October 2008). The RMP has been updated with information regarding the sought indication in children and adolescents aged 10-17 years and the PLUTO study supporting this application.

The sought indication and dosage in children and adolescents and demographics, exposure of the study population in the PLUTO study have been added to the Safety specification.
The section 'Potential for off-label paediatric use' has been updated to reflect that experience in children younger than 10 years of age is limited to a small number of children (aged 8 years and above) with homozygous familial hypercholesterolaemia. The MAH states that therefore, in the EU, rosuvastatin is only indicated in children aged 10 to 17 years with heterozygous familial hypercholesterolaemia and is not recommended for use in children younger than 10 years of age. While there may be a potential for off-label use in children, the MAH's safety database suggests that such off-label use is not widespread in clinical practice. This potential for off-label use will be mitigated through routine risk minimisation measures (i.e. SPC and PIL wording).

With the completion of the PLUTO study, paediatric safety signals will now be evaluated from spontaneous adverse event reports.

A statement is included that no new safety concerns have been identified since the submission of the preceding EU-RMP.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Non-clinical
As a follow-up measure it was noted, that in order to substantiate the safety of rosuvastatin for growing children in the age of 10-17 years, a juvenile toxicity study should be provided in which special attention is paid to reproductive function, neurological development and skeletal muscle development. The duration of the study should be sufficient to account for the full range of development from the age of 10 years into adulthood and taking into account possible differences in exposure/pharmacokinetics between young and adult animals and humans.

Pharmacokinetics
The pharmacokinetics study provided information on the most important pharmacokinetic parameters for children of 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia. Pharmacokinetic parameters seem to be dose-related. The most important pharmacokinetic values are increased when higher doses are administered as shown in adult studies. Exposure in paediatric patients, also in relation to age, is to some extent comparable to the exposure in adult patients.
Studies in the accepted modified PIP should provide further information on the comparison of rosuvastatin PK in children and adolescents with hypercholesterolaemia to adult patients with hypercholesterolaemia. However, in the analyses of these studies, the issue of dose proportionality in paediatric patients should be incorporated as this issue was not addressed.

Clinical Efficacy
The study provided information on efficacy for different doses of rosuvastatin. In general, a clear reduction in LDL-C, with a dose related difference in effect size was demonstrated. This was generally supported by most of the secondary endpoints, except that for TG where only a significant change was found for the 10 mg dose. This is unexpected compared to what is usually observed in adults. The number of patients achieving LDL-C of less than 110 mg/dL was sufficient, when taking into account that approximately 90% of patients had LDL-C levels of more than 190 mg/dL at baseline. Results from the open label period demonstrate that most patients need the 20 mg dose to reach target goal (LDL-C <110 mg/dL). The goal of less than 110 mg/dL for LDL-C seems too optimistic as only approximately 40% of the patients reached this goal during the first 12 weeks. For the 130 mg/dL goal, up to 68% reached goal, which is considered a more acceptable result. A role of hsCRP seems not to be apparent from the provided data. In addition, deviations in the trial did not indicate to alter outcome.

Clinical Safety
The safety profile seems to be in line with that of the adult population. Rosuvastatin was generally well tolerated. Although the numbers of patients and follow-up were limited, it can currently be assumed that in general no safety issues emerge within this patient population. However, CK elevations >10xULN and muscle symptoms were more frequent in paediatric patients. This has been reflected in the SPC. Additional study data as planned in the PIP should provide more information on the safety of rosuvastatin in children of 10 to 17 years of age treated with rosuvastatin. Particularly, because the age group of 10 to 14 years of age was underrepresented and current follow-up was very short to give any useful data on impact on growth and maturation. In addition, it remains unclear whether some patients had their rosuvastatin dose reduced because of adverse events as this was not actively followed. A negligible/zero AE rate is important to keep these young patients compliant to their lifelong therapy. Therefore, dose reductions in patients experiencing AEs should be protocolised and specfically evaluated in the planned PIP approved long term trial. However, it is acknowledged that a large proportion of patients will need a 20 mg dose to reach treatment goal. Achieving treatment goal while maintaining a negligble AE rate will always be a field of tension in these young patients. Furthermore, the limited data that were available in children between 10 and 14 years of age will be addressed in following PIP for which already agreement is reached on a trial in long term safety evaluation.

Environmental Risk Assessment
The Environmental Risk Assessment is acceptable.

Pharmacovigilance System and Risk Management Plan

Assessment of the detailed description of the pharmacovigilance system (PVS) (version 9.0, dated 2 February 2009, and signed) together with the response document of the MAH submitted in the context of variation NL/H/0343/II/034, and a Risk Management Plan (dated 24 March 2009) led to the following conclusions for incorporation in the updated RMP:

- The MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
- The MAH added information concerning the PLUTO study and use of rosuvastatin in children and adolescents to the RMP. No identified or potential risks have been deleted or added. No changes have been made to the risk minimisation activities.
- The MAH should propose post-marketing surveillance plans for monitoring the safety in this population, not limited to spontaneous reporting.
- The proposed study will provide reassurance regarding the long term safety. This study, along with targeted follow-up of any neuro-psychiatric reactions and any muscle/renal reactions, is acceptable. The MAH is requested to establish the post-marketing safety surveillance during three months after this procedure is finilised.

These conclusions were addressed in an updated EU RMP (dated 22 March 2010), which was approved upon completion of this procedure.

IV.1 SPC changes

Only the SPC paragraphs which are altered are displayed, with added text indicated in blue:

4.1 Therapeutic indications

Adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see Section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see Section 4.8), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see Section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

Crestor may be given at any time of day, with or without food.

Paediatric population

Paediatric use should only be carried out by specialists.

Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1 year post-menarche)
In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see Section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

The 40 mg tablet is not suitable for use in paediatric patients.

Children younger than 10 years
Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolaemia. Therefore, Crestor is not recommended for use in children younger than 10 years.

Use in the elderly

A start dose of 5 mg is recommended in patients >70 years (see Section 4.4). No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Crestor in patients with severe renal impairment is contraindicated for all doses. (See Section 4.3 and Section 5.2).

Dosage in patients with hepatic impairment

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see Section 5.2). In these patients an assessment of renal function should be considered (see Section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Crestor is contraindicated in patients with active liver disease (see Section 4.3).

Race

Increased systemic exposure has been seen in Asian subjects (see Section 4.4 and Section 5.2). The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.

Dosage in patients with predisposing factors to myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see Section 4.4).
The 40 mg dose is contraindicated in some of these patients (see Section 4.3).

4.4 Special warnings and special precautions for use

Renal Effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Crestor, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see Section 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle Effects
Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see Section 4.5) and caution should be exercised with their combined use.
As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Crestor in post-marketing use is higher at the 40 mg dose.

Creatine Kinase Measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before Treatment

Crestor, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see Section 5.2)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on Treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Crestor or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.
In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Crestor and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Crestor and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Crestor with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate. (See Section 4.5 and Section 4.8.)

Crestor should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver Effects
As with other HMG-CoA reductase inhibitors, Crestor should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.
It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Crestor should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Crestor.

Race
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see Section 4.2 and Section 5.2).

Protease inhibitors
The concomitant use with protease inhibitors is not recommended (see Section 4.5).

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 10 to 17 years of age taking rosuvastatin is limited to a one-year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see Section 5.1). The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown.

In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults (see Section 4.8).

4.8 Undesirable effects

The adverse events seen with Crestor are generally mild and transient. In controlled clinical trials, less than 4% of Crestor-treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders
Rare: hypersensitivity reactions including angioedema

Nervous system disorders
Common: headache, dizziness

Gastrointestinal disorders
Common: constipation, nausea, abdominal pain
Rare: pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders
Common: myalgia
Rare: myopathy (including myositis) and rhabdomyolysis

General disorders
Common: asthenia

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Crestor. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Crestor and clinical trial data show that the occurrence is low.

Skeletal muscle effects: **Effects on skeletal muscle e.g.myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg.**

A dose-related increase in CK levels has been observed inpatients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued (see Section 4.4).

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

Post Marketing Experience:
In addition to the above, the following adverse events have been reported during post marketing experience for CRESTOR:
Gastrointestinal disorders: Not known: diarrhoea
Hepatobiliary disorders: Very rare: jaundice, hepatitis; *rare:* increased hepatic transaminases.
Musculoskeletal disorders: Very rare: arthralgia
Nervous system disorders: Very rare: polyneuropathy, memory loss
Renal disorders: Very rare: haematuria
Skin and subcutaneous tissue disorders: Not known: Stevens-Johnson syndrome

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

Paediatric population: Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults (see Section 4.4). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects
Crestor reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Crestor also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 1 Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	Apo B	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy
Crestor is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

From pooled phase III data, Crestor has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Crestor from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to Crestor 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Crestor has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see Section 4.4).

Rosuvastatin has not been proven to prevent the associated complications of lipid abnormalities, such as coronary heart disease as mortality and morbidity studies with Crestor have not yet been completed.

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestor 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see Section 4.2).

Paediatric population

In a doubleblind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10-13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10, and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/l.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see Section 4.4). The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown. This trial (n=176) was not suited for comparison of rare adverse drug events.

5.2 Pharmacokinetic properties

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion: Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity: Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers (see "Paediatric population" below).

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and Cmax in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Paediatric population: The pharmacokinetic parameters in paediatric patients with heterozygous familial hypercholesterolaemia aged 10 to 17 years have not been fully characterised. A small pharmacokinetic study with rosuvastatin (given as tablets) in 18 paediatric patients demonstrated that exposure in paediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

ANNEX II – Addition of the indication *Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event* (Type II variation NL/H/343/001-004/II/035)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variation application NL/H/0343/001/II/035 for Crestor® for the indication of "Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (See Section 5.1), as an adjunct to correction of other risk factors'' is approvable.

Major objections have been solved and the SPC has been amended accordingly.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

Rosuvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor and a member of the statin class of lipid-lowering agents. It was first approved for marketing in the Netherlands on 6 November 2002 and was first launched on 19 February 2003, in Canada. It is indicated for the treatment of primary hypercholesterolaemia, mixed dyslipidaemia, and homozygous familial hypercholesterolaemia.

In April 2009, the MAH submitted a Type II variation (NL/H/343/001-004/II/35) for Crestor® via the Mutual Recognition Procedure. The initial new claimed indication was: 'Reduce the risk of major cardiovascular events in adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular risk markers such as age, hypertension, low HDL-C, elevated hsCRP, smoking or a family history of premature coronary heart disease''. One pivotal trial (JUPITER) was submitted to support the indication. The dose used in the study was 20 mg once daily.
Taking into account this new indication, the Paediatric Committee granted a waiver regarding the PIP on 3 April 2009.

II.2 Supplementary paragraph

The major effect of the statins is to lower LDL-cholesterol levels through inhibition of the enzyme HMG-CoA reductase. Studies using statins have reported 20 to 60 percent lower LDL-cholesterol levels in patients on these drugs. Statins also reduce elevated triglyceride levels and produce a modest increase in HDL-cholesterol. Statins are used for treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. For simvastatin, atorvastatin and pravastatin, studies have shown a beneficial effect in reduction of cardiovascular mortality and morbidity as a primary and/or secondary prevention strategy.
An indication for (primary) prevention of cardiovascular events is currently not accepted for any statin or other cardiovascular agent based on a risk score or estimation that includes the risk marker hsCRP.
hsCRP has currently not been recognized as a biomarker for cardiovascular risk prevention by the EMA.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A.

III.2 Non-clinical aspects

No new data have been submitted. However a potential effect on reproductive function, neurological development and skeletal muscle development could not be excluded. Additional data on these aspects was needed.

Environmental Risk Assessment
The MAH has provided an expert report, based on the Environmental Risk Assessment (ERA) guideline (CHMP/SWP/4447/00-final).

The ERA submitted for the current procedure is identical to that submitted in the registration procedure of Crestor. The previous ERA resulted in the conclusion that the risk for all compartments was acceptable.

In both the original ERA (submitted during registration) and the ERA of the first variation procedure, the MAH has used an F_{pen} of 0.021 to calculate $PEC_{surface\ water}$.
Since this F_{pen} was higher than the default F_{pen} of 0.01 (which is allowed as maximum F_{pen} according to the EMA guideline), a further refinement of F_{pen} as a result of expected increased use was not deemed necessary.

In the current ERA, submitted with the present variation (treatment of hypercholesterolaemia and prevention of cardiovascular events), the MAH presents an F_{pen} of 0.017, which is lower than the F_{pen} values presented in the earlier ERAs. The lower figure was the result of an updated calculation using a more accurate method. In this particular case, the updated F_{pen} figure is thus judged to be more accurate although it is at the same time less than the previous F_{pen} estimate.

III.3 Clinical aspects

The goal of this efficacy evaluation is to determine the efficacy of rosuvastatin calcium as a primary prevention strategy of cardiovascular events in patients with an increased risk for cardiovascular disease. The pivotal study to support such a strategy is the randomized, double-blind, placebo-controlled, multicenter JUPITER trial, a trial in patients with low levels of LDL and increased hsCRP with the primary aim to show a reduction in cardiovascular events. The secondary objectives of that study were to investigate the safety of long-term treatment with rosuvastatin compared with placebo through comparisons of total mortality, noncardiovascular mortality, and adverse events (AEs), and to investigate whether therapy with rosuvastatin reduces the incidence of diabetes mellitus, venous thromboembolic events, or the incidence of bone fractures.

III.3.1 Clinical pharmacology

No new data have been submitted.

III.3.2 Clinical efficacy

Main study

JUPITER trial

III.3.2.1 Aim of the study

The purpose of the study was to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo would decrease the rate (based on time to first event after randomization) of major cardiovascular events (combined endpoint of cardiovascular death, stroke, myocardial infarction (MI), unstable angina, or arterial revascularization) among individuals with low LDL-C (<130 mg/dL [3.36 mmol/L]) and elevated levels of hsCRP (≥2.0 mg/L).

III.3.2.2 Patients

Patients were included when they were men aged 50 years and over; women aged 60 years and over with a fasting LDL-C value <130 mg/dL (3.36 mmol/L) at screening visit 1 (-6 weeks) and hsCRP value ≥2.0 mg/L (at screening visit 1, and a triglycerides (TG) value <500 mg/dL (5.6 mmol/L).
Patients were excluded if they were

- previously treated with a statin within 6 weeks before visit 1 or previously demonstrated hypersensitivity reactions to statins.
- using one or more of the following medications: other lipid lowering therapy, (for women) HRT treatment, immunosupressive therapy at study entry, oral hypoglycemics, and chronic steroid therapy.
- patients with prior cardiovascular incidence (MI, unstable AP, stroke, arterial revascularisation, CHD risk equivalent to NCEP ATPIII) were excluded.
- patients with a chronic inflammatory condition such as severe arthritis, lupus, or inflammatory bowel disease were excluded.
- patients with liver abnormalities, diabetes mellitus, high creatine kinase, high serum creatinine, uncontrolled hypertension, history of malignancies, and uncontrolled hypothyroidism.

The Framingham-based CHD 10-year risk estimate was calculated for each subject according to the NCEP ATP III guidelines (Expert Panel (NCEP) 2001). The estimate depended on age, sex, total cholesterol (TC), and HDL levels, smoking status, systolic blood pressure, and antihypertensive drug use. The European SCORE global risk algorithm (Conroy et al 2003) was also calculated to further profile the randomized population. These risk scores give an estimate of the probability of a CHD event within 10 years and helped profile the level of risk in the randomized population.

Comments RMS:
In the JUPITER trial elderly patients with low LDL-C levels and an elevated hsCRP level were included, at least part of whom would otherwise not be considered eligible for statin therapy according to current treatment guidelines. In these guidelines treatment with a statin is based on the future risk of cardiovascular disease, estimated from an aggregate of established risk factors, including age, sex, smoking, blood pressure and lipid levels, and typically not including CRP levels. Importantly, patients with these established risk factors, such as hypertension, low-HDL-C, smoking and a family history of premature coronary heart disease, were, however, not excluded. The result is that a heterogeneous group of patients with variable CV risk was included, as shown by the baseline characteristics (see below). This has major implications for the benefit/risk assessment as will be discussed later.

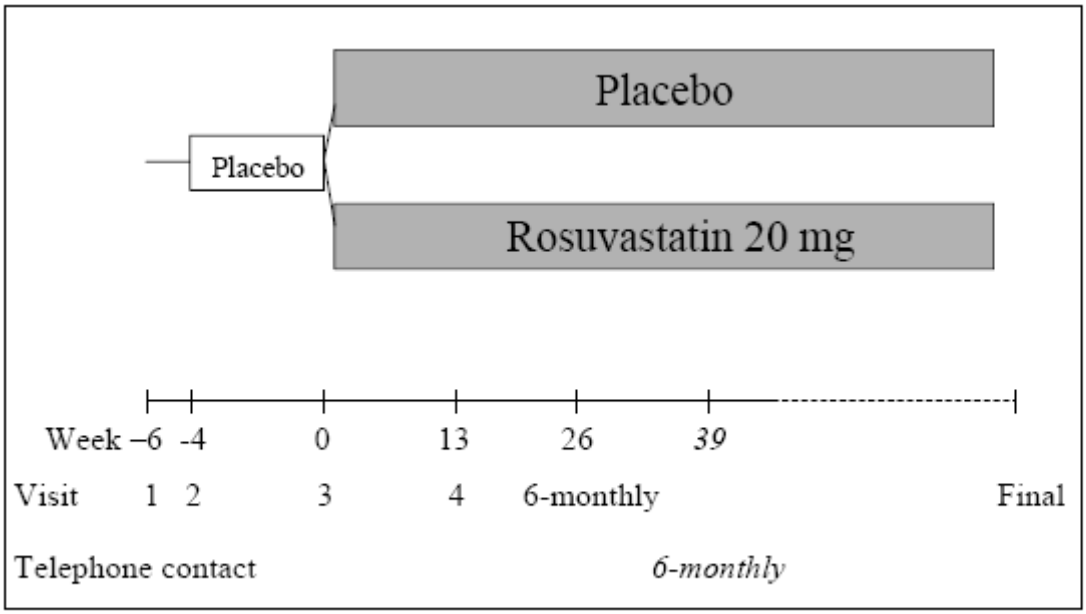
With respect to hsCRP, this is an unspecific biomarker that can be elevated in many clinical situations e.g. infections, chronic diseases and malignancies. Patients with a chronic inflammatory condition and malignancies were excluded, but other causes might still have been present. Exclusion of these causes could quite possibly have reduced unnecessarily treated patients and thus the number needed to treat. hsCRP is currently not accepted as a CV risk marker by the EMA.

Strict exclusion criteria were employed to prevent patients at high risk for adverse events. Patients at high risk for adverse events, such as patients with high creatinine kinase, high creatinine level, hypothyroidism, patients with certain concomitant medication etc., were excluded. This seems understandable but it might have favourably influenced the safety finding.

III.3.2.3 Design

The design of the study was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study of 17,802 randomized patients to evaluate the effect of rosuvastatin on cardiovascular endpoints. Patients were randomized to rosuvastatin 20 mg or matching placebo in 2 parallel treatment arms in a 1:1 ratio.

hsCRP was measured during prescreening visit 1 (week -6) and 2 (week -4), at baseline, at month 3 and every year during study. Cholesterol parameters were measured during visit 2, at 12 months, and at final visit.
Following Screening visit 1, all potentially eligible subjects were to come back for screening visit 2 and were enrolled in the initial 4-week, run-in phase and received placebo therapy. If found eligible for the main study on the basis of appropriate levels of baseline LDL, hsCRP (mean of visit 1 and 2), and run-in phase compliance (>80% of pills taken), subjects were randomized to active or placebo therapy at the randomization visit (visit 3; baseline).



NOTE: The run-in phase is the interval between visits 2 and 3. The randomized treatment phase is from visit 3 onward.

Figure 1: Study design

Comments RMS:
The chosen design is essentially a straight forward placebo-controlled trial design. The initial placebo-run-in phase is considered acceptable. The duration of the 6 week washout period of previous lipid lowering therapy is considered acceptable.

Active recruitment methods were used, which is acceptable in a trial setting although this does not reflect clinical practice. Patients were indeed not patients who would routinely visit a physician for CV-related problems and would in that sense be eligible for rosuvastatin treatment. However, irrespective of the study design to be different from other primary preventive statin studies, a clearly defined high risk patient population with a positive benefit/risk of rosuvastatin treatment has been identified. In clinical practice, it is expected that, as with other high risk groups in other statin trials, these patients can be identified in clinical practice.

As LDL-C was only measured at visit 1, patients could have been included with LDL-C levels > 3.36 mmol/L at time of randomisation. It is unlikely though that, LDL-C levels fluctuated extensively between visit 1 and 3, and it is therefore not expected that this would have significantly changed the outcome of the study.

In addition, inclusion based on hsCRP was based on the mean of visit 1 and 2. This raises the question whether some patients were no longer eligible after visit 3 because elevation was no longer present. However, since hsCRP is not considered in the final indication proposed, this is acceptable.

III.3.2.4 Measuring efficacy

Study subjects were asked about possible primary clinical endpoints every 3 months as indicated in the study plan. Each suspected endpoint was adjudicated by two independent physician reviewers.
A *post-hoc* analysis of the primary endpoint was also conducted including all events confirmed by the CEC (Clinical Evaluation Committee) as meeting the definition of a primary endpoint through subjects' final visits.

Comments RMS:
The method of measuring efficacy and the adjudication of the primary endpoint is sufficiently assured.

III.3.2.5 Efficacy assessment
Primary endpoint: Time to first occurrence of a major cardiovascular event (cardiovascular death, stroke, MI, hopitalization due to unstable angina, or arterial revascularization).
Secondary endpoints: Time to first occurrence of the following:
− total mortality
− noncardiovascular mortality
− discontinuation of blinded study medication due to adverse effects
− development of diabetes mellitus
− development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
− bone fractures
− incidence of adverse events
− incidence of abnormal laboratory values.

Comments RMS:
The chosen primary endpoint is the more often used MACE (major adverse cardiac event) endpoint. In line with the CV disease prevention guideline [EMA/CHMP/EWP/311890/2007] composite endpoints in prevention trials with low event rates are considered acceptable but should consist of hard clinical events. Arterial revascularisation and hospitalization due to unstable angina are endpoints subjective to clinician decision making and as such considered less robust. When statistical significance is primarily driven by the subjective component(s) in the endpoint, this can be considered a problem. Therefore, the assessment of the individual components of the composite endpoint is considered to be important. In this case CV death is objectively and conservatively defined and part of the composite endpoint, which is acceptable, provided that non-CV mortality and all cause mortality are not negatively affected.

The other secondary endpoints are not adjudicated separately, which is acceptable as no specific efficacy claims are made. These endpoints are of considerable interest for assessing any safety signal of using this potent statin in a relatively healthy population for an undefined but likely life-long duration.

III.3.2.6 Patient demographics at baseline

17,802 patients were randomized in 2 treatment arms (rosuvastatin and placebo) to produce a minimum of the planned 6,000 evaluable patients in each randomized group (see also figure 1). Table 1 shows that approximately similar numbers of patients deviated from the protocol for similar reasons.

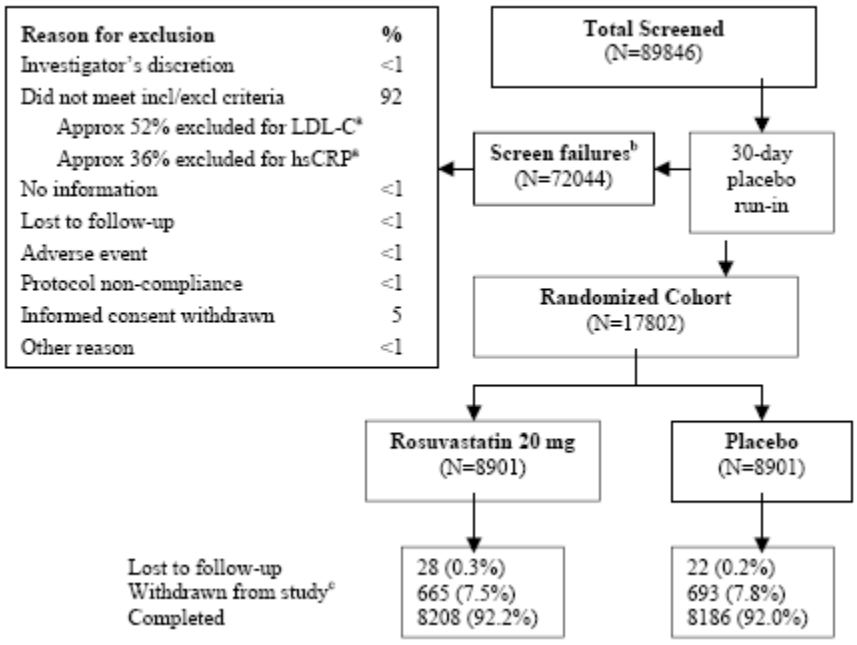


Figure 2: JUPITER patient disposition

Table 1: Protocol deviations during study follow-up

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
Protocol deviation	**n**	**(%)**	**n**	**(%)**
Misrandomization (randomized out of sequence)	137	(1.5)	128	(1.4)
Ineligible (violated entry criteria)	24	(0.3)	30	(0.3)
Compliance with study medication (<80% over entire study)	1085	(12.2)	1152	(12.9)
Started disallowed statin medication after randomization	140	(1.6)	295	(3.3)
Developed criteria for discontinuing study medication but did not stop medication	79	(0.9)	86	(1.0)
Received incorrect study medication	328	(3.7)	323	(3.6)

Data derived from Table 11.1.1.9.2.1

Comments RMS:

Ninety-two percent of all screened patients were excluded from the trial mainly because they did not meet criteria with respect to LDL-C and hsCRP levels. These are patients who are not expected to visit a clinician for cardiovascular problems. However, irrespective whether the study design is different from other primary preventive statin studies, a clearly defined high cardiovascular risk patient population with a positive benefit/risk of rosuvastatin treatment has been identified in the trial based on acknowledged CV risk factors as discussed below. In clinical practice, it is expected that, as with other high risk groups in other statin trials, these patients can be identified in clinical practice.

Nearly 8% of patients withdrew from the study in both treatment arms. Reasons for withdrawal were similar, and therefore acceptable.

Table 2: Baseline characteristics

		Treatment group		
		Rosuvastatin 20 mg (N=8901)	Placebo (N=8901)	Overall (N=17802)
Demographic characteristics				
Gender, n (%) of subjects	Male	5475 (61.5)	5526 (62.1)	11001 (61.8)
	Female	3426 (38.5)	3375 (37.9)	6801 (38.2)
	Not recorded	0	0	0
Age (years) at entry	Mean (SD)	66.0 (7.64)	66.0 (7.79)	66.0 (7.71)
	Median	66.0	66.0	66.0
	Range	49 to 94	50 to 97	49 to 97
Age group at entry,[a] n (%)				
Males	<50 years	1 (0.0)	0	1 (0.0)
	50-64 years	3044 (55.6)	3144 (56.9)	6188 (56.2)
	65-74 years	1838 (33.6)	1722 (31.2)	3560 (32.4)
	75+ years	592 (10.8)	660 (11.9)	1252 (11.4)
	Not recorded	0	0	0
Females	<60 years	1 (0.0)	1 (0.0)	2 (0.0)
	60-74 years	2755 (80.4)	2733 (81.0)	5488 (80.7)
	75-84 years	618 (18.0)	572 (16.9)	1190 (17.5)
	85+ years	52 (1.5)	69 (2.0)	121 (1.8)
	Not recorded	0	0	0
Race, n (%)	Caucasian	6358 (71.4)	6325 (71.1)	12683 (71.2)
	Black	1100 (12.4)	1124 (12.6)	2224 (12.5)
	Asian	147 (1.7)	136 (1.5)	283 (1.6)
	Hispanic	1121 (12.6)	1140 (12.8)	2261 (12.7)
	Other	173 (1.9)	176 (2.0)	349 (2.0)
	Not recorded	2 (0.0)	0	2 (0.0)
Baseline characteristics				
Education, n (%)	≤High school	5294 (59.5)	5281 (59.3)	10575 (59.4)
	Some college	1532 (17.2)	1608 (18.1)	3140 (17.6)
	College graduate	1276 (14.3)	1306 (14.7)	2582 (14.5)
	Post-graduate	789 (8.9)	704 (7.9)	1493 (8.4)
	Not recorded	10 (0.1)	2 (0.0)	12 (0.1)
Exercise,[b] n (%)	Rarely/never	4490 (50.4)	4588 (51.5)	9078 (51.0)
	<once a week	462 (5.2)	461 (5.2)	923 (5.2)
	Once a week	568 (6.4)	590 (6.6)	1158 (6.5)
	2-3 times/week	1574 (17.7)	1460 (16.4)	3034 (17.0)

	4-6 times/week	697 (7.8)	713 (8.0)	1410 (7.9)
	Daily	1105 (12.4)	1086 (12.2)	2191 (12.3)
	Not recorded	5 (0.1)	3 (0.0)	8 (0.0)
Alcohol consumption[c]	Never or <1/month	4124 (46.3)	4024 (45.2)	8148 (45.8)
n (%)	1-3 drinks/month	1113 (12.5)	1140 (12.8)	2253 (12.7)
	1-4 drinks/week	1448 (16.3)	1486 (16.7)	2934 (16.5)
	5-6 drinks/week	587 (6.6)	559 (6.3)	1146 (6.4)
	1-3 drinks/day	1349 (15.2)	1376 (15.5)	2725 (15.3)
	4-5 drinks/day	199 (2.2)	232 (2.6)	431 (2.4)
	6+ drinks/day	77 (0.9)	81 (0.9)	158 (0.9)
	Not recorded	4 (0.0)	3 (0.0)	7 (0.0)
Current smoking	(Last month)	1400 (15.7)	1420 (16.0)	2820 (15.8)
Hypertension, n (%)		5079 (57.1)	5129 (57.6)	10208 (57.3)
Family history of CHD, n (%)		997 (11.2)	1048 (11.8)	2045 (11.5)
Low HDL, <40 mg/dL (1.04 mmol/L), n (%)		1980 (22.2)	2023 (22.7)	4003 (22.5)
Family history of stroke, n (%)		1792 (20.1)	1873 (21.0)	3665 (20.6)
Family history of diabetes, n (%)		2069 (23.2)	2101 (23.6)	4170 (23.4)
FSG ≥100 mg/dL (5.6 mmol/L)[d], n (%)		2755 (31.0)	2817 (31.6)	5572 (31.3)
Framingham risk score	Mean (SD)	11.6 (7.0)	11.6 (6.9)	11.6 (7.0)
Framingham risk	Low, n (%)	3615 (40.6)	3602 (40.5)	7217 (40.5)
category[e]	Intermediate, n (%)	4485 (50.4)	4516 (50.7)	9001 (50.6)
	High, n (%)	786 (8.8)	772 (8.7)	1558 (8.8)
	Not calculable, n (%)	15 (0.2)	11 (0.1)	26 (0.1)
SCORE risk score[f]	Mean (SD)	7.27 (6.6)	7.30 (6.5)	7.29 (6.5)
	<5, n (%)	4267 (47.9)	4207 (47.3)	8474 (47.6)
	≥5, n (%)	4619 (51.9)	4683 (52.6)	9302 (52.3)
	Not calculable, n (%)	15 (0.2)	11 (0.1)	26 (0.1)
eGFR, mL/min/1.73 m^2	Mean (SD)	75.4 (17.5)	75.4 (17.3)	75.4 (17.4)
	Median	73.3	73.6	73.6
	Range	27-206	21-181	21-206

Body mass index, kg/m^2	Mean (SD)	29.1 (6.69)	29.0 (5.67)	29.0 (6.20)
	Median	28.3	28.4	28.4
Waist circumference (cm)				
Men	Mean (SD)	100.9 (13.52)	100.9 (13.59)	100.9 (13.56)
	Median	100.0	100.0	100.0
Women	Mean (SD)	95.8 (13.90)	95.9 (13.95)	95.9 (13.92)
	Median	95.0	95.0	95.0
Systolic BP, mmHg	Mean (SD)	135.6 (16.75)	135.6 (16.79)	135.6 (16.77)
	Median	134.0	134.0	134.0
Diastolic BP, mmHg	Mean (SD)	80.7 (9.09)	80.7 (8.96)	80.7 (9.02)
	Median	80.0	80.0	80.0
Pulse, bpm	Mean (SD)	70.4 (9.65)	70.4 (9.84)	70.4 (9.74)
	Median	70.0	70.0	70.0

Total cholesterol	8899	183 (24.7)	8901	183 (24.2)	183 (24.4)
Triglycerides, median	8899	118 (73.4)	8901	118 (73.5)	118 (73.4)
HDL-C	8899	51 (15.3)	8901	51 (15.2)	51 (15.3)
LDL-C	8899	104 (18.9)	8899	105 (18.5)	104 (18.7)
Apolipoprotein A-I	8863	166 (31.0)	8857	165 (30.5)	165 (30.7)
Apolipoprotein B	8861	109 (21.7)	8856	109 (21.0)	109 (21.4)
hsCRP[g], median	**N**	**mg/L[h]**	**N**	**mg/L[h]**	**mg/L[h]**
Men and women	8901	4.2	8901	4.3	4.3
Men	5475	4.0	5526	4.1	4.1
Women	3426	4.6	3375	4.7	4.6

Metabolic syndrome	Yes	3652 (41.0)	3725 (41.8)	7377 (41.4)
	No	5218 (58.6)	5146 (57.8)	10364 (58.2)
	Unknown[a]	31 (0.3)	30 (0.3)	61 (0.3)
Criteria for the metabolic syndrome				
Waist circumference	>40 inches (men)[b]	2349 (42.9)	2375 (43.0)	4724 (42.9)
	>35 inches (women)[b]	2317 (67.6)	2295 (68.0)	4612 (67.8)
Triglycerides	>150 mg/dL[b]	2899 (32.6)	2936 (33.0)	5835 (32.8)
SBP ≥130 or DBP ≥85 mmHg		7068 (79.4)	7088 (79.6)	14156 (79.5)
Fasting blood glucose ≥100 mg/dL		2755 (31.0)	2817 (31.6)	5572 (31.3)
HDL-C	<40 mg/dL[b] (men)	1612 (29.4)	1626 (29.4)	3238 (29.4)
	<50 mg/dL[b] (women)	1220 (35.6)	1230 (36.4)	2450 (36.0)
Number of metabolic syndrome criteria[c]				
	0[d]	595 (6.7)	606 (6.8)	1201 (6.7)
	1	2053 (23.1)	1992 (22.4)	4045 (22.7)
	2	2570 (28.9)	2548 (28.6)	5118 (28.7)
	3	2050 (23.0)	2082 (23.4)	4132 (23.2)
	4	1194 (13.4)	1241 (13.9)	2435 (13.7)
	5	408 (4.6)	402 (4.5)	810 (4.6)

1 risk factor (age only[a]), n (%)	2199 (24.7)	2080 (23.4)	4279 (24.0)
2 risk factors[b], n (%)	4373 (49.1)	4423 (49.7)	8796 (49.4)
3 risk factors[b], n (%)	1931 (21.7)	2017 (22.7)	3948 (22.2)
4 risk factors[b], n (%)	371 (4.2)	361 (4.1)	732 (4.1)
5 risk factors[b], n (%)	27 (0.3)	20 (0.2)	47 (0.3)

Over 75% of subjects had 2 or more conventional risk factors (older age [men ≥50 years, women ≥60 years]; hypertension; low HDL-C; cigarette smoking; or a family history of premature CHD). As targeted, the randomized population had low baseline LDL-C levels (mean 104 mg/dL [2.70 mmol/L]). At baseline, the median hsCRP level was 4.3 mg/L. Approximately 70% of subjects had hsCRP >3 mg/L and 30% of subjects had a hsCRP ≤3 mg/L.

Comments RMS:
Disposition and protocol deviations were approximately similar between both treatment arms and are therefore not expected to affect the observed results.

The trial is restricted to patients of medium to older age. Twenty five percent of patients had no other CV risk factor. However, more than 50% had two and 25% three or more established CV risk factors. This resulted in approximately half of the patients being at intermediate or high CV risk according to the Framingham or SCORE (see table 2) risk scores that may have been eligible to statin therapy also according to current treatment guidelines. Therefore, as expected (see above) the study included a heterogeneous group of patients, containing not only a low risk, but also an intermediate/high risk population. Also, approximately 60% of patients had hypertension, the mean eGFR was only 73 ml/min, and the mean BMI of 29 was high.

Therefore, different conclusions of the benefit/risk balance may apply to the low or intermediate/high risk subgroups. However, a CV prevention indication for high risk patients was eventually proposed based on individual risk assessment by risk score (Framingham or SCORE). In JUPITER the observed relative risk reduction is indeed consistent across different risk groups, but more absolute beneficial effect, as expected, is observed in the highest risk patient groups (SCORE>5% and Framingham>20%). Treatment with statins of these high risk CV patients is also in line with current guidelines (e.g. ESC guideline CVD Prevention in clinical practice, EJCPR 2007; vol 14 (suppl 2:S1-S113). In these populations treatment with rosuvastatin shows similar absolute beneficial effects and NNTs as other statins. For instance, atorvastatin is also accepted for the primary prevention of CV events in high risk patients. Although in JUPITER patients were not included based on assessment of risk scores, these were prospectively assessed and an acceptable number of patients in the highest CV risk categories was included; 3130 on rosuvastatin, 3177 on placebo with a SCORE > 5% estimated 10-year risk of fatal cardiovascular disease.

III.3.2.7 Statistical analysis
The ITT population was the primary analysis population for efficacy analyses. The primary efficacy analysis used a likelihood ratio test based on a proportional hazards model to test the null hypothesis of

no association between rosuvastatin treatment and risk of the primary variable with an unadjusted proportional hazards model to estimate the HR with 95% CI. Kaplan-Meier plots were presented for time-to-event variables. The study was designed to provide sufficient power for the composite primary endpoint but not necessarily the individual components; however, to look for consistency of effect across components, separate analyses were done for each component of the primary endpoint The protocol did not specify control for multiplicity of testing secondary variables that were used to assess robustness of the primary endpoint.
Exploratory proportional hazards models of MCE and of the composite endpoint including cardiovascular death, nonfatal MI, and nonfatal stroke determined whether simultaneous control for pre-specified (in the SAP) baseline cardiovascular risk factors had any effect on the relative risk associated with randomized treatment. The likelihood ratio test was used to test for statistical significance of the interaction. A forest plot showed HRs and CIs of treatment effects within subgroups. Stopping rules were adequately predefined.

Sample size estimation
The sample size estimate included an assumption of a 25% reduction in the risk of sustaining a major cardiovascular event with rosuvastatin. This level of risk reduction was consistent with the 24% reduction in risk reported in the Heart Protection Study. In order to detect a 25% reduction from the placebo event rate with 90% power, the study needed to observe 514 events. This was rounded to 520 events. If the accrual period was 1 year and the mean follow-up was 3.5 years, then 12,000 subjects would have needed to be randomized; the sample size estimate was raised to 15,000 randomized subjects. Two interim analyses were planned at 37.5% (195 confirmed primary endpoints) and 75% (390 confirmed primary endpoints) of primary events.

Comments RMS:
Power calculation and sample size calculation are sufficiently justified. The proposed and conducted statistical methods are considered sufficient for calculating treatment effects of rosuvastatin on cardiovascular primary and secondary endpoints.

III.3.2.8 Efficacy results

Primary endpoint
There were 142 primary events in the rosuvastatin patients and 252 in the placebo group after the trial was earlier terminated after 1.9 years of mean follow-up (Event rate/ 1000 patient years 7.6 vs 13.6, p<0.001). This translated in a treatment effect of a 44% reduction in the risk of experiencing a primary endpoint event (HR: 0.56; 95% CI 0.46, 0.69; p <0.001). This was statistically significant within 6 months of randomization with rosuvastatin treatment (post-hoc HR 0.62; 95% CI 0.40, 0.96; p=0.029). For the combined endpoint of CV death/MI/stroke, 83 (0.9%) endpoints were observed for rosuvastatin versus 158 (1.8%) for placebo with a hazard ratio of 0.52 (95% CI 0.40-0.68, p<0.001).

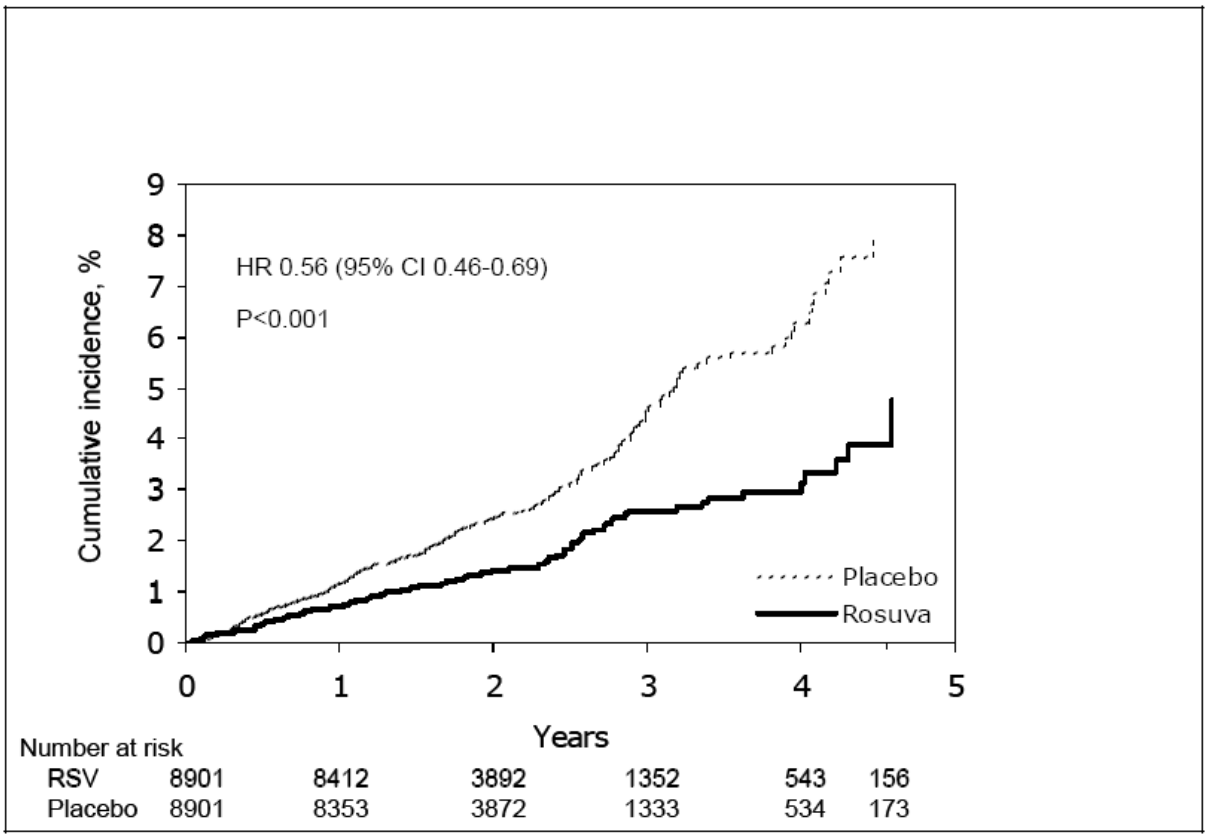


Figure 3: Kaplan-Meier curve of the primary composite endpoint

Individual components of the combined primary endpoint

As observed in table 3, rosuvastatin treatment was effective versus placebo in reducing the number of nonfatal strokes (p=0.003), nonfatal MIs (p<0.001), and arterial revascularizations (p<0.001). When stratifying the outcome according to CV risk scores (Framingham and SCORE), a similar treatment effects was observed, however, the absolute risk reduction was much lower for patients with a low risk score (see table 3).

Table 3: Number of events and treatment effect for individual components of the primary endpoint

	Number (%) of subjects with event[a]			
	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)	HR (95% CI)	P value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51, 1.24)	0.315
Nonfatal stroke	30 (0.3)	58 (0.7)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (0.2)	62 (0.7)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54 (0.41, 0.72)	<0.001

As could be expected patients with a lower CV risk as calculated by Framingham or Euro-SCORE had fewer MCE endpoints (table 4).

Table 4: Number of patients reaching primary endpoint according to their Framingham and Euro-SCORE risk scores

Risk stratum	n of MCE	n of subjects	HR (95% CI)	MCE event rate per 1000 patient-years		Absolute risk reduction per 1000 patient-years
				Rosuva 20 mg	Placebo	
Framingham[a,b]						
Low, ≤10%	105	8874	0.57 (0.38, 0.85)	4.2	7.4	3.2
Intermediate-High >10%	288	8902	0.55 (0.43, 0.70)	10.8	19.6	8.8
Euro-SCORE[c]						
Not high, <5%	100	8500	0.44 (0.29, 0.68)	3.5	7.9	4.4
High, ≥5%	294	9302	0.61 (0.48, 0.78)	11.5	18.8	7.3

In terms of absolute risk reduction (ARR), which take baseline risk into account, the benefit is greater in the high risk group than for the overall population as would be expected. The magnitude of ARR and number needed to treat (NNT) in the JUPITER study is in line with other large prevention studies, including ASCOT-LLA on which the atorvastatin primary prevention indication is partly based. For the primary endpoint in ASCOT-LLA, non-fatal MI plus fatal CHD, incidence is 6 per thousand per year in the atorvastatin group and 9.4 in the placebo group (Sever et al 2003), giving a total number of 300 patients to be treated one year to avoid one fatal or non-fatal MI. If fatal and non fatal stroke are added to the primary endpoint, assuming that stroke and coronary events are independent, the incidence of this composite endpoint is 11.4 per thousand in the atorvastatin group and 16.8 in the placebo group, giving a one year NNT of 180.

In JUPITER, the overall corresponding figures are 4.5 per 1000 patient years in the rosuvastatin group and 8.5 in the placebo group, giving a total number of 250 patients to be treated one year to avoid one fatal or non-fatal MI or stroke. In the high risk subgroup defined by SCORE ≥5% using the extrapolated model, the corresponding figures are 6.9 in the rosuvastatin group and 12 in the placebo group per 1000 patient years, giving a one year NNT of 190. Using the SCORE model with age capped at 65 years, the absolute risk reduction is 6.9 per 1000 patient years and a one year NNT of 144.
The following NNT values can be calculated for 2 years NNT; for the high risk subpopulation defined by SCORE ≥5%, the 2 year NNT for the endpoint major cardiovascular event (primary endpoint) is 75 and the 2 year NNT for the combined endpoint CV death/MI/stroke is 104. For the high risk subpopulation defined by Framingham >20%, the 2 year NNT for the endpoint major cardiovascular event (primary endpoint) is 75 and the 2 year NNT for the combined endpoint CV death/MI/stroke is 50.

Secondary endpoints

Table 5: Secondary endpoints

Endpoint	Rosuvastatin	Placebo	HR	95% CI	P value
Death	198 (2.2%)	247 (2.8%)	0.80	0.67, 0.97	0.021
Non CV Death	105 (1.2%)	126 (1.4%)	0.84	0.65, 1.08	0.172
Discontinuation due to AE	495	486	-	-	-
Development of DM	251 (2.8%)	205 (2.3%)	1.27	-	0.015
Venous thromboembolic events	26 (0.3%)	46 (0.5%)	0.57	0.35, 0.91	0.018
Bone fractures	226 (2.5%)	214 (2.4%)	1.06	0.88, 1.28	0.548

The percentage of randomized subjects permanently discontinuing study medication was 19.2% for the rosuvastatin group and 21.6% for the placebo group.

The risks for death and venous thromboembolic events were significantly lower, and for non-CV death also lower but not significant. The risk for diabetes mellitus demonstrated to be significantly higher on rosuvastatin treatment. The risk for bone fractures was slightly higher but not significant.

Laboratory efficacy findings

Table 6: Lipid related findings during follow-up

	Baseline		After 12 months		At Final visit (LOCF)	
	Rosuvastatin 20 mg	Placebo	Rosuvastatin 20 mg	Placebo	Rosuvastatin 20 mg	Placebo
TC (mg/dL)[a]						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	183.23 (24.71)	183.39 (24.16)	139.15 (33.31)	188.85 (30.02)	144.02 (35.87)	187.18 (31.24)
Median	186.00	185.00	133.00	188.00	137.00	188.00
Range	76.0 to 291.0	71.0 to 340.0	62.0 to 297.0	76.0 to 352.0	57.0 to 327.0	69.0 to 530.0
HDL-C (mg/dL)[a]						
N	8899	8901	7960	7927	8157	8151
Mean (SD)	51.36 (15.34)	51.26 (15.20)	54.66 (16.33)	52.22 (15.60)	55.36 (17.29)	53.26 (16.50)
Median	49.00	49.00	52.00	50.00	52.00	50.00
Range	11.0 to 145.0	13.0 to 145.0	12.0 to 164.0	10.0 to 149.0	18.0 to 165.0	8.0 to 180.0
LDL-C (mg/dL)[a]						
N	8899	8899	7949	7909	8154	8150
Mean (SD)	104.34 (18.91)	104.57 (18.51)	61.64 (27.57)	109.10 (25.02)	65.72 (30.39)	107.15 (25.99)
Median	108.00	108.00	55.00	110.00	57.00	108.00
Range	12.0 to 148.0	6.0 to 170.0	0.0 to 205.0	6.0 to 254.0	1.0 to 245.0	9.0 to 254.0
TG (mg/dL)[a]						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	137.76 (73.42)	137.80 (73.46)	114.91 (64.90)	138.39 (75.71)	115.25 (68.80)	134.39 (82.07)
Median	118.00	118.0	99.00	119.00	99.00	115.00
Range	19.0 to 499.0	24.0 to 496.0	18.0 to 1385.0	25.0 to 796.0	16.0 to 2146.0	12.0 to 3150.0
hsCRP (mg/L)[a,b]						
N	8901	8901	7950	7923	8613	8630
Mean (SD)	6.629 (8.588)	6.923 (9.169)	4.535 (9.857)	6.010 (10.259)	5.213 (10.720)	6.755 (12.051)
Median	4.200	4.300	2.200	3.500	2.600	3.700
Range	1.10 to 192.00	0.55 to 174.50	0.10 to 294.60	0.07 to 213.00	0.11 to 294.60	0.20 to 281.0

Variable values were observed for median hsCRP during run-in with 4.2 and 4.3 mg/dL at week -6, 3.7 and 3.8 mg/dL at week -4, and 4.2 and 4.3 at baseline for rosuvastatin and placebo, respectively.

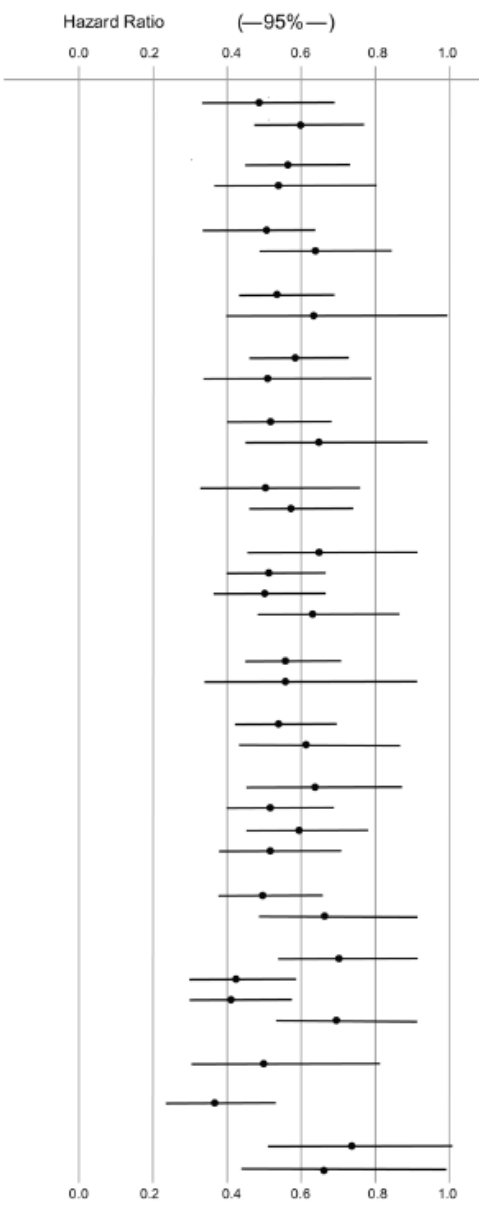
Mean LDL-C was 45% lower among rosuvastatin-treated subjects than placebo-treated subjects after 1 year ($p<0.001$). Median hsCRP levels were reduced 47% from baseline among rosuvastatin-treated subjects but were also reduced 20% from baseline among placebo-treated subjects after 1 year (the mean and median hsCRP were 29% and 27% lower for rosuvastatin; $p<0.001$); the median hsCRP level was 4.2 mg/L at baseline and remained above the 2.0 mg/L inclusion level (2.2 mg/L) at 1 year and 2.6 mg/L at final visit. The treatment group difference was maintained throughout the duration of the study ($p<0.001$ at each timepoint).

Subgroup analyses

Treatment effect was stronger for patients with a LDL level above the median compared to LDL levels below the median. In contrast, treatment effect was less with hsCRP levels above the median compared to hsCRP levels below the median.

Table 7: Subgroup analyses

Baseline characteristic	N of events[a] Rosuva 20 mg (N=8901) n (rate)[a]	Placebo (N=8901) n (rate)[a]	HR (95% CI)	P value for interaction
Age				
≤65 years at baseline	42 (4.9)	90 (10.3)	0.48 (0.33, 0.69)	0.338
>65 years at baseline	100 (9.9)	162 (16.6)	0.60 (0.47, 0.77)	
Sex				
Male	103 (8.8)	182 (15.5)	0.57 (0.45, 0.73)	0.817
Female	39 (5.6)	70 (10.4)	0.54 (0.37, 0.80)	
Age by sex				
Male <65 y, Female <75 y	55 (4.7)	120 (10.1)	0.46 (0.34, 0.64)	0.128
Male ≥65 y, Female ≥75 y	87 (12.9)	132 (20.1)	0.64 (0.49, 0.84)	
Race				
Caucasian	111 (7.8)	202 (14.4)	0.54 (0.43, 0.69)	0.561
Non-Caucasian	31 (7.0)	50 (11.1)	0.63 (0.40, 0.99)	
Smoker				
No	110 (6.9)	190 (12.1)	0.58 (0.46, 0.73)	0.644
Yes	32 (11.7)	62 (22.6)	0.51 (0.34, 0.79)	
Body Mass Index				
≤30 kg/m²	94 (8.2)	179 (15.9)	0.52 (0.40, 0.67)	0.313
>30 kg/m²	47 (6.6)	73 (10.2)	0.65 (0.45, 0.94)	
HDL-C				
< 40 mg/dL (1.0 mmol/L)	32 (7.6)	65 (15.3)	0.50 (0.33, 0.76)	0.512
≥40 mg/dL (1.0 mmol/L)	110 (7.7)	187 (13.1)	0.58 (0.46, 0.74)	
LDL-C				
≤100 mg/dL (2.6 mmol/L)	55 (8.7)	86 (13.5)	0.65 (0.46, 0.91)	0.304
>100 mg/dL (2.6 mmol/L)	87 (7.1)	166 (13.7)	0.52 (0.40, 0.67)	
Above median[b]	68 (7.0)	138 (14.1)	0.50 (0.37, 0.67)	0.236
Below median[b]	74 (8.3)	114 (13.1)	0.64 (0.48, 0.86)	
Triglycerides				
<200 mg/dL (2.2 mmol/L)	117 (7.6)	208 (13.6)	0.56 (0.45, 0.71)	0.974
≥200 mg/dL (2.2 mmol/L)	25 (7.7)	44 (13.7)	0.56 (0.34, 0.91)	
Hypertension				
Yes	89 (8.5)	166 (15.8)	0.54 (0.42, 0.70)	0.559
No	53 (6.6)	86 (10.8)	0.61 (0.43, 0.86)	
Region				
US	58 (10.7)	94 (16.9)	0.63 (0.45, 0.87)	0.395
Countries other than US	84 (6.4)	158 (12.2)	0.52 (0.40, 0.68)	
US or Canada	81 (9.7)	137 (16.3)	0.60 (0.45, 0.78)	0.536
Countries other than US/Canada	61 (6.0)	115 (11.4)	0.52 (0.38, 0.71)	
Metabolic syndrome				
No	75 (6.9)	149 (14.0)	0.50 (0.38, 0.66)	0.167
Yes	67 (8.7)	102 (13.1)	0.67 (0.49, 0.91)	
Baseline hsCRP				
above median[b]	89 (9.7)	128 (13.7)	0.71 (0.54, 0.92)	0.015
below median[b]	53 (5.6)	124 (13.5)	0.42 (0.30, 0.58)	
≤4 mg/L	50 (5.6)	119 (13.8)	0.41 (0.30, 0.57)	0.014
>4 mg/L	92 (9.5)	133 (13.5)	0.70 (0.54, 0.91)	
Baseline LDL-C and hsCRP				
below median LDL and hsCRP	24 (5.6)	47 (11.3)	0.50 (0.30, 0.81)	
above median LDL and below median hsCRP	29 (5.7)	77 (15.3)	0.37 (0.24, 0.57)	
below median LDL and above median hsCRP	50 (10.9)	67 (14.7)	0.74 (0.51, 1.07)	
above median LDL and hsCRP	39 (8.5)	61 (12.8)	0.66 (0.44, 0.99)	0.094



Comments RMS:

Rosuvastatin demonstrated a statistically significant reduction in the risk for the composite primary endpoint. The trial was discontinued early by the Data Monitoring Board, since a predefined difference in subjects reaching the primary endpoint had been observed; 142 events in the rosuvastatin versus 252 in the placebo groups.

Considering the individual components of the primary endpoint 40 percent (202 out of 496) were related to coronary vascularisation procedures, which is subjective to clinical decision making, but significant effects were also noted for the occurrence of non-fatal MI and stroke and a trend for hospitalizations due to unstable angina. Only numerically a benefit was seen for CV death, but a significant reduction was seen in overall death that was measured during the whole study as a secondary endpoint.

Beneficial effects are reported as (reductions in) relative risk. However, the overall absolute risk reduction was only 0.9% for the combination of the more robust endpoints CV death, MI and stroke (Citrome, Int J Clin Pract, 2009). The absolute risk reduction, in addition to expression as number needed to treat, puts the beneficial effect of rosuvastatin into a better perspective in the discussion on the benefit/risk of treating patients (and certainly low-risk patients) with rosuvastatin. For the high risk patient group in JUPITER the NNT is in line with other primary prevention trials.

Although hsCRP is eventually not proposed to be used as a prognostic tool for clinical management in the indication some argumentation why it was eventually excluded is discussed below. The design and results of the trial provide only limited information on the value of hsCRP testing as a prognostic tool for clinical management. The trial did not compare subjects with and without high hsCRP, nor was hsCRP compared with other CV risk factors. Subgroup analyses demonstrated a negative correlation with hsCRP value at baseline (lower hsCRP, better effect and visa versa), although it is acknowledged that this was the opposite in other clinical trials. Importantly, with increasing baseline risk (eg indicated by higher CRP levels) the effect of cardiovascular preventive interventions can be expected to increase and not decrease. In contrast to hsCRP, in the JUPITER trial LDL-C at baseline did indeed show the expected greater reduction in CV events for patients with a higher baseline LDL level, whereas no other (single risk factor) subgroup analysis demonstrated a significant p for interaction with treatment effect. In addition, high variability was observed in the hsCRP measurements. The difference in hsCRP-levels between visit 1 and 2 (2 weeks difference) was approximately 12%, and placebo hsCRP-levels were reduced by approximately 20% during the first year. Standardisation of the method may be an additional problem between different laboratories.
HsCRP has currently not been recognized as a biomarker for cardiovascular risk prevention by the EMA. While the association between between CRP and risk of cardiovascular disease is not doubted, (hs)CRP is a nonspecific biomarker and considered to be of limited predictive value of CV events (Hingorani et al Clin Chem 2009). [Of note: Early 2011 in a post hoc analysis of the Heart Protection Study it was shown that statin treatment was associcated with a similar reduction in vascular events irrespective of baseline concentrations of CRP (Heart Protection Study Collaborative Group. Lancet 2011)]

With respect to the other secondary endpoints a significant increase in patients diagnosed with diabetes is observed. This is discussed further in the safety section.

III.3.2.7 Supportive studies
N/A

III.3.2.8 Clinical studies in special populations
No submitted data.

III.3.2.9 Analysis performed across trials (pooled analyses and meta-analysis)
No submitted data.

III.3.3 Clinical safety

III.3.3.1 Patient exposure

The safety population included all subjects who were randomized and who started treatment. There were 17,733 subjects in the safety population (8869 randomized to rosuvastatin treatment and 8864 randomized to placebo treatment). Additionally, 1 subject was not properly randomized in the IVRS, but did receive study medication. This individual was excluded from all analyses.

Table 8: Overview of exposure

Exposure by duration of treatment (days)[a]	Rosuvastatin 20 mg (N=8869)	Placebo (N=8864)
Mean (SD)	700.5 (358.19)	689.5 (352.00)
Median	657.0	648.0
Range	0 to 1827	0 to 1967

Assessor's comments
Exposure to treatment assignment was approximately similar.

III.3.3.2 Adverse events

General adverse events

Table 9: General findings on adverse events

Category of adverse event	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any AE	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
AE leading to discontinuation from the study (DAE)	143 (1.6)	158 (1.8)
Serious AE (SAE)	1341 (15.1)	1372 (15.4)

Table 10: Most common adverse events

Preferred term	Rosuva 20 mg (N=8901)		Placebo (N=8901)	
	n	(%)	n	(%)
Most common treatment-emergent AE[a]				
Urinary tract infection	772	(8.7)	764	(8.6)
Nasopharyngitis	679	(7.6)	642	(7.2)
Back pain	679	(7.6)	616	(6.9)
Myalgia	678	(7.6)	590	(6.6)
Bronchitis	643	(7.2)	631	(7.1)
Upper respiratory tract infection	630	(7.1)	676	(7.6)
Hypertension	624	(7.0)	695	(7.8)
Arthritis	516	(5.8)	495	(5.6)
Cough	475	(5.3)	472	(5.3)
Bone pain	449	(5.0)	451	(5.1)
Diarrhoea	417	(4.7)	406	(4.6)

For the system/organ classification groups 'hepatobiliary' and 'renal and urinary disorders', there was no difference in the frequencies between the rosuvastatin or placebo groups. By MedDRA preferred term, the most commonly occurring AEs were urinary tract infection (rosuvastatin 8.7%, placebo 8.6%), followed by nasopharyngitis (rosuvastatin 7.6%, placebo 7.2%), back pain (rosuvastatin 7.6%, placebo 6.9%), and myalgia (rosuvastatin 7.6%, placebo 6.6%).

Discontinuation due to adverse events

Discontinuation due to adverse events was slightly lower for rosuvastatin than for placebo (1.6% vs. 1.8%). However, the highest number of discontinuations was for musculoskeletal disorders and gastrointestinal disorders and were highest in the rosuvastatin group (musculoskeletal disorders (37 (0.4%) vs 31 (0.3%)) and gastrointestinal disorders (22 (0.2%) vs 11 (0.1%)).
One of the secondary outcome endpoints of the JUPITER study was time to discontinuation of study medication due to AEs.

Comments RMS:
The safety profile of rosuvastatin is already well established as there is a large database of patients treated with rosuvastatin and several PSURs have been submitted and evaluated after registration. In the relatively low risk CV patients included in the JUPITER trial the 20 mg dose was well tolerated. A higher frequency of adverse events was reported for known adverse events associated with rosuvastatin in particular myalgia, but differences were small. This also applied to discontinuations due to adverse events, which was higher for musculoskeletal disorders and gastrointestinal disorders. This is in accordance with the known safety profile.

III.3.3.3 Serious adverse events and deaths
Investigators categorized 4 AEs leading to death as treatment-related: 1 in the rosuvastatin treatment group (pneumonia) and 3 in the placebo group (acute renal failure, colon cancer, pulmonary embolism). There were 13 rosuvastatin-treated subjects who had treatment-emergent gastrointestinal AEs leading to death versus 1 placebo-treated subject. The higher number of gastrointestinal deaths in the rosuvastatin group was, according to the MAH, due to very small numbers of deaths that were widely dispersed among specific gastrointestinal organs and had no specific pattern. Rosuvastatin-treated subjects had gastrointestinal death reported by investigators to be due to gastrointestinal haemorrhage (2 subjects), pancreatitis acute (2), peritonitis (2), abdominal pain (1), duodenal ulcer (1), gastrooesophageal reflux disease (1), inguinal hernia (1), intestinal obstruction (1), intra-abdominal haemorrhage (1), oesophageal haemorrhage (1), and oesophageal rupture (1).

Table 11: Adverse events leading to death

System organ class	Rosuva 20 mg (N=8901)		Placebo (N=8901)	
	n	**(%)**	**n**	**(%)**
Any death	**141**	**(1.6)**	**179**	**(2.0)**
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	40	(0.4)	65	(0.7)
General disorders and administration site conditions	39	(0.4)	40	(0.4)
Infections and infestations	22	(0.2)	24	(0.3)
Respiratory, thoracic, and mediastinal disorders	14	(0.2)	20	(0.2)
Gastrointestinal disorders	13	(0.1)	1	(0.0)
Cardiac disorders	8	(0.1)	8	(0.1)
Injury, poisoning, and procedural complications	3	(0.0)	8	(0.1)
Nervous system disorders	3	(0.0)	4	(0.0)
Psychiatric disorders	3	(0.0)	1	(0.0)
Metabolism and nutrition disorders	2	(0.0)	0	
Vascular disorders	2	(0.0)	5	(0.1)
Blood and Lymphatic system disorders	1	(0.0)	0	
Hepatobiliary disorders	1	(0.0)	1	(0.0)
Renal and urinary disorders	1	(0.0)	4	(0.0)

Table 12: Serious adverse events

	Rosuva 20 mg (N=8901)		Placebo (N=8901)	
System organ class	**n**	**(%)**	**n**	**(%)**
Any SAEs	**1341**	**(15.1)**	**1372**	**(15.4)**
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	286	(3.2)	306	(3.4)
Infections and infestations	215	(2.4)	234	(2.6)
Gastrointestinal disorders	193	(2.2)	172	(1.9)
Injury, poisoning, and procedural complications	164	(1.8)	150	(1.7)
Cardiac disorders	157	(1.8)	181	(2.0)
Musculoskeletal and connective tissue disorders	154	(1.7)	140	(1.6)
Respiratory, thoracic, and mediastinal disorders	111	(1.2)	122	(1.4)
General disorders and administration site conditions	93	(1.0)	100	(1.1)
Nervous system disorders	89	(1.0)	92	(1.0)
Hepatobiliary disorders	58	(0.7)	61	(0.7)
Renal and urinary disorders	57	(0.6)	78	(0.9)
Vascular disorders	46	(0.5)	74	(0.8)
Reproductive system and breast disorders	43	(0.5)	41	(0.5)
Metabolism and nutrition disorders	35	(0.4)	37	(0.4)
Psychiatric disorders	28	(0.3)	16	(0.2)
Blood and lymphatic system disorders	27	(0.3)	33	(0.4)
Eye disorders	14	(0.2)	20	(0.2)
Skin and subcutaneous tissue disorders	13	(0.1)	12	(0.1)
Endocrine disorders	12	(0.1)	7	(0.1)

SOCs with the greatest number of rosuvastatin severe AEs were neoplasms, infections and infestations, and gastrointestinal disorders. A slightly higher frequency of severe AEs for rosuvastatin were found for gastrointestinal disorders, musculoskeletal and connective tissue disorders, and psychiatric disorders, while infections and infestations, cardiac disorders, respiratory thoracic and mediastinal disorders, renal and urinary disorders, vascular disorders, and blood and lymphatic system disorders were slightly lower.

Comments RMS:
Numerically, fewer deaths were observed in the rosuvastatin group. The number of deaths related to GI disorders (both treatment related and unrelated) may pose a signal and should be followed closely in the PSUR cycle. Overall, similar levels of serious adverse events are observed between both treatment groups. Reassuringly, earlier identified potential rosuvastatin-related serious adverse events; neoplasms, hepatobiliary and renal and urinary disorders, were all reported less frequently in the active treatment arm. Also musculoskeletal disorders were only slightly increased, but high-risk patients were excluded (see also below).

III.3.3.3 Specific adverse events

Diabetes
Development of diabetes mellitus (DM) was a secondary endpoint in the JUPITER study. DM was included as an endpoint, because at time of the design of the study the results from the WOSCOPS study suggested a potential risk reducing effect on the development of diabetes with pravastatin.

In the JUPITER study, new onset of diabetes mellitus was defined as reported new use of insulin or an oral hypoglycaemic agent, a history of having a positive glucose tolerance test, a random glucose level over 200 mg/dL (11.1 mmol/L) or repeated fasting glucose levels in excess of 126 mg/dL (7.0 mmol/L) (see case report form, figure 4). These cases were reported by the investigator, and not centrally adjudicated (there is no confirmation that a diagnosis of diabetes was made before, for example, treatment with an oral hypoglycaemic agent was initiated). DM was reported by investigators in 251 (2.8%) rosuvastatin-treated subjects and 205 (2.3%) placebo subjects. A proportional Cox regression analysis demonstrated a significantly higher Hazard Ratio for rosuvastatin (unadjusted HR 1.27, 95% CI 1.05, 1.53; p=0.0015; K-M plot figure 5). The analysis on diabetes-free survival (measuring the occurrence of DM or death as a combined end-point) did not find a higher risk for rosuvastatin (HR 1.02; 95% CI 0.89, 1.16; p=0.817).

Secondary Endpoint Report

Diabetes Mellitus

Date of diagnosis [2][0] year mm dd

Diagnosis confirmed by: (Check all that are applicable)

	No	Yes
New use of insulin	☐	☐
New use of oral hypoglycemic agent	☐	☐
Positive glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L) at 2 hours	☐	☐
Repeated fasting glucose > 126 mg/dL (7.0 mmol/L)	☐	☐
Random blood sugar ≥ 200 mg/dL (11.1 mmol/L) associated with symptoms of polyuria, polydipsia, and unexplained weight loss	☐	☐

Patients with DM endpoints (table 11.3.6.1.2.12)

rosuvastatin		placebo	
n	%	n	%
8	0,09	5	0,06
122	1,37	106	1,19
55	0,62	38	0,43
151	1,70	130	1,46
28	0,31	19	0,21

Figure 4: Case report form Diabetes Mellitus JUPITER

Investigators could have assigned one or more of these criteria to diagnose diabetes mellitus (figure 4). Most reports were based on repeated fasting glucose >126 mg/dL (63%) or new use of an oral hypoglycaemic agent (52%). New use of insulin was reported in only 8 subjects in the rosuvastatin group and 5 subjects in the placebo group (figure 4).

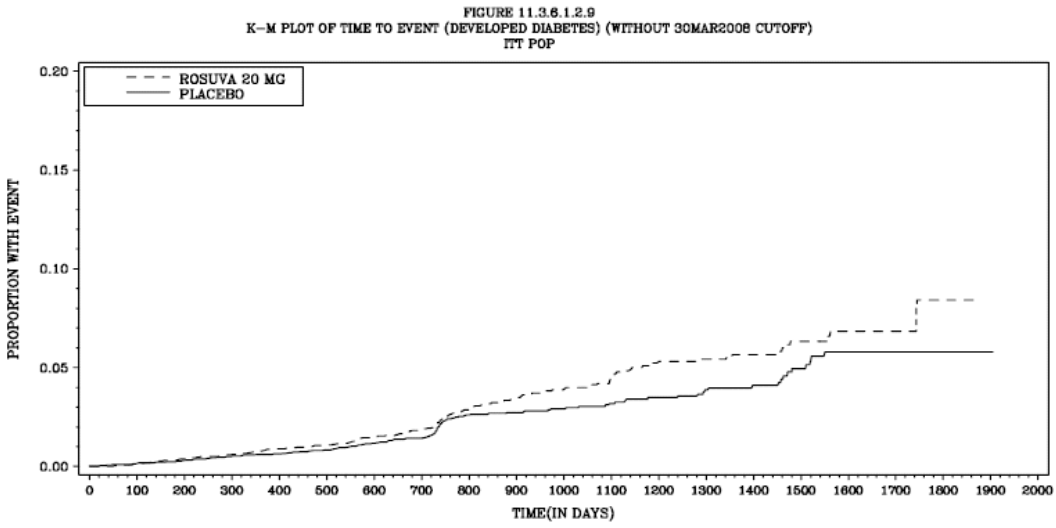


Figure 5: KM-plot, time to investigator reported diabetes, JUPITER.

Fasting glucose and glycosylated hemoglobin were measured at baseline, year 2, annually thereafter, and at the final visit. Subjects were assessed for clinical endpoints, including the diabetes endpoint, every 3 months.

Although more patients treated with rosuvastatin experienced investigator reported DM compared with placebo-treated patients, change (based on measurements in the central laboratory) in mean fasting glucose (rosuvastatin 3 mg/dL, placebo 3 mg/dL, p=0.078) and HbA1c levels (rosuvastatin 0.30 %, placebo 0.22%, p<0.001) differed only marginally at final measurement compared to baseline (table 13 and 14). However, HbA1c was significantly higher during follow-up for the rosuvastatin group versus the placebo group (table 14). The differences are all small though, less than 0.1%.

Table 13: Fasting glucose and change in fasting glucose during the trial

	Rosuvastatin 20 mg		Placebo		
	N	Mean value (SD)	N	Mean value (SD)	P value[a]
Fasting glucose, mg/dL					
Baseline	8875	95 (11.5)	8878	95 (11.8)	0.134
Year 2	3520	100 (17.9)	3502	100 (18.0)	0.344
Year 3	1198	100 (19.3)	1140	99 (15.9)	0.137
Year 4	440	99 (15.3)	414	98 (15.5)	0.147
Final	7124	98 (19.7)	7002	98 (18.9)	0.442
Change in fasting glucose, mg/dL					
Baseline to Year 2	3515	5 (16.0)	3499	4 (16.2)	0.057
Baseline to Year 3	1197	4 (17.0)	1140	3 (14.2)	0.097
Baseline to Year 4	440	2 (13.1)	414	2 (14.1)	0.423
Baseline to Final	7104	3 (18.3)	6985	3 (17.6)	0.078

Table 14: HbA1c and change in HbA1c during the trial

	Rosuvastatin 20 mg		Placebo		
	N	Mean value (SD)	N	Mean value (SD)	P value[a]
Hb_{A1c}, %					
Baseline	8856	5.7 (0.42)	8853	5.7 (0.45)	0.0014
Year 2	3514	5.9 (0.48)	3497	5.8 (0.47)	<0.0001
Year 3	1195	5.9 (0.46)	1134	5.8 (0.42)	<0.0001
Year 4	439	5.9 (0.49)	409	5.9 (0.43)	0.038
Final	7136	6.0 (0.50)	7054	6.0 (0.49)	<0.0001
Change in Hb_{A1c}, %					
Baseline to Year 2	3506	0.29 (0.34)	3480	0.19 (0.33)	<0.0001
Baseline to Year 3	1191	0.29 (0.33)	1131	0.19 (0.29)	<0.0001
Baseline to Year 4	438	0.31 (0.34)	406	0.21 (0.33)	<0.0001
Baseline to Final	7115	0.30 (0.35)	7013	0.22 (0.40)	<0.0001

In addition, the MAH provided data on developing diabetes mellitus based on these HbA1c or FSG measurements or both. Significantly more patients developed DM according to these criteria at every time point for HbA1c measurements (numbers of DM based on HBA1c at final visit: 12.6% vs 9.3%, p<0.001, table 14). Non-significant but higher numbers were found in FSG measurements (numbers of DM based on FSG at final visit: 5.9% vs 5.3%, p=0.151, table 15). Significant more numbers in the combined endpoint of HbA1c and FSG criteria at every years time point (numbers of DM based on HbA1c and FSG at final visit 15.3% vs 12.0%, p<0.001, table 16).

Table 15: Development of DM using HbA1c criteria (>6.5%)

DEVELOPED DIABETES MELLITUS	ROSUVA 20 MG N=8,901	PLACEBO N=8,901	P-VALUE [1]
MONTH 24 (OR WEEK 104)			
YES	326 / 3,474 (9.4)	227 / 3,454 (6.6)	<0.001
MONTH 36 (OR WEEK 156)			
YES	113 / 1,184 (9.5)	57 / 1,122 (5.1)	<0.001
MONTH 48 (OR WEEK 208)			
YES	45 / 431 (10.4)	24 / 401 (6.0)	0.020
FINAL			
YES	900 / 7,132 (12.6)	653 / 7,054 (9.3)	<0.001

Table 16: Development of DM using Fasting serum glucose criteria (>=126 mg/dL)

DEVELOPED DIABETES MELLITUS	ROSUVA 20 MG N=8,901	PLACEBO N=8,901	P-VALUE [1]
MONTH 24 (OR WEEK 104)			
YES	180 / 3,486 (5.2)	178 / 3,461 (5.1)	0.969
MONTH 36 (OR WEEK 156)			
YES	82 / 1,188 (6.9)	58 / 1,129 (5.1)	0.075
MONTH 48 (OR WEEK 208)			
YES	25 / 432 (5.8)	21 / 407 (5.2)	0.690
FINAL			
YES	422 / 7,120 (5.9)	374 / 7,000 (5.3)	0.151

Table 17: Development of DM using Fasting serum glucose or HbA1c criteria as a combined endpoint.

DEVELOPED DIABETES MELLITUS	ROSUVA 20 MG N=8,901	PLACEBO N=8,901	P-VALUE [1]
MONTH 24 (OR WEEK 104)			
YES	405 / 3,500 (11.6)	331 / 3,481 (9.5)	<0.001
MONTH 36 (OR WEEK 156)			
YES	152 / 1,192 (12.8)	93 / 1,132 (8.2)	<0.001
MONTH 48 (OR WEEK 208)			
YES	54 / 433 (12.5)	32 / 407 (7.9)	<0.001
FINAL			
YES	1,100 / 7,196 (15.3)	855 / 7,102 (12.0)	<0.001

The MAH further explores, baseline characteristics of study subjects who had or did not have investigator-reported DM (table 18) and reports that most of the cases of investigator-reported DM occurred among subjects who had prediabetes (fasting serum glucose (FSG) ≥100 mg/dL (5.6 mmol/L)).

Table 18: Baseline characteristics of subjects with and without investigator-reported diabetes

Baseline characteristics of subjects with and without investigator-reported diabetes

	Diabetes		No diabetes	
	Rosuva 20 mg	Placebo	Rosuva 20 mg	Placebo
N	251	205	8650	8696
Fasting serum glucose ≥100 mg/dL (5.6 mmol/L), %	76.5	76.1	29.6	30.6
Fasting serum glucose (mean), mg/dL[a]	107.3	108.8	94.3	94.6
BMI ≥25 kg/m^2, %	92.4	91.7	76.3	76.6
TG ≥150 mg/dL (1.7 mmol/L), %	57.0	51.7	31.9	32.5
Metabolic syndrome, %	77.7	79.0	40.0	41.0

Data derived from Table 26 of the Summary of Clinical Safety in Module 2, Section 2.7.4.
BMI Body mass index; TG Triglycerides; Rosuva Rosuvastatin.
[a] Fasting serum glucose conversion: mg/dL x 0.0555= mmol/L

The MAH reports a slightly greater weight gain during the period of follow-up in the rosuvastatin group when compared to placebo group (mean change 0.44 kg rosuvastatin vs 0.15 kg placebo). The MAH states that this raises the possibility that there may have been undetected differences in diet, exercise, or other lifestyle characteristics in a certain subset of subjects who received rosuvastatin versus placebo and that such differences account for the difference in investigator reported diabetes in the study.

Comments RMS:
Both numbers of new onset of DM and time to onset of new DM show a higher risk associated with the treatment of rosuvastatin, although differences were small. The MAH presented 2 HR to quantify the risk for DM: a) the Cox proportional HR from the analysis that censored subjects who died in the absence of reported diabetes that gave an HR of 1.27 (95% CI 1.05, 1.53; p=0.015); b) the difference in diabetes-free survival that analysed the occurrence of DM and/or death as a combined endpoint (HR 1.02; 95% CI 0.89, 1.16; p=0.817). Although estimate b) is nice to know from a public health point of view that takes into account both benefits and risks, measurement a) is appropriate when assessing whether rosuvastatin use is a risk factor for DM.
Information on DM endpoints was collected in a standardized way on a separate case report form designed to study DM as a secondary efficacy endpoint (figure 4). However, the DM endpoint was not centrally adjudicated, which could have introduced some subjectivity in the endpoint.
The numbers of new cases of DM presented in the definite study report are different from those presented in the original publication of Ridker, because analyses were based on investigator reported diabetes case report form in contrast to the academic investigators analyses also including cases identified through adverse event reporting, respectively.

Mean changes of annual measurements at the central lab of HbA1c levels differed only marginally in a non-clinical significant level (table 14), and FSG levels were similar (table 13). However, expressed as the number of DM cases based on these same HbA1c and FSG values during follow-up demonstrated a higher incidence of DM based on HbA1c measurements (table 15 and 16). These data, therefore, confirm the higher incidence of DM in the rosuvastatin treated group.

The observation of the MAH is supported that patients with a higher baseline risk of developing diabetes had a higher incidence of investigator reported diabetes compared to patients with lower baseline risk for diabetes. Although there are higher absolute risks for diabetes in both groups, the relative risks of developing diabetes were comparable in the subgroup of patients with normal fasting glucose at baseline (HR 1.33 [0.89-1.99]) and the patients with prediabetes at baseline (HR 1.28 [1.03-1.60]). The fact that rosuvastatin use was not significantly associated with the occurrence of DM among patients with normal fasting glucose levels at baseline could be related to the lower absolute numbers of patients with

diabetes observed and therefore a lack of power to identify a difference. We regard the excess risk of diabetes mellitus among pre-diabetic individuals treated with rosuvastatin to be established and it should be included in the RMP as an identified risk. Over a period of 5 years, 6.97% of the pre-diabetic individuals treated with rosuvastatine developed diabetes mellitus, compared to 5.54% of the placebo treated pre-diabetic individuals. The number needed to harm calculated from these absolute risks is 70 in 5 years. The excess risk among patients with normal fasting glucose levels remains inconclusive, and therefore should be mentioned under potential risks.
Whether this is increase in DM is due to rosuvastatin or whether confounding factors were present remains unclear. Possibly, weight gain could have contributed to the new onset of DM, but this currently remains only speculative.

Hepatic AEs

Table 19: Hepatic related adverse events

System organ class Preferred term	Rosuvastatin 20 mg (N=8901) n (%)	Placebo (N=8901) n(%)
Any hepatic-related AE[a]	216 (2.4)	186 (2.1)
Investigations	165 (1.9)	134 (1.5)
ALT increased	127 (1.4)	93 (1.0)
Hepatic enzyme increased	30 (0.3)	31 (0.3)
AST increased	7 (0.1)	6 (0.1)
GGT increased	7 (0.1)	5 (0.1)
Blood alkaline phosphatase increased	4 (0.0)	3 (0.0)
Liver function test abnormal	2 (0.0)	2 (0.0)
Blood bilirubin increased	1 (0.0)	4 (0.0)
Blood lactate dehydrogenase increased	1 (0.0)	0
Hepatobiliary disorders	48 (0.5)	53 (0.6)
Hepatic steatosis	17 (0.2)	22 (0.2)
Hepatic function abnormal	13 (0.1)	6 (0.1)
Hepatomegaly	6 (0.1)	6 (0.1)
Hepatic cirrhosis	3 (0.0)	4 (0.0)
Hepatitis	3 (0.0)	2 (0.0)

The slight increase in the number of hepatic AEs in the rosuvastatin treatment groups was due to laboratory abnormalities (Investigations). No liver deaths or liver transplantations due to liver failure were observed.

Muscle related AEs

Table 20: Muscle related adverse events

System organ class Preferred term	Rosuvastatin 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any muscle-related AE[a]	**1421 (16.0)**	**1375 (15.4)**
Investigations	63 (0.7)	38 (0.4)
Blood creatine phosphokinase increased	61 (0.7)	34 (0.4)
Blood creatine increased	2 (0.0)	4 (0.0)
Myoglobin blood increased	1 (0.0)	0
Musculoskeletal and connective tissue disorders	1297 (14.6)	1225 (13.8)
Myalgia	714 (8.0)	639 (7.2)
Muscle spasms	333 (3.7)	314 (3.5)
Musculoskeletal pain	295 (3.3)	319 (3.6)
Muscular weakness	84 (0.9)	72 (0.8)
Musculoskeletal discomfort	16 (0.2)	12 (0.1)
Myositis	9 (0.1)	8 (0.1)
Muscle disorder	8 (0.1)	4 (0.0)
Muscle tightness	8 (0.1)	1 (0.0)
Muscle fatigue	4 (0.0)	5 (0.1)
Muscle twitching	3 (0.0)	1 (0.0)
Musculoskeletal disorder	3 (0.0)	4 (0.0)
Muscle haemorrhage	1 (0.0)	0
Myosclerosis	1 (0.0)	1 (0.0)
Rhabdomyolysis	1 (0.0)	0
Myopathy	0	1 (0.0)
Injury, poisoning, and procedural complications	112 (1.3)	154 (1.7)
Muscle strain	99 (1.1)	133 (1.5)
Muscle injury	14 (0.2)	20 (0.2)
Muscle rupture	2 (0.0)	2 (0.0)

Myalgia was the most common AE, reported for 8.0% of rosuvastatin and 7.2% of placebo subjects. Myositis was reported by 9 rosuvastatin subjects (0.1%) and 8 placebo subjects (0.1%). Myopathy was reported for 1 subject (placebo) and rhabdomyolysis for 1 subject (rosuvastatin). The latter occurred after study closure in a 90-year-old man still taking study medication pending his final visit. At the hospital, CK was 13,000 and creatinine 1.5 mg/dL (132 µmol/L) (baseline creatinine 4 years prior was 1.3 mg/dL [114 µmol/L]). Following hydration, he recovered fully; creatinine at final visit was 1.1 mg/dL [97 µmol/L]).

Renal AEs

Table 21: Renal events

System organ class Preferred term	Rosuvastatin 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any renal-related AE[a]	**535 (6.0)**	**480 (5.4)**
Investigations	110 (1.2)	93 (1.0)
Urine analysis abnormal	40 (0.4)	43 (0.5)
Blood creatinine increased	39 (0.4)	30 (0.3)
Red blood cells urine	18 (0.2)	12 (0.1)
Blood urea increased	5 (0.1)	1 (0.0)
Protein urine present	5 (0.1)	8 (0.1)
Glomerular filtration rate decreased	3 (0.0)	1 (0.0)
Urine output decreased	3 (0.0)	0
Blood urine present	2 (0.0)	1 (0.0)
Protein urine	2 (0.0)	0
Red blood cells urine positive	2 (0.0)	0
Urine colour abnormal	1 (0.0)	0
Renal and urinary disorders	452 (5.1)	406 (4.6)
Haematuria	241 (2.7)	203 (2.3)
Proteinuria	149 (1.7)	127 (1.4)
Renal failure	25 (0.3)	23 (0.3)
Renal failure chronic	23 (0.3)	28 (0.3)
Renal failure acute	19 (0.2)	16 (0.2)
Renal impairment	11 (0.1)	8 (0.1)
Urine flow decreased	8 (0.1)	15 (0.2)
Renal disorder	5 (0.1)	4 (0.0)
Microalbuminuria	4 (0.0)	3 (0.0)

Proteinuria (rosuvastatin 1.7%, placebo 1.4%) and haematuria (rosuvastatin 2.7%, placebo 2.3%) were reported as an AE slightly more frequently among subjects assigned to rosuvastatin treatment.

Cognitive function

The overall frequencies of cognition related AEs (dementia, cognitive disorder, confusional state, personality change) were 0.4% in the rosuvastatin treatment group and 0.3% in the placebo group.

Comments RMS:
Although the general safety profile is approximately similar between active and placebo treated patients, slightly higher numbers of adverse events were found for hepatic, muscle, and renal specified areas. Although reassuring, these findings should be weighed in the context of a selective, relative healthy patient group with regard to the benefit/risk.

III.3.4 Laboratory findings

III.3.4.1 ULN elevation (hepatic)

The percentage of subjects with ALT>3xULN at any time was slightly greater in the rosuvastatin treatment group compared to the placebo group (1.4% and 1.0%, respectively). Elevations of ALT>3xULN on 2 consecutive occasions occurred with slightly higher frequency in the rosuvastatin group (rosuvastatin 0.3%, placebo 0.2%).

III.3.4.2 CK elevation (skeletal muscle)

CK elevation (CK>10xULN) was rare and occurred with similar frequency in the rosuvastatin (n=2) and placebo groups (n=1).

III.3.4.3 Serum creatinine elevation (renal)

Elevations of serum creatinine >100% above baseline were rare and occurred with slightly higher frequency in the rosuvastatin group (10 vs. 6). Change from baseline in mean serum creatinine on treatment was similar in the rosuvastatin and placebo groups. Mean eGFR fell similar in both groups (-7.23 vs -7.72 ml/min/1.73 m2)

III.3.4.4 Blood cells (haematology)

The mean platelet count decreased slightly from baseline to final visit in both the rosuvastatin and placebo treatment groups. There were no appreciable changes in red blood cell counts or white blood cell counts from baseline to the final visit.

III.3.4.5 Vital signs

Sitting systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were similar at baseline and at the final visit in the rosuvastatin and placebo treatment groups.

Mean (SD) body weight increase was slightly greater in the rosuvastatin treatment group than in the placebo group (0.44 [9.62] kg in the rosuvastatin group and 0.15 [5.42] kg in the placebo group.

Comments RMS:

Laboratory markers for possible damage to specific areas as liver, muscle and kidney were followed. In more patients in the rosuvastatin group, higher levels of these markers were found, although numbers of patients with higher levels were small. These findings are in line with the known safety profile of rosuvastatin. Therefore, no new unexpected results were noticed.

III.3.5 Safety in special populations

III.3.5.1 Diabetes in other trials

In the integrated study database (33 trials performed until 16 September 2005, excluding JUPITER, METEOR and CORONA) there was no evidence of an association of rosuvastatin treatment with diabetes (reported as an AE) (Table 22).

Table 22: Number and frequencies of treatment-emergent adverse events possibly suggestive of glucose disorders during the treatment phase in the Placebo Controlled Pool of the Integrated Study Database

Number and frequencies of treatment-emergent adverse events possibly suggestive of glucose disorders during the treatment phase in the Placebo Controlled Pool of the Integrated Study Database

MedDRA PT[a]	Rosuvastatin (n=1062)		Placebo (n=483)	
	n	%	n	%
Blood glucose increased	1	0.1	0	0
Diabetes mellitus	1	0.1	0	0
Urine output increased	1	0.1	1	0.2
Vision blurred	1	0.1	1	0.2

Data derived from the All Placbo Controlled Pool of the ISD.
A patient may have experienced more than 1 of the above PTs.

Comments RMS:
The data from the placebo controlled pool of the integrated study database are considered of limited value for the demonstration of the absence of an increased risk of diabetes associated with rosuvastatin. The numbers of patients and incidences were too low and follow-up was too short to draw any conclusions. Furthermore, glucose disorders including diabetes were not actively followed-up.

As stated by the MAH, the studies in the integrated study database had several limitations for assessing the effect of rosuvastatin on diabetes. Therefore, apart from the JUPITER trial 2 other placebo-controlled studies, METEOR and CORONA are discussed, as they may provide long-term data on investigator-reported diabetes.

The METEOR trial

The MAH has performed the METEOR trial (A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase III Study Measuring Effects on Intima Media Thickness (IMT): an Evaluation Of Rosuvastatin 40 mg) to study the effects of rosuvastatin on IMT among 984 patients with subclinical atherosclerosis (702 rosuvastatin 40 mg/day, 282 placebo), mean duration of follow-up was 622 days (1.7 years). The frequency of AEs considered possibly suggestive of glucose disorders was generally similar among patients on rosuvastatin (n=9/700) and in the placebo (n=7/281) group (Table 23). In addition, there was no difference in fasting glucose levels at baseline or final measurements.

Table 23: Number and frequency of treatment-emergent adverse events possibly suggestive of glucose disorders during the treatment phase in the METEOR study (randomized safety population)

Number and frequency of treatment-emergent adverse events possibly suggestive of glucose disorders during the treatment phase in the METEOR study (randomized safety population)

	Rosuvastatin 40 mg (n=700)		Placebo (n=281)	
MedDRA PT[a]	n	%	n	%
Blood glucose increased	5	0.7	1	0.4
Diabetes mellitus	1	0.1	4	1.4
Diabetes mellitus non-insulin dependent	0	0	1	0.4
Glucose urine	1	0.1	0	0
Hepatic steatosis	0	0	1	0.4
Hyperglycaemia	1	0.1	0	0
Polydipsia	0	0	1	0.4
Thirst	1	0.1	0	0

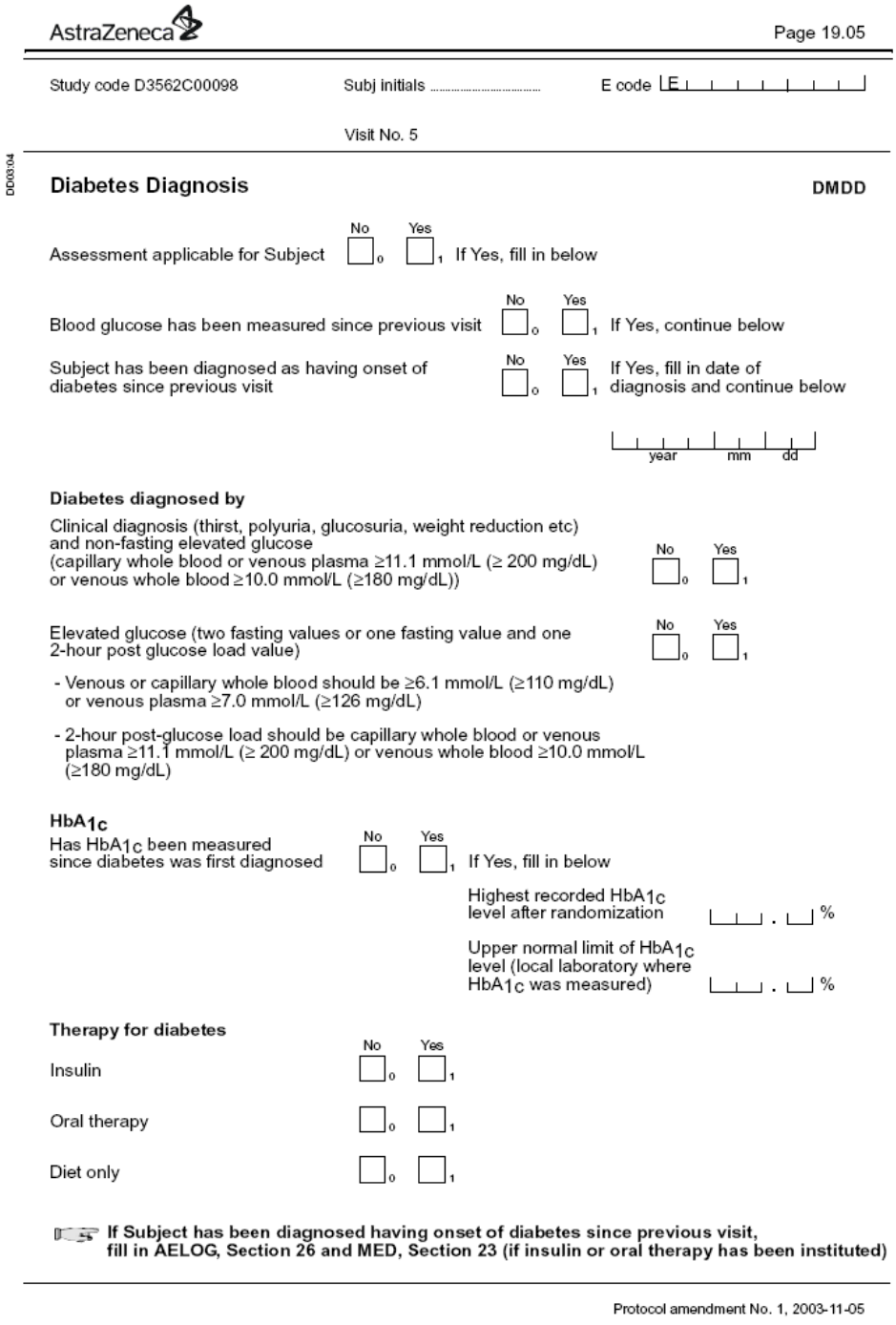
Data derived from the METEOR CSR, see Table 11.3.2.2.2 of Module 5, Section 5.3.5.4.
a A patient may have experienced more than 1 of the above PTs, therefore, the total number of PTs (eg, numerator) may count a patient more than once (eg, denominator).
MedDRA: Medical Dictionary for Regulatory Activities; PT Preferred Term.

The CORONA trial

The MAH has performed the CORONA trial (A randomized, Double-Blind, Placebo Controlled Phase III Study with Rosuvastatin in Subjects with Chronic Symptomatic Systolic Heart Failure) to study the effects of rosuvastatin (combined endpoint of cardiovascular death or non-fatal myocardial infarction (MI) or nonfatal stroke) among 5011 patients with a history of heart failure (2514 rosuvastatin 10 mg/day, 2497 placebo), mean duration of follow-up was 2.3 years (840 days rosuvastatin, 822 days placebo). The study included both diabetic (29.5%) and non-diabetic patients. Neither fasting glucose nor Hb1AC levels were measured. DM was included as a tertiary endpoint and was monitored throughout the study using a standardised case report form (figure 6). Hundred patients in the rosuvastatin group (1.6 per 100 patient years) and 88 patients in the placebo group (1.4 per 100 patient years) developed DM (Cox HR 1.13

[95%CI 0.85-1.51], p=0.4024, figure 7). Excluding patients who were reported to have diabetes at baseline, gave a hazard ratio of 1.15 (95% CI 0.86 to 1.53).
The frequency of AEs considered possibly suggestive of glucose disorders was slightly higher in the rosuvastatin group (n=55) than in the placebo (n=43) group.

Figure 6. Case report form to assess newly diagnosed diabetes in CORONA.



AstraZeneca

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Study code D3562C00098 Subj initials ..... E code E

Visit No. 5

DD03:04

Diabetes Diagnosis **DMDD**

Assessment applicable for Subject No ☐0 Yes ☐1 If Yes, fill in below

Blood glucose has been measured since previous visit No ☐0 Yes ☐1 If Yes, continue below

Subject has been diagnosed as having onset of diabetes since previous visit No ☐0 Yes ☐1 If Yes, fill in date of diagnosis and continue below

year mm dd

Diabetes diagnosed by

Clinical diagnosis (thirst, polyuria, glucosuria, weight reduction etc) and non-fasting elevated glucose (capillary whole blood or venous plasma ≥11.1 mmol/L (≥ 200 mg/dL) or venous whole blood ≥10.0 mmol/L (≥180 mg/dL)) No ☐0 Yes ☐1

Elevated glucose (two fasting values or one fasting value and one 2-hour post glucose load value) No ☐0 Yes ☐1

- Venous or capillary whole blood should be ≥6.1 mmol/L (≥110 mg/dL) or venous plasma ≥7.0 mmol/L (≥126 mg/dL)
- 2-hour post-glucose load should be capillary whole blood or venous plasma ≥11.1 mmol/L (≥ 200 mg/dL) or venous whole blood ≥10.0 mmol/L (≥180 mg/dL)

HbA_{1c}

Has HbA_{1c} been measured since diabetes was first diagnosed No ☐0 Yes ☐1 If Yes, fill in below

Highest recorded HbA_{1c} level after randomization ☐☐.☐ %

Upper normal limit of HbA_{1c} level (local laboratory where HbA_{1c} was measured) ☐☐.☐ %

Therapy for diabetes

	No	Yes
Insulin	☐0	☐1
Oral therapy	☐0	☐1
Diet only	☐0	☐1

If Subject has been diagnosed having onset of diabetes since previous visit, fill in AELOG, Section 26 and MED, Section 23 (if insulin or oral therapy has been instituted)

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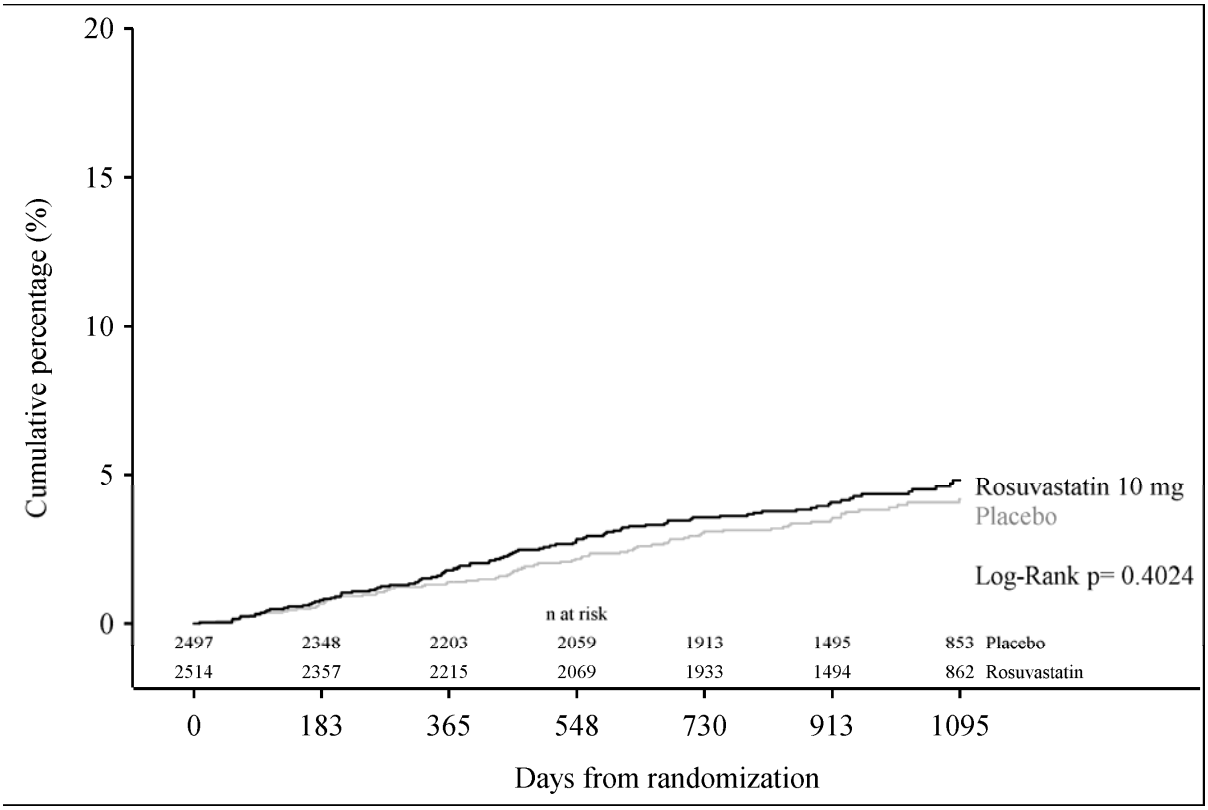
Figure 7 Kaplan-Meier estimate of the cumulative percentage of patients regarding newly diagnosed diabetes, CORONA



The MAH questions the validity of the method used to ascertain the diabetes endpoint in the JUPITER trial because:

- there was no statistical difference between these groups in diabetes reported as an AE in the 2 previously reported long-term, placebo controlled studies of rosuvastatin (METEOR and CORONA)
- There was very little if any difference in the protocol specified fasting glucose or HbA1c levels that were measured in the central laboratories in JUPITER subjects who were treated with rosuvastatin or placebo.

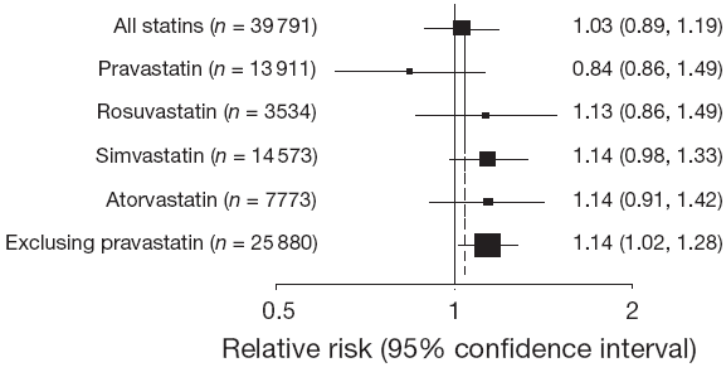
In addition, rosuvastatin reduced the risk of primary CV endpoint events by 34% among prediabetic subjects who entered the JUPITER study, and adults with diabetes are at particularly high risk for CV events and clearly benefit from statin therapy. Therefore, the all-cause mortality benefit with rosuvastatin clearly speaks to the benefit exceeding the risk of treatment.

Comments RMS:

METEOR
No real differences were found between treatment with rosuvastatin or placebo for signs of new onset of DM in the METEOR study. The number of patients with signs of possible new onset of DM was very limited. This does not allow for any conclusions on this.

CORONA
The CORONA study (figure 7) shows a similar non-significant trend, for new onset of diabetes during follow-up as in the JUPITER trial (figure 5). One should bear in mind that the JUPITER study population was about 3.5 times larger than the CORONA study population. In addition, subjects in the JUPITER trial were treated with 20 mg rosuvastatin daily, whereas subjects in the CORONA study were treated with 10 mg daily. The lack of statistical significance in the CORONA-trial could be due to limited power and/or lower dose.At baseline 29.5% of the CORONA patients had DM, whereas patients with DM at baseline were excluded from JUPITER. However, excluding these patients gives similar results.

Other statins
A meta-analysis (Coleman, 2008) demonstrated no increased risk for new onset of diabetes for all statins combined. However, when pravastatin was excluded, a higher risk was found 1.14 (95%CI 1.02-1.28) (see also figure below).



Overall, new onset of diabetes cannot be excluded as a risk when patients are treated with rosuvastatin. Similar trends in higher risk for diabetes were observed in the JUPITER trials as well as the CORONA trial. Therefore, this problem remains unclear and further follow-up is warranted.

III.3.6 Pharmacovigilance Systen and Risk Management Plan

Amongst others, a detailed description of the pharmacovigilance system (PVS) were submitted.

Comments RMS:
This response document has been taking into account in the current assessment report.

Assessment of the Pharmacovigilance System
The MAH has provided documents that set out a detailed description of the system of pharmacovigilance (version 9.0, dated 2 February 2009, and signed). The RMS considered that the Pharmacovigilance system as described by the MAH had a few deficiencies.
In the context of procedure NL/H/0343/001/II/034, the MAH responded to the RMS comments. In the response document the location of the database and the responsibilities for ensuring corrective and preventive action were made clear. The MAH committed to add this information will be added to the next version of the PVS.

Comments RMS:

Following the assessment of the MAH's PVS version 9.0, dated 2 February 2009, and the related response document of the MAH the RMS concludes that the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Assessment of the Risk Management Plan
The RMP submitted supersedes the previous RMP (dated 16 October 2008). The RMP has been updated with information regarding the sought indication in children and adolescents aged 10-17 years, the PLUTO study supporting this application (procedure NL/H/0343/II/033) and with information regarding the JUPITER study that supports the sought indication for the prevention of cardiovascular events in adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular risk markers such as age, hypertension, low HDL-C, elevated hsCRP, smoking or a family history of premature coronary heart disease.

The changes made to the RMP with the extension of the indication to children and adolescents aged 10-17 years (procedure NL/H/0343/II/033) were also incorporated (see Annex I to this PAR).

The sought indications and related dosages and demographics, exposure of the study population in the JUPITER study have been added to the Safety Specification.
Diabetes in patients with fasting glucose >5.6 mmol/L has been added as an identified risk and diabetes in patients with normal fasting glucose has been added as a potential risk. The risk of diabetes mellitus is mitigated through routine risk minimisation measures (i.e. SPC and PIL). Furthermore, this risk will we monitored in routine pharmacovigilance (i.e. PSURs).

The following has been included in section 4.4 of the SPC:

Diabetes Mellitus
In patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus (see Section 4.8).

Section 4.8 states:
Endocrine disorders
Common: diabetes mellitus[1]

[1] *Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.*

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Efficacy

Rosuvastatin demonstrated a statistically significant reduction in the risk for the composite primary endpoint. A large proportion of the observed cardiovascular (CV) events were related to coronary vascularisation procedures and hospitalizations due to unstable angina, which is subjective to clinical decision making, but significant effects were also noted for the occurrence of non-fatal MI and stroke. Only numerically a benefit was seen for CV death, but a significant reduction was seen in overall death that was measured as a secondary endpoint. Also, for the combined endpoint of CVdeath/MI/stroke a significant risk reduction was observed.

Notwithstanding this overall significant effect, the population in the JUPITER trial is heterogenous and the MAH was asked to identify an appropriate target population at risk of developing CV disease using established definitions of CVD risk. This CV risk of the target population was not accurately identified in the first round as it was based on age and increased CRP-levels only. The overall absolute risk reduction for the total study population was only 0.9% for the combination of the more robust endpoints CV death, MI and stroke (Citrome, Int J Clin Pract, 2009). This absolute risk reduction, in addition to the reported numbers needed to treat, puts the beneficial effect of rosuvastatin into perspective. Especially, in view of the discussion on the benefit/risk of treating included low-risk patients with rosuvastatin. The MAH did not provide these data, but in their published paper on JUPITER [NEJM 2008;359:2195] Ridker et al. reported a NNT of 95 and extrapolated to 5 years resulted in a NNT of 25 to prevent the occurrence of one primary endpoint. This is in line with other primary prevention trials, such as WOSCOPS, but comparison is difficult as baseline CV risk was higher in WOSCOPS. NNT will be considerably higher in low risk populations than in higher risk populations. The problem is, as mentioned above, that inclusion was not based on established CV risk scores, but only on age and an elevated hsCRP (and low LDL-C levels). In contrast, the initial claimed indication in the first round ("increased risk") not only included an elevated hsCRP, but also mentioned other risk factors (but excluding elevated LDL-cholesterol!). The use of hsCRP as inclusion criterium in the Jupiter study was questioned. Whether an elevated hsCRP level is an independent risk factor (not explainable by classic risk factors), could not be evaluated on the basis of this study due to reasons further discussed below. According to the guideline of the "evaluation of medicinal products for cardiovascular disease prevention" (EMA/CHMP/EPW/311890/2007), an accurate definition of the CV risk of the target population was considered fundamental. This was not possible on the basis of the results of the Jupiter study, neither was it acceptable to extrapolate these findings to the initial proposed broad indication ("increased risk").

In the second round the MAH was able to identify a sufficiently high CV risk patient population who could be eligible for rosuvastatin therapy based on a justified benefit/risk balance. The data provided demonstrate that if patients fall within a lower risk category (according to Framingham and SCORE risk scores), the absolute risk reduction is two to three times smaller than in patients at higher CV risk (Framingham >10% and SCORE ≥ 5%). Therefore these low-risk patients should not be eligible for rosuvastatin therapy and are therefore correctly excluded from the ultimately proposed indication. In addition, atorvastatin has also been approved for a similar indication, although the study design on which the indication was based was different from that of JUPITER as this study only included a high risk population. The way of recruitment and background non-pharmacological therapy in relation to translation in clinical practice were points of discussion. However, this does not alter the conclusion that the MAH was able to identify a clinically acceptable risk group eligible for rosuvastatin treatment. It is considered that these patients can also be identified in clinical practice in a similar way as for instance with atorvastatin.

The dose used for CV prevention of 20 mg in JUPITER is higher than the starting dose for lipid management. However, in view of the targeted high risk patient population this seems acceptable. Furthermore, it is in line with earlier experience with e.g. pravastatine and simvastatin where in the primary prevention trials only experience with the 40 mg dose of this –admittedly less potent - statin were obtained. Thus although benefit/risk data of lower dose rosuvastatin strategies are not available the revised SPC adequately reflects this uncertainty. It describes – in line with pravastatine – that the primary prevention data were obtained with a 20 mg dose only, while maintaining an alternative strategy of a more gradual uptitration for treatment of hyperlipidaemia.

The design and results of the trial provided only limited information of the value of hsCRP as a prognostic tool for clinical management. The trial did not compare subjects with and without high hsCRP, nor was hsCRP compared with other CV risk factors. Subgroup analyses demonstrated a negative correlation with hsCRP value at baseline (lower hsCRP, better effect and visa versa), although it is acknowledged that this was the opposite in other clinical trials.[1] Importantly, with increasing baseline risk (eg indicated by higher CRP levels) the effect of cardiovascular preventive interventions can be expected to increase and not decrease. In contrast to hsCRP, in the JUPITER trial LDL-C at baseline did indeed show the expected greater reduction in CV events for patients with a higher baseline LDL level, whereas no other (single risk factor) subgroup analysis demonstrated a significant *p* for interaction with treatment effect. In addition, high variability was noticed for the hsCRP measurements. Differences in hsCRP between visit 1 and 2 (2 weeks difference) was approximately 12%, and placebo hsCRP was reduced by approximately 20% during the first year. Standardisation between different laboratories of the method may be an additional problem. The MAH acknowledges that the JUPITER trial has some limitations to establish the value of hsCRP as a tool to assess CV risk. This was, however, not further discussed as hsCRP was eventually not considered to be included in the proposed indication. While the association between between CRP and risk of cardiovascular disease is not doubted, (hs)CRP is a nonspecific biomarker and considered to be of limited predictive value of CV events (Hingorani et al Clin Chem 2009) In addition, hsCRP has currently not been recognized as a biomarker for cardiovascular risk prevention by the EMA.

Safety

Rosuvastatin was relatively well tolerated in these relatively healthy patients. Apart from a higher incidence of patients diagnosed with diabetes no new safety issues emerged. The important and known statin specific adverse events such as liver and musculoskeletal problems were also observed more in the rosuvastatin treatment arm, but differences were small. Reassuringly, earlier identified potentially rosuvastatin-related serious adverse events; neoplasms, hepatobiliary and renal and urinary disorders, were all reported less frequently in the active treatment arm. In addition, musculoskeletal disorders were not clearly increased.

For the significantly higher risk of newly diagnosed diabetes, an extensive evaluation was provided as addressed in several questions to the MAH. The JUPITER trial identified a statistically significant increased risk for DM, using a predefined secondary endpoint, measured on a standardised case report form (HR 1.27, 95% CI 1.05, 1.53) in a population that was free of DM at baseline. The validity can be questioned to some extent, as this endpoint was only determined by the local investigator and not centrally adjudicated. Early HbA1c was only slightly higher and fasting glucose was similar. However, when expressed as the number of DM cases based on HbA1c and fasting glucose measurements at every year time point, significantly higher numbers of DM were found based on HbA1c criteria, although differences were not large. This partly confirmed the higher incidence of DM for rosuvastatin, although most patients who developed DM could be considered already at risk of developing DM (fasting glucose >100 mg/dl) at baseline. In the second round, this was confirmed in survival analysis for subgroups of patients at risk for diabetes. Low risk patient for diabetes conferred into low numbers of diabetes with no significant difference between treatment groups. However, in the first round DM was considered an important safety signal to be further evaluated, also based on the safety position paper titled 'Crestor and Glucose Disorders' (published literature, pre-clinical trials, post-marketing studies, post-marketing AE reports and the potential underlying pathophysiological mechanisms) which still had to be assessed at that time. According to Jerome [Int J Clin Pract. March 2009; 63(3): p347-352] of each 167 (NNH) patients treated with rosuvastatin one develops DM within the duration (median 1.9 years) of the JUPITER trial. Based on the answers provided by the MAH, the following conclusions were drawn. In addition to the signal of potential DM risk in the JUPITER trial, the analyses on the smaller CORONA trial were not inconsistent with an increased risk of diabetes when patients are treated with rosuvastatin, also when baseline DM patients were excluded. Nevertheless, overall, the conclusion is that at this moment in the treatment target group of high CV risk patients, the beneficial effects outweigh this slight potential risk for DM. In addition, diabetes risk for other statins is inconclusive. Still, the excess risk of diabetes mellitus among pre-diabetic individuals treated with rosuvastatin should be included in the RMP as an identified

[1] *Early 2011 in a post hoc analysis of the Heart Protection Study it was shown that simvastatin treatment was associcated with a similar reduction in vascular events irrespective of baseline concentrations of CRP (Heart Protection Study Collaborative Group. Lancet 2011)*

risk. The excess risk among patients with normal fasting glucose levels remains inconclusive, and therefore should be mentioned under potential risks in the RMP.

An additional issue is whether patients should be treated until low LDL-C levels are reached. Although current views encourage aggressive treatment to low LDL-C levels, safety in low levels of LDL-C is somewhat unknown. Long term data on very low LDL-C obtained with rosuvastatin are relatively scarce. Nevertheless, very low levels have also been obtained with other statins in CARDS (atorvastatin) or e.g. in a sizeable subpopulation of HPS (simvastatin). Furthermore, post-marketing data and data from METEOR and ASTEROID add to our knowledge of long-term safety. Nevertheless, long-term safety of treating a primary prevention population with a potent statin should be monitored closely by the MAH. The MAH should specifically address this in their pharmacovigilance activities and RMP.

In conclusion, JUPITER demonstrates a significantly reduced relative risk of a first CV event for patients treated with rosuvastatin. The MAH demonstrated that a subpopulation in this study with a relative high CV risk (SCORE ≥ 5% or Framingham >20%) shows a consistent relative risk reduction and a more absolute risk reduction than lower CV risk patients, and that this result is consistent with other statin trials on primary prevention.
Rosuvastatin was found to be well tolerated, but shows an increased risk of developing diabetes mellitus in pre-diabetic patients. However, in a high CV risk target population for treatment, these beneficial effects outweigh the risk of DM. Nevertheless, this risk is adequately reflected in the SPC as well as in the RMP.

IV.1 PL and labelling

PL and labelling are harmonised for this product.

IV.2 SPC changes

Only the paragraphs which are altered are displayed, with added text indicated in blue and removed text in red/strikethrough:

4.1 Therapeutic indications

Treatment of hypercholesterolaemia

Primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

Crestor may be given at any time of day, with or without food.

Treatment of hypercholesterolaemia

The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see Section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see Section 4.8), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see Section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

~~Crestor may be given at any time of day, with or without food.~~

Prevention of Cardiovascular Events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily (see Section 5.1). ~~Patients with hypercholesterolaemia will require conventional lipid measurement and to follow dose recommendations as specified above (treatment of hypercholesterolaemia).~~

Paediatric use

Safety and efficacy have not been established in children. Paediatric experience is limited to a small number of children (aged 8 years or above) with homozygous familial hypercholesterolaemia. Therefore, Crestor is not recommended for paediatric use at this time.

Use in the elderly

A start dose of 5 mg is recommended in patients >70 years (see Section 4.4). No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Crestor in patients with severe renal impairment is contraindicated for all doses. (See Section 4.3 and Section 5.2).

Dosage in patients with hepatic impairment

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see Section 5.2). In these patients an assessment of renal function should be considered (see Section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Crestor is contraindicated in patients with active liver disease (see Section 4.3).

Race

Increased systemic exposure has been seen in Asian subjects (see Section 4.4 and Section 5.2). The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.

Dosage in patients with predisposing factors to myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see Section 4.4). The 40 mg dose is contraindicated in some of these patients (see Section 4.3).

4.4 Special warnings and special precautions for use

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Crestor, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see Section 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see Section 4.5) and caution should be exercised with their combined use.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Crestor in post-marketing use is higher at the 40 mg dose. ***Creatine Kinase Measurement***

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before Treatment

Crestor, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see Section 5.2)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on Treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Crestor or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Crestor and concomitant therapy. However, an increase in the incidence of myositis and

myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Crestor and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Crestor with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate. (See Section 4.5 and Section 4.8.)

Crestor should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver Effects
As with other HMG-CoA reductase inhibitors, Crestor should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Crestor should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Crestor.

Race
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see Section 4.2 and Section 5.2).

Protease inhibitors
The concomitant use with protease inhibitors is not recommended (see Section 4.5).

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Diabetes Mellitus
In patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus (see Section 4.8).

4.8 Undesirable effects

The adverse events seen with Crestor are generally mild and transient. In controlled clinical trials, less than 4% of Crestor-treated patients were withdrawn due to adverse events.

The frequencies of adverse events are ranked according to the following: Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders
Rare: hypersensitivity reactions including angioedema

Endocrine disorders
Common: diabetes mellitus[1]

Nervous system disorders
Common: headache, dizziness

Gastrointestinal disorders
Common: constipation, nausea, abdominal pain
Rare: pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders
Common: myalgia
Rare: myopathy (including myositis) and rhabdomyolysis

General disorders
Common: asthenia

[1] Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Crestor. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Crestor and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g.myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Crestor-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed inpatients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued (see Section 4.4).

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

Post-Marketing Experience:
In addition to the above, the following adverse events have been reported during post marketing experience for CRESTOR:
Gastrointestinal disorders: Not known: diarrhoea
Hepatobiliary disorders: Very rare: jaundice, hepatitis; *rare:* increased hepatic transaminases.
Musculoskeletal disorders: Very rare: arthralgia
Nervous system disorders: Very rare: polyneuropathy, memory loss
Renal disorders: Very rare: haematuria
Skin and subcutaneous tissue disorders: Not known: Stevens-Johnson syndrome

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects
Crestor reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1). Crestor also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 1 Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	Apo B	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy
Crestor is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

From pooled phase III data, Crestor has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Crestor from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. 33% of patients reached EAS guidelines for LDL-C levels (<3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to Crestor 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Crestor has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see Section 4.4).

~~Rosuvastatin has not been proven to prevent the associated complications of lipid abnormalities, such as coronary heart disease as mortality and morbidity studies with Crestor have not yet been completed.~~

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Crestor 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see Section 4.2).

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% (p<0.001) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high risk group (p=0.076).

In the JUPITER trial there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).