Drug product:	Rosuvastatin tablets 20 mg and 40 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
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A 48-Week Open-Label, Non-Comparative, Multicentre, Phase IIIb Study To Evaluate The Efficacy and Safety of the Lipid-Regulating Agent Rosuvastatin 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 148 centres: Australia (9 centres), Canada (14 centres), France (9 centres), Israel (7 centres), South Africa (7 centres), US (102 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	21 February 2002	Therapeutic confirmatory (IIIb)
Last patient completed	6 January 2004[a]	

[a] Last visit – follow up by phone call was performed for the last patient on 5 February 2004

Objectives

Primary objective

The primary objective of the study was to assess the efficacy and long-term safety of once-daily rosuvastatin 40 mg in patients with Type IIa and Type IIb dyslipidaemia, including heterozygous familial hypercholesterolaemia. Efficacy was evaluated by determining the number and percentage of patients attaining National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline treatment goals, including those for low-density lipoprotein cholesterol (LDL-C) C after 12 weeks of treatment. Safety was

evaluated by the incidence and severity of adverse events (AEs) and abnormal laboratory values.

Secondary objectives

The secondary objectives of the study were to assess the efficacy of once-daily rosuvastatin 40 mg in patients with Type IIa and Type IIb dyslipidaemia, including heterozygous familial hypercholesterolaemia, over 48 weeks, by measuring:

- The number and percentage of patients, overall and by risk category, who achieved their NCEP ATP III optimal LDL-C goal after 12 (by risk category only), 24, 36 and 48 weeks of treatment.
- The number and percentage of patients, overall and by risk category, who achieved their NCEP ATP III optimal non-high-density lipoprotein cholesterol (nonHDL-C) goal after 12 weeks of treatment.
- The number and percentage of patients who maintained their NCEP ATP III optimal LDL-C goal from Week 12 to Week 48 of treatment.
- The number and percentage of patients who achieved their European optimal LDL-C goal after 12 weeks of treatment.
- The percentage change from baseline in LDL-C, total cholesterol (TC), HDL-C, triglyceride (TG), nonHDL-C, apolipoprotein-B (Apo-B), apolipoprotein-A (ApoA-I), LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C and Apo-B/Apo-A-I after 12, 24, 36 and 48 weeks of treatment.

Note that the secondary objectives are those described in the statistical analysis plan and not those described in the protocol. The changes were: omission of the investigation of maintenance of nonHDL-C goal between Week 12 and 48 (patients were titrated to their LDL-C goal at Week 12 and at all times after Week 12 which renders maintenance of this goal as meaningless), and addition of a Week 36 timepoint to the 1st, 3rd and 5th objectives (further useful information obtained by collection of data at Week 36).

Study design

This was a 48-week, open-label, non-comparative, multicentre, Phase IIIb study, followed by an optional 48-week, open-label, non-comparative extension phase. The extension phase of the study will be presented in a separate Clinical Study Report.

Target patient population and sample size

Male and female patients aged 18 years and older with Type IIa and Type IIb dyslipidaemia, including heterozygous familial hypercholesterolaemia. Following a 6-Week dietary lead-in period (Therapeutic Lifestyle Change Diet), patients must have had a baseline fasting LDL-C ≥ 190 mg/dL (4.91 mmol/L) and ≤ 260 mg/dL (6.72 mmol/L).

A total of 1177 patients were required to enter the study to satisfy both the efficacy and safety requirements of the study; namely, 1000 patients completing a full year on rosuvastatin 40 mg.

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

Open-label rosuvastatin (ZD4522) 40 mg (Formulation No: 12821; Batch Nos: 10011011, 10011513, 10011664, 10011813, 10011864, 10011884, 10011894, 10011907, 10011909, 10011911, 10011913, 10011918, 10012336, 10014749, 10014996, 10015046, 100154246, 10015048, 10015244, 10016055, 10017443, 10017592, 10018046, 20000276, 20000286, 20000302, 20000321, 20000338, 20000357, 20002860, 82884I01, 82994I01, 82994101, 82995F01, 90557I02, 90557J02, B2994101) or 20 mg (Formulation No: 12673; Batch Nos: 10012330, 10012332, 10012334, 10012336, 10012338, 10014753, 10015007, 10015108, 10015167, 10015169, 10017594, 10019189, 20000302, 82998P01, 90528H02, 90530F02, 90537G02, 90528H02). Doses were administered once daily as a single tablet.

Duration of treatment

A 6-Week dietary lead-in period followed by a 48-Week treatment period with rosuvastatin 40 mg. Patients whose LDL-C fell to below 50 mg/dL (1.29 mmol/L) could be down-titrated to 20 mg rosuvastatin at the discretion of the investigator.

At the investigator's discretion and after consultation with the AstraZeneca physician, a patient may have been down-titrated from rosuvastatin 40 mg to 20 mg when there were alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels increased >3 x ULN or creatine kinase (CK) elevations >10 x ULN, or mild muscle pains without CK elevation. Down-titration of rosuvastatin should only have occurred when both the investigator and the AstraZeneca physician felt it would be in the best interest of the patient to continue in the study at the lower dose. Additionally, a patient may have been down-titrated if they experienced a condition or AE, which, in the investigator's opinion, merited this course of action (see Study Protocol, Appendix 12.1.1). Note that the 40 mg dose could be reintroduced in patients who had been down-titrated to rosuvastatin 20 mg at the discretion of the investigator and AstraZeneca study physician.

Patients who did not meet their goals after 12 weeks of therapy with rosuvastatin 40 mg had other appropriate lipid-lowering therapies co-administered (with the exception of other statins, which were prohibited) with 40 mg rosuvastatin or may have been discontinued from the study at the discretion of the investigator.

Patients who successfully completed this phase of the study had the option of entering a 48-week extension phase (with the exception of any US patients who had been enrolled in a site with less than 3 patients).

Treatment groups

Patients were initially administered rosuvastatin fixed dose 40 mg at Visit 4 (Week 0). However, during the treatment period, down-titration to rosuvastatin 20 mg was allowed for safety or efficacy reasons, while additional lipid lowering therapy to rosuvastatin 40 mg was allowed for patients not achieving their NCEP ATP III LDL-C goal after Week 12. Thus, any of the following treatments could be administered during the treatment period: rosuvastatin 40 mg alone, rosuvastatin 20 mg, or rosuvastatin 40 mg plus other lipid lowering therapy.

Treatment groups analysed were:

- Rosuvastatin 40 mg alone.
- Rosuvastatin 40/20 mg (for patients down-titrated to rosuvastatin 20 mg during the treatment period).
- Rosuvastatin 40 mg plus other lipid lowering therapy.

The following treatment groups were derived from the above:

- Rosuvastatin 40 mg only – for patients who received rosuvastatin 40 mg alone at all treatment visits.
- Rosuvastatin 40 mg total – combined group for patients receiving 40 mg rosuvastatin alone and those receiving 40 mg rosuvastatin co-administered with another lipid lowering therapy.
- Total – combined group for patients receiving rosuvastatin 40 mg alone, rosuvastatin 20 mg or rosuvastatin 40 mg plus another lipid lowering therapy.

There was a large degree of overlap between the above categories since patients could appear in more than one category during the course of the study. The treatment group of principal interest for the long-term effect of rosuvastatin 40 mg treatment was rosuvastatin 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 on rosuvastatin 40 mg plus other lipid lowering therapy was small compared with the other treatment groups. For this reason data and results for this treatment group 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.

In this report efficacy results are summarised by dose at that visit. For the safety results AEs and laboratory values of specific interest are summarised by dose at onset and standard laboratory results by dose at that visit.

Criteria for evaluation (main variables)

Efficacy

Primary variable (endpoint):

- Percentage of patients overall who achieved NCEP ATP III guideline treatment goal for LDL-C at Week 12 of treatment with 40 mg rosuvastatin.

Secondary variables (endpoints):

- Percentage of patients (overall and by risk category) who achieved NCEP ATP III guideline treatment goal for LDL-C at Weeks 12 (by risk category only), 24, 36 and 48 of treatment with 40 mg rosuvastatin.
- Percentage of patients (overall and by risk category) who achieved NCEP ATP III guideline treatment goal for nonHDL-C at Week 12 of treatment with 40 mg rosuvastatin.
- Percentage of patients who maintained NCEP ATP III guideline treatment goal for LDL-C from Week 12 to Week 48 of treatment.
- Percentage of patients who achieved European guidelines (1998) treatment goal for LDL-C at Week 12 of treatment with 40 mg rosuvastatin.
- Percentage change from baseline in LDL-C, TC, HDL-C, TG, nonHDL-C, Apo-B, ApoA-I, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C and Apo-B/Apo-A-I after 12, 24, 36 and 48 weeks of treatment with 40 mg rosuvastatin.

Note that the secondary variables are those described in the statistical analysis plan (see under 'Secondary Objectives' for a summary of the changes).

Safety

Primary variable (endpoint):

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

Effects on the liver (by measurements of ALT and assessment of AEs and symptoms possibly related to liver effects) and on muscle (by measurement of CK and assessments of AEs and symptoms possibly related to muscle effects) were carefully monitored in this study as these are known side effects of rosuvastatin and of statins in general. Renal effects of rosuvastatin 40 mg were also carefully monitored and included: AEs and symptoms related to renal-urinary system; incidence of shift in urine dipstick protein from 'none' or 'trace' at baseline to ≥ ++ ('proteinuria'), shift in urine dipstick haem from 'none' or 'trace' at baseline to ≥ + ('haematuria') and development of concurrent proteinuria and haematuria; evaluation of urinary protein sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE)

excretion pattern (for all patients at baseline and at Week 4 and, thereafter, only for patients with positive urine dipstick values at visits where positive dipstick values were recorded); assessment of patients with increase >30% from baseline in serum creatinine; and change in creatinine clearance and glomerular filtration rate (GFR) from baseline at Week 48.

Statistical methods

Efficacy data was evaluated based on the ITT and PP populations. The primary analysis of the primary efficacy endpoint was performed as last observation carried forward (LOCF) in the ITT population. The rosuvastatin 40 mg alone group was of primary interest.

Results were presented by treatment received. Analysis was performed on treatment group by final dose, dose at that time, dose at onset, and dose at any time.

Patient population

In total 3428 patients entered the dietary lead-in period (of a planned 2943) and 1383 patients entered the treatment period (of a planned 1177).

The majority of patients entering the treatment period were Caucasian (90%) and between 18 and 84 years of age. There were approximately equal numbers of males and females (51% males and 49% females) 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.

Of the 1383 patients entering the treatment period, 1382 were allocated study treatment – 1 patient did not receive study medication in error and was withdrawn. Two of the 1382 patients did not take their study treatment and were excluded from the safety population and a total of 143 patients were withdrawn, leaving 1239 patients who completed the study.

Overall, (total treatment group) there were 1380 patients in the safety population and 1369 and 822 patients in the ITT population and PP population by final dose, respectively. A total of 1380 patients took rosuvastatin 40 mg alone, 134 patients took rosuvastatin 20 mg, and 38 patients took rosuvastatin 40 mg plus other lipid lowering therapy at some point during the treatment period; 1000 patients only took rosuvastatin 40 mg alone at all visits of the treatment period.

Efficacy results

Table S1 presents: the primary analysis of the percentage of patients overall who achieved NCEP ATP III guideline treatment goal for LDL-C at Week 12 of treatment with 40 mg rosuvastatin; the percentage of patients achieving NCEP goal at Week 12 by NCEP risk category; and the percentage of patients overall and by risk category achieving their NCEP LDL-C goal at Week 48.

Table S1 Percentage of patients overall and by risk category achieving their NCEP LDL-C goal at Week 12 and Week 48 (ITT population with LOCF)

	Treatment Group [a]			
NCEP ATP III LDL-C goal	**Rosuvastatin 40 mg alone**	**Rosuvastatin 40 mg total**	**Rosuvastatin 40/20 mg**	**Total**
Primary efficacy endpoint: All NCEP ATP III categories at Week 12				
At Week 12 overall, % (n/N[b])	82.7 (1070/1294)	NC	78.4 (40/51)	82.5 (1110/1345)
Key secondary NCEP endpoints: NCEP ATP III categories % (n/N[b]) at Week 12 by risk category, and at Week 48 overall and by risk I				
At Week 12 by risk category, % (n/N[b])				
High	61.7 (259/420)	NC	52.2 (12/23)	61.2 (271/443)
Medium	87.3 (310/355)	NC	100.0 (6/6)	87.5 (316/361)
Low	96.5 (501/519)	NC	100.0 (22/22)	96.7 (523/541)
At Week 48, overall and by risk category, % (n/N[b])				
Overall	80.8 (999/1236)	80.0 (1012/1265)	78.6 (81/103)	79.9 (1093/1368)
High	63.9 (251/393)	62.7 (261/416)	60.0 (21/35)	62.5 (282/451)
Medium	81.6 (283/347)	81.1 (283/349)	84.2 (16/19)	81.3 (299/368)
Low	93.8 (465/496)	93.6 (468/500)	89.8 (44/49)	93.3 (512/549)

[a] N under treatment groups = overall number of ITT patients in treatment group by final dose.
[b] n/N where n = Number of patients reaching NCEP ATP III LDL-C goal at Week 12 or Week 48 and N = Number of evaluable patients (excluding patients with values not recorded) in a category at baseline. NC = not calculated. Number and percentage of patients achieving NCEP ATP III LDL-C goal was not calculated for rosuvastatin 40 mg total treatment group at Week 12.

For the efficacy parameters the primary analysis of interest was from the ITT population using LOCF data and dose at that timepoint (with the exception of the secondary parameters maintenance of NCEP ATP III LDL-C goal from Week 12 to 48, which used observed data).

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

For the primary efficacy objective the majority of rosuvastatin 40 mg alone patients (all NCEP risk categories combined) achieved their NCEP ATP III LDL-C goal at Week 12: 83%, 95% CI (81, 85%). The expected response rate of at least 65% was exceeded. The majority of patients also achieved their NCEP ATP III LDL-C goal at Week 12 in the high (62%),

medium (87%) and low-risk (97%) categories. Additionally, the majority of patients also achieved their NCEP ATP III LDL-C goals at Weeks 24, 36 and 48 in all categories combined (>80%), and the high (>61%), medium (>81%) and low-risk (>93%) categories. The majority of patients in the rosuvastatin 40 mg alone group who achieved their LDL-C goal at Week 12 maintained their goal at Week 48 (89%) and at Week 12 and all intervening visits to Week 48 (82%). At Week 12, most of the patients achieved their European LDL-C (78%) and NCEP nonHDL-C goal (patients with baseline TG ≥ 200 mg/dL; 94% overall). The proportion of patients who were co-administered other lipid lowering therapy for failing to meet their lipid target goal at any time during the treatment period was low – 3% (38 patients). Percentage change from baseline in lipids, lipid ratios, apolipoproteins and apolipoprotein ratio indicated an overall improvement in atherogenic lipid profile that was maintained throughout the 48-Week treatment period. There were statistically significant reductions from baseline at all timepoints in LDL-C, TC, TG, nonHDL-C and lipid ratios (LDL-C/HDL-C, TC/LDL-C, nonHDL-C/HDL-C), ApoB and apolipoprotein ratio (ApoB/ApoA-I), and statistically significant increases in HDL-C and ApoA-I at all timepoints ($p<0.0001$ for all lipids, apolipoproteins and ratios at all timepoints). At Weeks 12 and 48 there was a 55% [95% CI = (53; 55)] and 53% [95% CI = (51; 53)] reduction, respectively, from baseline in LDL-C, and an 11% [95% CI = (10; 12)] and 12% [95% CI = (10; 13)] increase, respectively, from baseline in HDL-C (lipids of principal interest).

Results from the rosuvastatin 40 mg total, rosuvastatin 40/20 mg and total treatment groups were in general agreement with results from the rosuvastatin 40 mg alone group.

Safety results

The rosuvastatin 40 mg alone and total treatment groups were of principal interest for the safety analysis. Key safety results are summarised in Table S2.

Table S2 Treatment-emergent AEs and key laboratory data (safety population)

	Treatment Group[a]							
	Rosuvastatin 40 mg alone		**Rosuvastatin 40 mg total**		**Rosuvastatin 40/20 mg**		**Total**	
	N = 1380		**N = 1380**		**N = 134**		**N = 1380**	
Category of AE[b]	**Number (%) of patients who had an AE in each category**							
Any AEs	1108	(80.3)	1112	(80.6)	87	(64.9)	1117	(80.9)
Serious AEs	103	(7.5)	103	(7.5)	10	(7.5)	113	(8.2)
Serious AEs leading to death	3	(0.2)	3	(0.2)	0	(0)	3	(0.2)
Discontinuations of study treatment due to AEs	63	(4.6)	64	(4.6)	9	(6.7)	73	(5.3)
Other significant AE[c]	145	(10.5)	148	(10.7)	6	(4.5)	150	(10.9)
	Total number of AEs							
Any AEs	3797		3859		244		4103	
Serious AEs (including events leading to death)	152		153		14		167	
Serious AEs leading to death	3		3		0		3	
AEs leading to discontinuation	112		115		15		130	
Other significant AEs	184		187		7		194	
Key laboratory findings	**Number (%) of patients**							
n	1367		1367		120[d]		1369	
ALT >3 x ULN on ≥ 2 consecutive visits	8 (0.6)		8 (0.6)		1 (0.8)[e]		9 (0.7)	
ALT >3 x ULN on ≥ 2 consecutive visits and withdrawn	3		3		1[e]		4	
CK >10 x ULN[f]	14 (1.0)		14 (1.0)		1 (0.8)		15 (1.1)	
Myopathy (CK >10 x ULN and associated muscle symptoms)[f]	10[e]		10		1[e]		11	
Myopathy and withdrawn	1		0		1[e]		2	
Myopathy and resolved on therapy	4		0		0		4	
Myopathy and resumed therapy after temporary interruption and completed the study as planned	3		0		0		3	

Table S2 Treatment-emergent AEs and key laboratory data (safety population)

	Treatment Group[a]			
	Rosuvastatin 40 mg alone	**Rosuvastatin 40 mg total**	**Rosuvastatin 40/20 mg**	**Total**
	N = 1380	**N = 1380**	**N = 134**	**N = 1380**
Increase >30% and >ULN in serum creatinine[g]	12 (0.9)	12 (0.9)	0 (0.0)	12 (0.9)
Increase >30% and >ULN in serum creatinine and withdrawn during the same period	1	1	0	2
Development of urine dipstick protein from 'none' or 'trace' at baseline to ≥++ (proteinuria) at Week 48 by final dose:				
n/N[h]	18/1119	18/1146	0/92	18/1238
% (95% CI)	1.6 (0.96, 2.53)	1.6 (0.93, 2.47)	0 (0.00, 3.93)	1.5 (0.86, 2.29)
Proteinuria at any time:				**Rosuvastatin 40 mg only[i], N = 1000**
n/N[g]				52/1000
% (95% CI)				5.2 (3.91, 6.76)
Persistence of proteinuria, n (%)				
Persistent proteinuria (shift in urine protein to ≥++ and all subsequent visits ≥++)				4 (0.4)
Final (shift in urine protein to ≥++ at the last visit)				5 (0.5)
Transient or intermittent (shift in urine protein to ≥++ and no subsequent visit ≥++ or ≥++, at least 1 subsequent visit to ≥++, and at least 1 subsequent visit <++)				43 (4.3)

[a] Treatment groups by dose at onset for AEs and by dose at first occurrence for laboratory findings. N under treatment groups = overall number of patients in safety population who took that treatment at any time.

[b] Patients with multiple AEs in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[c] Other significant AEs of interest are known side effects of statins, and conditions commonly associated with drug use in general.

[d] For CK elevations, n=121

[e] Includes: Patient 1048/0001 recorded on the database as receiving rosuvastatin 40 mg at onset of ALT >3 x ULN and CK >10 x ULN, but according to supplementary data was down-titrated to 20 mg and remained on this dose at onset of abnormal laboratory readings (patient was withdrawn due to ALT and CK elevations), and Patient 1111/0001 who was withdrawn due to myopathy and ALT >3 x ULN after completing the study period (recorded as completing study in the study database).

[f] Includes Patient 1077/0031 who was identified as having CK >10 x ULN from local lab values. Also includes 9 patients with myopathy (CK >10 x ULN with associated muscle symptoms) identified following review of supplementary information. Note the term myopathy was not reported in the study database.

[g] Includes Patient 4007/0002 as having serum creatinine increase >30% and >ULN from local labs (patient experienced acute renal failure and had an increase >100%)

[h] For n/N, n= the number of patients that developed a shift in urine dipstick protein at Week 48 or at any time, N=the total number of evaluable patients at Week 48 or at any time with a urine dipstick protein grade of 'none' or 'trace' at baseline.

[i] Patients only on rosuvastatin 40 mg alone throughout the treatment period.
95% CI = 95% Confidence Intervals (Clopper Pearson Exact Intervals). NA = not applicable. Proteinuria at any time was calculated only for the rosuvastatin 40 mg alone treatment group.

Rosuvastatin 40 mg and 20 mg was well tolerated during the 48-week treatment period. In the rosuvastatin 40 mg alone group 1108 (80%) patients experienced 3797 treatment–emergent AEs. The majority of AEs were of mild to moderate intensity. Overall, the pattern and incidence of treatment-emergent AEs, SAEs, AEs leading to withdrawal 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. Three SAEs leading to death were reported: bile duct cancer, myocardial infarction (MI), and cervical vertebra fracture following an accident; none were considered related to study treatment. The proportion of patients who were down-titrated to rosuvastatin 20 mg at any time during the treatment period was low – 10% (134 patients).

The study database was examined in detail for a combination of symptoms and abnormal laboratory values suggestive of hepatic disturbance; it was found that no patient had any such combination. A total of 22 (1.6%) patients had elevations in ALT >3 x ULN at any time during the treatment period of which 9 (0.7%) were clinically significant (ALT >3 x ULN at 2 or more consecutive visits). The clinically significant elevation in ALT was associated with CK >10 x ULN in 4/9 patients suggesting the raised transaminase was due to muscle rather than liver disturbance in these patients. For the majority of patients ALT elevation resolved or was resolving on treatment and no patient had any associated liver symptoms. Other hepatic laboratory data (AST, bilirubin, gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP]), and other significant AEs of interest related to liver symptomatology were generally unremarkable and, overall, did not give any safety concerns.

The study database was examined in detail for treatment-emergent AEs suggestive of muscle damage, such as muscle pain, myalgia, muscle tenderness or muscle weakness. The incidence and pattern of such AEs fell within the known safety profile of rosuvastatin 40 mg. A total of 117 (8.5%) patients experienced treatment-emergent myalgia. A total of 15 (1.1%) patients had an elevation in CK >10 x ULN, of which 11 patients had associated muscle symptoms, therefore conforming to the criteria for myopathy. One patient experienced muscle symptoms 3 days after peak CK elevation (when CK was < 5 x ULN) and was therefore not included in the number of myopathies. Exercise / increased physical activity was a possible contributory factor to the CK elevation / symptoms in 14 out of the 15 patients; symptomatic CK elevation >10 x ULN was considered by the investigator to be due to a combination of study drug and exercise in 2 patients. All 15 patients with CK >10 x ULN recovered: 12 patients continued in the study without further significant CK increases (6 patients recovered on study treatment and 6 off treatment but had a negative re-challenge), and 3 patients recovered off therapy (2 patients were withdrawn due to CK elevation and myopathy occurred 8 days after completion of study treatment in 1 patient).

Concerning renal biochemistry and urinalysis, 35 (2.6%) patients had an increase of >30% from baseline in serum creatinine at any time during the treatment period; in 12 (0.9%) patients the increase in serum creatinine was >30% and above ULN. For the majority of these 12 patients, the elevation in serum creatinine was transient and not associated with AEs indicating renal deterioration. Underlying disease conditions such as hypertension, diabetes, impaired renal function at baseline, or non-drug related AEs occurring during the treatment

period, were likely major contributory factors to the elevation. Four patients had >100% increase from baseline in serum creatinine. In all 4 patients, underlying disease condition and/or a non-drug related AE was responsible for the elevation in serum creatinine: 1 patient experienced acute renal failure (ARF) following a motor vehicle accident, aspiration pneumonia and septic shock (patient was withdrawn and recovered after 15 months of intermittent dialysis); 1 patient with diabetes and pre-existing chronic renal insufficiency experienced congestive heart failure during the treatment period (elevated serum creatinine was ongoing on treatment); 1 patient with pre-existing cardiac conditions experienced cardiac failure (elevated serum creatinine resolved on treatment); and 1 patient with renal artery stenosis and severely impaired renal function at baseline experienced urinary tract infection (elevated serum creatinine was resolving on treatment). Overall laboratory values revealed little change from baseline in serum creatinine, creatinine clearance and glomerular filtration rate (GFR) at Week 48.

In the rosuvastatin 40 mg alone group, the number and percentage of patients (ITT population) that at Week 48 developed urine dipstick protein of ≥++ or greater from 'none' or 'trace' at baseline (ie, proteinuria) was 18 patients (1.6%). The number and percentage of patients with proteinuria at any time during the treatment period (for patients receiving rosuvastatin 40 mg alone throughout the treatment period) was 52/1000 (5.2%). However, the number and percentage of patients with persistent proteinuria was low: 4/1000 (0.4%); urine dipstick protein laboratory data from the extension phase indicated a change from a persistent to intermittent pattern of proteinuria in 3 of these patients, while proteinuria resolved in the fourth patient following interruption of study treatment.

In the rosuvastatin 40 mg alone group at Week 48, 47 patients (4.1%) developed a shift in urine dipstick haem to ≥+ at from 'none' or 'trace' at baseline, while 6 patients (0.5%) developed a combined shift to ≥++ in urine dipstick protein and ≥+ in urine dipstick haem from 'none' or 'trace' at baseline in both parameters (based on the ITT population).

Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) was measured at baseline and Week 4, and from Week 8 to Week 48 only for patients with positive dipstick protein at visits where urine protein was detected. At baseline and Week 4 the majority of patients had a normal (normal or physiological) urinary pattern of excretion. A total of 1031 patients had baseline SDS-PAGE data. Of the 993 patients with normal SDS-PAGE at baseline: 41 (4.0%) patients shifted to tubular, 29 patients (2.8%) shifted to a glomerular pattern, 13 patients (1.3%) shifted to mixed, and 28 patients (2.7%) changed to various patterns during the treatment period. SDS-PAGE was abnormal at baseline in 38 (3.7%) patients but for 871 (85%) patients SDS-PAGE remained normal at every follow up visit up to Week 48 (there were no post-baseline SDS-PAGE data for 11 patients). Serum creatinine values, other available renal data and AEs in patients who developed an abnormal SDS-PAGE pattern during the treatment period, and in patients with an abnormal SDS-PAGE pattern at baseline and during the treatment period did not indicate any overall pattern of acute or progressive worsening renal disease.

Overall, results for other laboratory parameters (haematology, renal biochemistry, other biochemistry), vital signs and physical examination were unremarkable. There were no notable individual changes.

Date of the report

14th March 2005