Drug product:	Rosuvastatin tablets 40 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
Document No.:	001		
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Date:	16th June, 2005		

Final report of the open-label extension period.

A 6-Week Open-Label, Randomised, Multicentre, Phase IIIb, Parallel-Group Study, Which Describes the Renal Effects of the Lipid-Regulating Agents Rosuvastatin and Simvastatin in the Treatment of Patients with Fredrickson Type IIa and Type IIb Dyslipidaemia, Including Heterozygous Familial Hypercholesterolaemia.

International co-ordinating Investigator

Study centre(s)

This study was conducted at 52 centres: Belgium (9 centres), France (4 centres), Germany (7 centres), South Africa (3 centres), Israel (4 centres), US (25 centres).

Publications

There were none at the time of writing this report.

Study dates (open-label extension)		**Phase of development**
First patient enrolled	26th November, 2002	Therapeutic confirmatory (IIIb)
Last patient completed	30th March, 2004	

Objectives

The objective of the open-label extension was to assess the long-term safety and efficacy of rosuvastatin 40 mg.

Primary

The primary objective of the open-label extension period of the study was to assess urinary protein excretion (by urine dipstick) during treatment with once-daily rosuvastatin (20 mg or 40 mg with or without additional lipid lowering therapy) in patients with Type IIa and Type IIb dyslipidaemia, including heterozygous familial hypercholesterolaemia.

Secondary

The secondary objectives of the open label extension were:

- To assess the renal effect of treatment with rosuvastatin by evaluation of:
  - The excretion of urinary protein and albumin when corrected for urine creatinine excretion
  - Urinary excretion of blood by urine dipstick (haem) measurements
  - Urinary excretion of concurrent urine protein and blood by dipstick measurements
  - Changes in serum creatinine
  - The pattern of urinary protein excretion by sodium dodecyl sulphate – polyacrylamide gel electrophoresis (SDS-PAGE)
- To evaluate the safety of treatment with rosuvastatin.
- To assess the efficacy of treatment with rosuvastatin by the evaluation of:
  - Percentage of patients who achieve National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III target goals
  - Effects on lipids and lipoproteins.

Study design

This study comprised:

- A 6-week, open-label, randomised, multicentre, Phase IIIb, parallel-group study, investigating the renal effects of treatment with rosuvastatin 40 mg or simvastatin 80 mg (described in clinical study report dated 19th March, 2004).
- Following the randomised period, an open-label, non-comparative extension study investigating long-term renal effects of rosuvastatin 40 mg.

There was an option to down titrate rosuvastatin 40 mg to the 20 mg dose and/or addition of other lipid lowering therapy for patients not achieving lipid goal.

Scope of this clinical study report

This is the final report presenting results from the open-label extension period of the study. A clinical study report presenting results from the randomised treatment period was completed on 19th March, 2004. The study objectives, plans and procedures are as described in the clinical study protocol for the main (randomised) study period, and in the statistical analysis plan for the open-label extension period.

Target population and sample size

The sample size of the extension period was dependent on the number of patients completing the randomised treatment period. All patients completing the randomised treatment period were given the option to enter the open-label extension period.

The study population in the extension period was defined by the selection criteria at study entry: namely, male and female patients aged 18 years and over with documented Type IIa and Type IIb dyslipidaemia, familial heterozygous or non-familial hypercholesterolaemia. The target low density lipoprotein cholesterol (LDL-C) criterion for a patient's entry into the randomised treatment period was – after a 4 to 5-week dietary lead-in period (Therapeutic Lifestyle Changes Diet) – a baseline fasting LDL-C ≥175 mg/dL (≥ 4.52 mmol/L) and ≤350 mg/dL (≤9.04 mmol/L).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Rosuvastatin 40 mg: Formulation No: F12821; Batch Numbers: 19683102, 51683102, 82994101, 82994I01, 82994I0I, 90556B02, 90557J02, 91634F02, 91681102, 91683102, 91683103, 91683106, 91683108, 91683201, 91683I02, 91683IC2, 91684702, 91684F02, 91684F04, 91684I02, 91688F02, 91863I02, 93001H02, 9300IH02, 9I683102, F000IH02, 91683102, 91684F02, 93001H02, E01676-08L2, E01676-11L3, E01676-11L4, E01676-12L3, E01676-12L4, E01676-15L3, E01676-15L4, E01676-15L5, E01676-15L6, E01676-16L08, E01676-16L10, E01676-16L8, 10015128, 10015254, 10016055, E01676-017L08, E01676-017L09, E01676-017L10, E01676-11L5, E01676-11L6, E01676-12L06, E01676-12L6, E01676-15L0, E01676-15L06, E01676-15L10, E01676-15L2, E01676-15L7, E01676-15L8, E01676-15L9, E01676-16L02, E01676-16L03, E01676-16L04, E01676-16L05, E01676-16L06, E01676-16L3, E01676-16L4, E01676-16L6, E01676-17L08, E01676-17L09, E01676-17L10, E01676-17L9, E01676-19L6, E01676-UIL5, EO1676-11L5, EO1676-15L0, P0E1676-16L04, E01676-017L09, E01676-15L9, E01676-16L04, E01676-17L09, 2000032070, 2000035788, 2000041560, 2000043333, 2000028600, 2000032063, 2000032070, 2000032187, 2000035788, 2000041560.

Rosuvastatin 20 mg: Formulation No: F12673; Batch Numbers: 82995F01, 90528H02, 90530F02, 90530I02, 90541902, 90541J02, 93623H02, 10014753, 2000030210, 2000032063, 2000032066.

In addition, simvastatin 80 mg medication was temporarily continued in the extension period in error for 18 patients: Formulation No: F12600; Batch Numbers: 93073G02, 93429K02, 2000043333, 2000032069, 10015132, 10015256, 10016287.

Doses of study medication in the extension period were administered once daily as a single tablet.

Duration of treatment

The final visit for the open-label extension was completed before 30th March, 2004 when the study was stopped irrespective of length of treatment received; the maximal possible treatment duration was therefore 72 weeks (6 weeks' randomised treatment plus 66 weeks' open-label extension treatment). In the randomised treatment period patients were treated with either rosuvastatin 40 mg or simvastatin 80 mg for 6 weeks.

The median duration of treatment during the extension period overall was 328 days (47 weeks); the majority of patients (56%) received at least 48 weeks' study treatment during the extension. Duration of study treatment over the whole study (randomised and extension periods) would include an additional 6 weeks of randomised treatment.

Treatment groups

Patients were initially administered rosuvastatin 40 mg at the start of the open-label extension phase. After the first 6 weeks of therapy in the open-label extension, down-titration to rosuvastatin 20 mg was allowed for safety or efficacy reasons, while additional lipid lowering therapy to rosuvastatin 40 mg or 20 mg was allowed for patients not achieving their NCEP lipid LDL-C goal. Thus, at Visit 7 (Week 12) or any subsequent visit of the extension period a patient might be receiving rosuvastatin 40 mg alone or with other lipid lowering therapy, rosuvastatin 20 mg alone or with other lipid lowering therapy.

Doses were categorised and analysed as follows:

- Rosuvastatin 40 mg alone
- Rosuvastatin 40 mg only – for patients who received rosuvastatin 40 mg alone at *all* treatment visits during the extension period (ie, this includes patients who received simvastatin 80 mg or rosuvastatin 40 mg during the randomised treatment period)
- Rosuvastatin 40 mg plus other lipid lowering therapy
- Rosuvastatin 20 mg total – combined group for patients receiving rosuvastatin 20 mg alone or rosuvastatin 20 mg plus another lipid lowering therapy
- Total – combined group for patients from all the above categories.

There was a large degree of overlap between the above categories since patients could appear in more than one category during the extension period, hence no treatment group comparisons

were made. The treatment group of principal interest for the long-term effect of rosuvastatin 40 mg treatment during the extension period was 40 mg alone (to enable direct comparison with findings on the 40 mg dose from other studies in the rosuvastatin clinical development programme) and the total treatment group. The number of patients who received rosuvastatin 40 mg plus other lipid lowering therapy or were down titrated to rosuvastatin 20 mg (alone or with other lipid lowering therapy) were small compared with the other treatment groups. For this reason data and results for these treatment groups are not presented in the tables in the main body of the report, but can be found in the appropriate summary tables in Section 11.

Criteria for evaluation (main variables)

Urinalysis and renal function endpoints were primary and secondary variables in this study along with other safety endpoints. Efficacy endpoints were secondary variables. See below for details.

Previous studies have shown the percentage of patients who develop a shift in urine dipstick protein from 'none' or 'trace' at baseline to a grade of ++ or greater (ie, proteinuria) on 40 mg rosuvastatin to be approximately 2% at final visit (Vidt et al 2004). In this study the development of proteinuria as well as the more sensitive lower urine dipstick protein grade of + or greater was investigated. The lower urine dipstick protein grade was the primary safety variable in this study. Shift in urine dipstick haem to + or greater from 'none' or 'trace' at baseline was a secondary variable.

In addition to the above, shifts in urine dipstick haem from 'none' or 'trace' at baseline to ++ or greater (haematuria) and combined shifts in urine dipstick protein and haem from 'none' or 'trace' at baseline to ++ or greater protein and to + or greater haem during the extension period were investigated as these parameters are also of clinical interest.

Analysis variables

Primary variable – extension safety population

- Percentage of patients who developed a shift in urine dipstick protein from 'none' or 'trace' at baseline (Week 0) to a grade of + or greater at any time during the extension period.

Secondary variables (urinalysis and renal function) –extension safety population

- Amount of urinary protein/creatinine and urine albumin/creatinine excretion after treatment with rosuvastatin

- Development of proteinuria (a shift in urine dipstick protein from 'none' or 'trace' at baseline to a grade of ++ or greater)

- Development of a shift in urine dipstick haem from 'none' or 'trace' at baseline to a grade of + or greater and development of haematuria (shift in urine dipstick haem from 'none' or 'trace' at baseline to a grade of ++ or greater)

- Development of concurrent shifts in urine dipstick protein and haem from 'none' or 'trace' at baseline to a grade of + or greater in both parameters, and to concurrent grades of ++ or greater in urine dipstick protein and + or greater in dipstick haem.

- Change from baseline in serum creatinine after treatment with rosuvastatin

- Assessment of patterns of renal protein excretion (normal, tubular, mixed or glomerular) by urine SDS-PAGE (only for patients with positive urine dipstick protein during the extension period at the visits where the positive urine occurred).

Secondary variables (other safety) – extension safety population

- Safety evaluation, as determined by the incidence and severity of adverse events (AEs) and abnormal laboratory values.

Secondary variables (efficacy) – extension intention to treat (ITT) population

- NCEP ATP III LDL-C goal at the final visit of the open-label extension period

- Change from baseline (percentage) in lipids and lipoproteins at all visits during the open-label extension period. The lipids and lipoproteins consisted of: LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), nonHDL-C, lipid ratios (LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C) apolipoprotein B (ApoB), ApoA-I and apolipoprotein ratio (ApoB/ApoA-I).

Due to inconsistencies in the protocol, ApoB and ApoA-I were not assessed for all patients in the extension period by the central laboratory and, therefore, results for these apolipoproteins are not presented in the main body of this report. However, results for ApoB, ApoA-I and ApoB/ApoA-I ratio can be found in the summary tables in Section 11.

Statistical methods

All variables were summarised by extension treatment using descriptive statistics or frequency distributions. In all analyses, baseline values were those from Visit 3 (Week 0). Urinalysis and renal parameters were also summarised by randomised treatment (rosuvastatin 40 mg or simvastatin 80 mg) in the randomised period.

Since patients could be enrolled on the extension period of the study for differing lengths of time, analyses at last visit were performed for primary and secondary variables.

Analysis sets were:

- Overall safety population – all patients in either open-label or randomised treatment periods of the study who had at least one dose of rosuvastatin

- Extension safety population – all patients in the extension period who had at least one dose of study medication during open-label extension

- Extension ITT population – all patients who received at least one dose of rosuvastatin in the extension period, that had a baseline reading and at least one scheduled reading for one or more lipids after extension entry (Visit 6, Week 6).

It was expected that, due to the short duration of the randomised treatment period (6 weeks), the overall and extension safety populations would be similar. Thus, analysis of the primary and secondary urinalysis and renal function variables, and safety evaluation of AEs and abnormal laboratory values were based on the extension safety population. Safety data for the overall safety population can be found in the listings to this clinical study report in Appendix 12.2. Efficacy analysis was performed on the extension ITT population using observed data.

Patient population

In total, 626 patients entered and 603 patients completed the randomised study period (295 on rosuvastatin 40 mg treatment and 308 on simvastatin 80 mg treatment). A total of 584 of the 603 patients completing the randomised treatment period entered the open-label extension period.

The majority of patients entering the extension treatment period were Caucasian (94%) and the age range for all patients was between 18 and 84 years of age. There were slightly more females than males (57% females to 43% males) and the baseline lipid levels, overall risk profile and medical history of the study population were representative of that seen in patients with primary hypercholesterolaemia in clinical practice.

All of the 584 patients entering the extension period were allocated study treatment. Due to an error 18 patients temporarily continued with simvastatin 80 mg, before being switched to rosuvastatin 40 mg extension treatment, and 1 patient started with rosuvastatin 20 mg dose. A total of 94 patients withdrew from the extension period leaving 490 patients who completed the extension period.

There were 603 patients in the overall safety population, 584 patients in the extension safety population and 577 patients in the extension ITT population (7 patients had no post-baseline lipid assessment during the extension period). At any time during the extension period 583 patients received rosuvastatin 40 mg alone, 53 patients took rosuvastatin 20 mg with or without other lipid lowering therapy (rosuvastatin 20 mg total) and 25 patients took rosuvastatin 40 mg plus other lipid lowering therapy; 492 patients took rosuvastatin 40 mg alone at all extension visits (rosuvastatin 40 mg only group).

Objectives relating to safety (extension safety population)

Interpretation of safety results during the extension period focuses on the rosuvastatin 40 mg alone treatment group, as this is the principal treatment group of interest. For the most important AEs and key laboratory abnormalities, the overall incidence from the total group and individual data from both the extension period and from the randomised period study are considered. Table S1 and S2 present results for the primary safety objective and selected key results from the secondary objectives relating to renal function and urinalysis.

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Table S1 Key results from safety renal objectives (extension safety population)

Parameter	Treatment Group[a]					
	Rosuvastatin 40 mg alone N = 583			Total N = 584		
Urine dipstick protein: shift from 'none' or 'trace' at baseline (Week 0) to:						
+ or (Primary objective)	**n/N[b]**	**%**	**(95% CI[c])**	**n/N[b]**	**%**	**(95% CI[c])**
At Week 6	NA	NA	NA	12/572	2.1	(1.09, 3.64)
At final visit	18/498	3.6	(2.16, 5.65)	20/565	3.5	(2.18, 5.41)
++ or greater (Secondary objective)						
At Week 6	NA	NA	NA	1/572	0.2	(0.00, 0.97)
At final visit	1/498	0.2	(0.01, 1.11)	1/565	0.2	(0.00 0.98)
Urine dipstick haem: shift from 'none' or 'trace' at baseline (Week 0) to:						
++ or greater (Secondary objective):	**n/N[b]**	**%**	**(95% CI[c])**	**n/N[b]**	**%**	**(95% CI[c])**
At Week 6	NA	NA	NA	13/563	2.3	(1.24, 3.92)
At final visit	11/486	2.3	(1.14, 4.01)	12/555	2.2	(1.12, 3.75)
Combined urine dipstick haem and protein shift from 'none' or 'trace' at baseline (Week 0) in both parameters to:						
++ or greater in urine dipstick protein and + or greater in urine dipstick haem (Secondary objective):	**n/N[b]**	**%**	**(95% CI[c])**	**n/N[b]**	**%**	**(95% CI[c])**
At Week 6	NA	NA	NA	0/554	0.0	(0.00, 0.66)
At final visit	1/480	0.2	(0.01, 1.16)	1/547	0.2	(0.00, 1.01)
Serum creatinine (Secondary objective)	**Rosuvastatin 40 mg alone, N = 583**			**Total, N = 584**		
Mean baseline value (SD), in in µmol/L	NA			91.4 (15.72)		
Mean change (SD) from baseline at final visit, in µmol/L	-3.0 (10.22)			-2.7 (10.39)		
> 100% increase from baseline at any time during the whole study, n (%)	0 (0.0)			0 (0.0)		

[a] N under treatment groups = overall number of patients in extension safety population by dose received at any time.
[b] For shift at Week 6 or at final visit: n/N, n= the number of patients in the extension safety population that developed a shift in urine dipstick protein and/or haem at the specified time point (study week) or at final visit; N=the total number of evaluable patients at the same time point or at final visit with a urine dipstick protein and/or haem grade of 'none' or 'trace' at baseline.
[c] 95% CI = 95% Clopper Pearson Exact Confidence Intervals
CI = Confidence Interval: NA = not applicable; SD = standard deviation.

Table S2 Results for development of urine dipstick protein and/or haem at any time during the extension period and whole study (extension safety population)

Parameter	Treatment Group[a]					
	Rosuvastatin 40 mg only[b], N = 492					
	+ or greater (primary objective)			++ or greater (secondary objective)		
Urine dipstick protein: shift from 'none' or 'trace' at baseline (Week 0) to +/++ or greater:						
	n/N[d]	**%**	**(95% CI[e])**	**n/N[d]**	**%**	**(95% CI[e])**
At any time during the extension period[c]	60/473	12.7	(9.82, 16.02)	8/473	1.7	(0.73, 3.31)
At any time during the whole study[c]	66/475	13.9	(10.91, 17.34)	9/475	1.9	(0.87, 3.57)
	Rosuvastatin 40 mg only[b], N[f] = 482					
Persistence of urine dipstick protein:	+ or greater, n[g] (%)			++ or greater, n[g] (%)		
Persistent – Shift (from 'none' or 'trace' at baseline) to + /++ or greater and at all subsequent visits in the extension period	3 (0.6)			0 (0.0)		
Intermittent – shift to +/++ or greater and at least one of the subsequent visits +/++ or greater and less than +/ less than ++ during the extension period	9 (1.9)			1 (0.2)		
Transient – Shift to +/++ or greater and no subsequent visit +/++ or greater during the extension period	39 (8.1)			6 (1.2)		
Final – Shift to +/++ or greater only at the last visit of the extension period	9 (1.9)			1 (0.2)		
	Rosuvastatin 40 mg only[b], N = 492					
	n/N[d]		**%**		**(95% CI[e])**	
Urine dipstick haem: shift from 'none' or 'trace' at baseline (Week 0) to ++ or greater (Secondary Objective):						
At any time during the extension period[c]	38/461		8.2		(5.90, 11.14)	
At any time during the whole study[c]	52/463		11.2		(8.50, 14.47)	
Combined urine dipstick haem and protein shift from 'none' or 'trace' at baseline (Week 0) in both parameters to ++ or greater in urine dipstick protein and + or greater in urine dipstick haem (Secondary objective):						
At any time during the extension period[c]	4/455		0.9		(0.24, 2.24)	
At any time during the whole study[c]	5/457		1.1		(0.36, 2.53)	

[a] N under treatment groups = overall number of patients in extension safety population by dose received at any time.
[b] Rosuvastatin 40 mg alone at all visits in the extension period.
[c] Based on the maximum urine dipstick protein and/or haem grade at any time during the extension period or whole study (extension safety population).
[d] For shift at any time: n/N n = the number of patients from the extension safety population that developed a shift in urine dipstick protein and/or haem on rosuvastatin at any time during the extension treatment period or whole study; N=the total number of evaluable patients during the extension period or during the whole study with a urine dipstick protein and/or haem grade of 'none' or 'trace' at baseline.
[e] 95% CI (Confidence Interval) = 95% Clopper Pearson Exact Intervals
[f] N= number of patients from the rosuvastatin 40 mg only group evaluable for persistence of urine dipstick protein during the extension period (10 patients with missing data)
[g] n = number of patients in category of persistence of urine dipstick protein

Primary objective and secondary objectives relating to urine protein dipstick analysis

The percentage of patients in the rosuvastatin 40 mg alone group that developed shifts in urine dipstick protein from 'none' or 'trace' at baseline to + or greater was low at each visit of the extension period eg, 3.6% patients at final visit. This was less than the percentage of patients that developed a maximal shift of + or greater in urine dipstick protein at any time during the extension period (12.7% patients [primary variable]) or during the whole study (13.9% patients). Shifts at any time were calculated for the rosuvastatin 40 mg only group, ie patients who received rosuvastatin 40 mg alone at all extension visits. These results indicate that the shifts occurred in different patients rather than persistently occurring in the same patients. This was confirmed by investigating persistence of + or greater protein shift for the patients in the rosuvastatin 40 mg only group. Only 0.6% of these patients experienced persistent urine dipstick protein and a predominantly transient or intermittent urine dipstick protein was observed in the majority of patients.

Similarly, the number and percentage of patients that developed proteinuria at any time during the extension period was low (eg 1 patient [0.2%] in the rosuvastatin 40 mg alone group at final visit). In the rosuvastatin 40 mg only group, 8 (1.7%) and 9 (1.9%) patients developed proteinuria at any time during the extension and whole study, respectively. Investigation of persistence again indicated predominantly transient or intermittent proteinuria with none of the patients developing persistent proteinuria. Investigation of AEs, renal parameters and other urinalysis data did not indicate a pattern of progressive worsening renal disease associated with development of proteinuria.

Secondary objectives relating to renal safety

Concerning protein/creatinine and albumin/creatinine ratios, the majority of patients remained within normal range throughout the extension period (protein/creatinine ratio ≤0.15 mg protein/ mg creatinine and albumin/creatinine ratio ≤0.03 mg albumin/ mg creatinine, respectively). At any given time point during the extension period, the number of patients with shift from normal urine protein/creatinine ratio at baseline to >0.50 mg protein/ mg creatinine (approximately >3 x ULN) was low (eg, 9 patients at final visit in the rosuvastatin 40 mg alone and total treatment groups). Similarly, the number of patients with a shift from normal urine albumin/creatinine ratio at baseline to >0.30 mg albumin/ mg creatinine (macroalbuminuria) at any time during the extension period was also low (eg, 0 and 2 patients at final visit in the rosuvastatin 40 mg alone and total groups, respectively). There was no association of normal to abnormal shifts in protein/creatinine or albumin/creatinine ratio with diabetic status.

The percentage of patients in the rosuvastatin 40 mg alone group that developed haematuria at any given time point during the extension period was low (eg, 2.3% patients at final visit) and was less than the percentage of patients in the rosuvastatin 40 mg only group with this shift at any time during the extension period (8.2% patients) or during the whole study (11.2% patients). Haematuria was mostly transient (4.2%); no patient in the rosuvastatin 40 mg only group had persistent haematuria. Few patients in the rosuvastatin 40 mg alone group developed a concurrent shift in urine dipstick protein ++ or greater, and urine dipstick

haem + or greater, during the extension period from 'none' or 'trace' at baseline in both parameters at any given time point during the extension period, or at any time during the whole study (see Table S1).

On average renal function was maintained over the long-term extension period treatment with rosuvastatin. The mean change in serum creatinine during the extension period was small, as was mean change in the glomerular filtration rate (GFR), irrespective of renal function at baseline. No patient had a clinically significant increase from baseline in serum creatinine (>100%). The total number and percentage of patients with an increase >30% from baseline to >ULN in serum creatinine during the extension period was low: 4 (0.7%). All 4 patients had underlying disease condition and/or concurrent illnesses (hypertension, diabetes, cardiac conditions) that were contributory factors to the elevation in serum creatinine. Increases >30% from baseline and > ULN in serum creatinine were not associated with AEs indicating deteriorating renal function.

SDS-PAGE was measured at baseline and, thereafter, only for the minority (66/584) of patients with positive urine dipstick protein at any time during the extension period. Of the 63 patients with normal SDS-PAGE at baseline and follow up measurements during the extension period: 28 exhibited no change from a normal pattern at baseline, 18 patients developed tubular proteinuria during the extension period (including 1 patient who reverted to a normal pattern at the final visit), 9 patients developed glomerular proteinuria and 3 patients developed mixed proteinuria. Investigation of serum creatinine values, AEs and available renal data did not indicate any overall pattern of acute or progressive worsening renal disease with development of an abnormal impression category during the extension period.

Secondary objectives relating to other safety parameters

Rosuvastatin 40 mg was well tolerated during the extension treatment period. In the total group 419 (71.7%) patients experienced 1174 treatment–emergent AEs. A total of 441 (75.5%) patients from the extension safety population experienced 1395 AEs during the whole study. For the majority of patients – 372 (63.7%) – the AEs were of mild to moderate intensity. Overall, the pattern and frequency of treatment-emergent AEs, SAEs, AEs leading to withdrawal from the study and other significant AEs was as expected given the study population, class of drug to which rosuvastatin belongs (statins) and long-term treatment under investigation. One patient experienced myocardial infarction (MI), was withdrawn, underwent cardiac surgery and subsequently died from cardiogenic shock. The MI and cardiogenic shock were not considered as related to study treatment by the investigator – this patient also experienced CK > 10 x ULN (see results below). The proportion of patients who were down titrated to rosuvastatin 20 mg at any time during the extension period was low – 9 % (53 patients). A total of 4% (24) patients experienced AEs leading to withdrawal from the extension period.

Investigation of the study database revealed that no patient had any combination of symptoms and abnormal laboratory values suggestive of drug-induced hepatic disease. A total of 3 (0.5%) patients experienced clinically significant elevation in ALT (> 3 x ULN on at least 2 consecutive visits) during the whole study (2 patients during the extension period and

1 patient during the randomised rosuvastatin 40 mg treatment). The elevations in ALT were considered by the investigator to be study drug-related AEs in all 3 patients. The clinically significant elevation in ALT led to withdrawal of 2 patients, and occurred at the last protocolled visit during the extension period in the third patient. ALT levels were resolving (<3 x ULN but above ULN) or resolved (<ULN) off study treatment in all 3 patients. No AEs suggestive of liver disturbance occurred in these 3 patients. Other hepatic laboratory data (AST, bilirubin, gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP]), and other AEs of interest related to liver symptomatology were generally unremarkable and, overall, did not give any safety concerns. Hepatic biochemistry results were consistent with the known safety profile of rosuvastastin 40 mg.

The type and frequency of treatment-emergent AEs suggestive of muscle damage and muscle biochemistry data reported during the extension period fell within the known safety profile of rosuvastatin 40 mg. A total of 36 (6.2%) patients experienced treatment-emergent myalgia during the extension period; 42 (7.2%) patients experienced treatment-emergent myalgia on rosuvastatin during the whole study. Three (0.5%) patients experienced clinically significant elevations in CK (>10 x ULN) while receiving rosuvastatin 40 mg during the whole study (occurred during the extension period for all 3 patients). The clinically significant elevation in CK was due to MI in 1 patient (an elevation in the cardiac CK isozyme), who was withdrawn and subsequently died from cardiogenic shock following surgery (see above). Clinically significant elevation in CK was associated with muscle symptoms (myopathy) in 1 patient. Exercise was a possible contributory factor to the myopathy in this patient, who recovered (CK <ULN and lack of any symptoms) off treatment after a 7-day interruption of rosuvastatin 40 mg treatment, which was restarted at the 20 mg dose without any further significant increase in CK. In the third patient the clinically significant CK elevation was considered by the investigator to be due to work-related physical activities. Study medication was discontinued due to an elevation in CK (>5 x ULN), however, CK level >10 x ULN only occurred 15 days after last dose of rosuvastatin 40 mg treatment and was still >10 x ULN when measured at an unscheduled follow-up visit. Overall, the incidence and pattern of muscle AEs and biochemistry fell within the known safety profile of rosuvastatin 40 mg.

AEs relating to the urinary-renal system reported during the extension period gave no cause for concern and fell within the known safety profile for rosuvastatin 40 mg.

Secondary objectives relating to efficacy (extension ITT population)

The rosuvastatin 40 mg alone treatment group was of principal interest for efficacy; results for this group are reported below.

The majority of patients in the rosuvastatin 40 mg alone group achieved their NCEP ATP III LDL-C goal at final visit in the extension period: 77% patients for all NCEP risk categories combined, and 61% of the high risk, 76% of the medium risk and 90% of the low-risk patients. The proportion of patients receiving rosuvastatin 40 mg plus other lipid lowering therapy for failing to meet their lipid target goal at any time during the treatment period was low – 4% (25 patients). Percentage change from baseline in lipids, lipid ratios, apolipoproteins and apolipoprotein ratio indicated an overall improvement in atherogenic lipid

profile during the extension period. There were large reductions from baseline at all time points in LDL-C, TC, TG, nonHDL-C and lipid ratios (LDL-C/HDL-C, TC/LDL-C, nonHDL-C/HDL-C), and increases in HDL-C at all time points. At Week 48 and at final visit there was a 54% reduction from baseline in LDL-C, and a 12 to 13% increase from baseline in HDL-C (lipids of principal interest).

Date of the report

16th June, 2005