AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin calcium
Study Code	D3569C00007
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A Randomized, Double-Blind, 52-Week, Parallel-Group, Multicenter, Phase IIb Study to Evaluate the Effects of Rosuvastatin 10 mg, Rosuvastatin 40 mg, and Atorvastatin 80 mg on Urinary Protein Excretion in Hypercholesterolemic Diabetic Patients with Moderate Proteinuria

PLANET I: Prospective evaLuation of proteinuriA and reNal function in diabETic patients with progressive renal disease

Study dates: First patient enrolled: 08 February 2006
Last patient completed: 03 March 2009

Phase of development: Therapeutic exploratory (IIb)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centers

This study was conducted at 147 centers from 11 countries: Argentina (5 centers), Brazil (8), Bulgaria (10), Canada (10), Denmark (9), France (17), Hungary (26), Italy (11), Mexico (8), Romania (9), and the United States (34).

Publications

At the time of this report, there are no publications describing the trial or its outcome.

Objectives

The primary objective of this study was to evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio from baseline to Week 52 in patients with Type 1 or 2 diabetes, moderate proteinuria, and hypercholesterolemia.

The secondary efficacy objectives of the study were:

- To evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio from baseline to Week 26
- To evaluate the effects of rosuvastatin and atorvastatin on urinary albumin excretion by evaluation of the change in urinary albumin/creatinine ratio from baseline to Weeks 26 and 52
- To evaluate the effects of rosuvastatin and atorvastatin on: low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), nonhigh-density lipoprotein cholesterol (nonHDL-C), apolipoprotein A-1 (ApoA-1), apolipoprotein B (ApoB), TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, and ApoB/ApoA-1 to explore the relationship between renal effects and lipid changes at Weeks 26 and 52
- To evaluate the effects of rosuvastatin and atorvastatin on renal function by evaluation of the change in estimated GFR (eGFR) predicted from the Modification of Diet in Renal Disease (MDRD) equation from baseline to Weeks 26 and 52

The secondary safety objective of this study was:

- To evaluate the effect of rosuvastatin and atorvastatin on the incidence and severity of adverse events (AEs) and laboratory data

Study design

This was a randomized, double-blind, parallel-group, multinational, multicenter, Phase IIb study evaluating the effects of rosuvastatin 10 mg, rosuvastatin 40 mg, and atorvastatin 80 mg over 52 weeks on urinary protein excretion in hypercholesterolemic, Type 1 or 2 diabetic patients with moderate proteinuria.

Target population and sample size

Male and female patients aged ≥18 years with Type 1 or 2 diabetes, moderate proteinuria (baseline urinary protein/creatinine ratio ≥500 mg/g and ≤5000 mg/g), hypercholesterolemia (fasting LDL-C ≥90 mg/dL [2.33 mmol/L]) and receiving current treatment with angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) for ≥3 months prior to Visit 1 were invited to attend the clinic.

The primary outcome variable for this study, which the sample size calculation had been based upon, is the change in urinary protein/creatinine ratio from baseline to Week 52. A 2-sided significance level of 5% was applied for hypothesis testing for a positive within treatment effect versus baseline; a 95% confidence interval (CI) was assessed for testing of no clinically significant deterioration from baseline for the primary outcome variable in each of the treatment groups. The required power was 90%. Data taken from the literature suggest that a coefficient of variation (CV) of 75% was a conservative estimate of the variability of the primary outcome variable. Assuming a treatment ratio (post:pre-treatment of urinary protein/creatinine) of 0.80 (20% reduction) and a CV of 75%, approximately 97 evaluable patients per group were required to show an effect versus baseline.

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

Table S1 summarizes the details of the investigational product used in this study.

Table S1 Details of investigational product and any other study drugs

Investigational product	Dosage form and strength	Manufacturer [a]	Formulation number	Batch number [b,c]
Rosuvastatin	5 mg encapsulated tablets	AstraZeneca	F13379	TS25025
				TX27037
				TX25038
Rosuvastatin	10 mg encapsulated tablets	AstraZeneca	F12927	TX15027
				TX16026
				TX15034
Rosuvastatin	20 mg and 40 mg encapsulated tablet	AstraZeneca	F12935	TX15027
				TX27042
				TX27041
				TX15034

Table S1 Details of investigational product and any other study drugs

Investigational product	Dosage form and strength	Manufacturer [a]	Formulation number	Batch number [b,c]
Atorvastatin	40 mg encapsulated tablet	Pfizer Ireland Pharmaceuticals	F12560	10435V
				05516V
				165116
				356057
				251107
				10435V

[a] Rosuvastatin was manufactured by IPR Pharmaceuticals, Inc.
[b]. Batch numbers are referenced in Appendix 12.1.6 of the CSR for all treated patients.
[c] Batch numbers are not required for non-investigational product/test drug.

Duration of treatment

Patients initially entered an 8-week lead-in period during which they underwent optimization of existing anti-hypertensive treatments, withdrawal of statin treatment if applicable, and dietary advice. At the end of the lead-in period, eligible patients were randomized with a 1:1:1 randomization ratio to receive blinded treatment with either rosuvastatin 10 mg, rosuvastatin 40 mg, or atorvastatin 80 mg. For the first 4 weeks of the active treatment period, patients randomized to rosuvastatin 40 mg or atorvastatin 80 mg received a half-dose of study drug to assess tolerability. If there were no safety concerns warranting the withdrawal of study drug after 4 weeks, then the treatment dose was doubled to the full randomized dose for 48 weeks. Patients randomized to receive rosuvastatin 10 mg received this dose for 52 weeks.

Criteria for evaluation - efficacy (main outcome variables)

The Intention-to-Treat (ITT) population, which was used for the primary analysis, consisted of all randomized patients who had a baseline reading and at least 1 post-baseline reading for the primary efficacy variable, and who had taken at least 1 dose of study drug. Missing data were imputed using the last observation carried forward (LOCF) method, which was defined as the last non-missing post-baseline value for a variable carried forward. The Per-protocol (PP) population consisted of all patients from the ITT population who did not have important protocol violations related to study inclusion or exclusion criteria or deviations during the study.

Primary outcome variable:

- Change in the log transformed urinary protein/creatinine ratio from baseline to 52 weeks (ITT and PP populations)

Secondary outcome variables:

- Change in the log transformed urinary protein/creatinine ratio from baseline to 26 weeks (ITT and PP populations)
- Change in the log transformed urinary albumin/creatinine ratio from baseline to 26 and 52 weeks (ITT and PP populations)
- Percent change from baseline in lipids and lipoproteins (LDL-C, TC, HDL-C, non-HDL-C, TG, ApoA-1, ApoB, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-1) at Weeks 26 and 52 and relationship between renal effects and lipid changes after 26 and 52 weeks (ITT population)
- Change in eGFR from baseline to 26 and 52 weeks (ITT and PP populations)

Criteria for evaluation - safety (secondary outcome variables)

The safety population consisted of all patients who were randomized and took at least 1 dose of study drug. Safety data were evaluated using actual treatment/dose received.

Safety was assessed by the evaluation of types, frequencies, severity, causality, and duration of reported AEs, and by the examination of clinical laboratory abnormalities, vital signs, and physical findings related to safety.

Statistical methods

Analyses were performed on ITT and PP data sets for the primary and secondary efficacy variables. Patients were grouped by randomized treatment in the ITT analysis of efficacy, and by actual treatment in the PP analysis of efficacy and safety. Efficacy analyses on the ITT population included both observed and LOCF data; efficacy analysis on the PP population included only observed data. All statistical tests were 2-sided with a statistical significance level of 5%.

The effects on urinary protein and albumin excretion were determined by calculating the geometric mean of the urinary protein/creatinine and urinary albumin/creatinine ratios at each evaluation time point. The outcome variable was the change from baseline in the log transformed ratio, where baseline values were determined from the available readings at Visit 3 (Week –1). The effect on change from baseline to 26 and 52 weeks was assessed by a paired t-test; a separate test was performed for each treatment arm. The results were exponentiated and presented as a mean ratio (post/pre-treatment), with associated 95% CIs and p-values. Hypothesis testing was undertaken to assess whether the decrease from baseline was significantly different from zero (ie, that a particular treatment had a positive effect). Evidence of change from baseline was also assessed using CIs. If the 95% CI was entirely below 1.0 and a statistically significant p-value ($p<0.05$) was found, then a positive effect compared with baseline was concluded. If the 95% CI for the post/pre-treatment ratio was entirely below 1.1, then no clinically significant deterioration from baseline was concluded.

The primary analysis was performed using LOCF after 52 weeks in the ITT population. As a robustness check or sensitivity analysis, all ITT analyses were repeated on the PP population. Analysis of change from baseline to 26 weeks was similarly performed as a secondary efficacy outcome variable. For tests of no clinically significant deterioration from baseline, the ITT and PP populations were considered equally important.

As a secondary exploratory analysis, 95% CIs were presented for the estimate of the difference in treatment effects between treatment groups using an analysis of covariance (ANCOVA) model that included treatment, region, and treatment by region as factors and baseline ratio as a covariate. A second ANCOVA using this same model assessed the contribution of baseline eGFR, age, gender, baseline blood pressure, weight, glycosylated haemoglobin (HbA1c), baseline HDL-C, baseline LDL-C, and duration of diabetes as covariates. An analysis of variance (ANOVA) was also performed with treatment and region as factors for comparison purposes. All tests performed in these ANOVA and ANCOVA models were based on Type III sum of squares. These analyses were for data description only since the study was not powered to show a difference between treatment groups. No adjustments were made for multiplicity. As with the primary analysis, the results were exponentiated for presentation purposes.

Percent change from baseline in lipids and lipoproteins at Weeks 26 and 52 for each treatment group was assessed using descriptive statistics, where baseline values were determined from the available readings at Visit 3 (Week –1) and Visit 4 (Week 0). An ANOVA was performed on the lipid and lipoprotein data at Weeks 26 and 52, comparing rosuvastatin 40 mg with atorvastatin 80 mg. Factors were included in the model for treatment and region. Adjusted means were weighted by region. The results from these comparisons were presented as adjusted means and the difference between adjusted means, with associated 95% CIs and p-values. Rosuvastatin 10 mg was not formally compared with atorvastatin 80 mg. Lipid and lipoprotein analyses were performed on the ITT population only.

The relationships between changes in lipids and renal effects were explored. Scatter plots were produced by visit (Week 26 and Week 52) to look at correlations between changes in urinary protein/creatinine ratio from baseline to Week 26 and Week 52, changes in urinary albumin/creatinine ratio from baseline to Week 26 and Week 52, and changes in eGFR from baseline to Week 26 and Week 52 on the y-axis versus percent change in lipid and lipoprotein parameters on the x-axis. Correlation coefficients and associated p-values were also calculated by visit and tabulated. These analyses were carried out for each treatment group separately (rosuvastatin pooled and atorvastatin) as well as the pooling of all treatment groups.

Glomerular filtration rate was estimated using the modified MDRD equation using serum creatinine. The outcome variable was the change from baseline in eGFR, where baseline values were determined from the available readings at Visit 3 (Week –1). Hypothesis testing (for superiority only) was performed on change from baseline to Week 26 and Week 52 based on the untransformed values. The change from baseline was assessed by a paired t-test. A separate paired t-test was performed for each treatment arm. Results were presented with associated 95% CIs and p-values. As an exploratory analysis, 95% CIs were presented for the

estimate of the difference in treatment effects between the three treatments using an ANCOVA model that included factors of treatment and region, treatment by region interaction, and baseline eGFR as a covariate.

Additional exploratory and sensitivity analyses were performed on the ITT data set after unblinding of study data.

Safety was assessed by the evaluation of types, frequencies, severity, and duration of reported AEs, and by examination of clinical laboratory abnormalities, vital signs, and physical findings. Detailed listings of individual safety data were provided. Serious adverse events (SAEs), AEs leading to death, AEs leading to discontinuation (DAEs), and other AEs of interest (OAEs) were tabulated. Descriptive statistics of changes in urinary immunoglobulin (IgG), urinary retinol binding protein (RBP), and blood pressure were presented. No formal testing was performed.

Subject population

Of the total number of patients screened for the study (N=1642), 353 patients (21.5%) were randomized to treatment (Table S2). Of these, 349 (98.9%) received at least one dose of study drug, 276 (78.2%) completed the study, and 77 (21.8%) discontinued during treatment. The most common reasons for discontinuation during the randomized treatment phase included AE (8.8%) and voluntary discontinuation (5.4%).

Table S2 Subject disposition

	Rosuvastatin 10/10 mg N (%)	Rosuvastatin 20/40 mg N (%)	Atorvastatin 40/80 mg N (%)	Total N (%)
Randomized	118 (100)	124 (100.0)	111 (100.0)	353 (100)
Safety Population	116 (98.3)	123 (99.2)	110 (99.1)	349 (98.9)
ITT Population [a]	107 (90.7)	116 (93.5)	102 (91,9)	325 (92,1)
PP Population [b]	75 (63.6)	102 (82.3)	83 (74.8)	260 (73.7)
Completed Study	93 (78.8)	101 (81.5)	82 (73.9)	276 (78.2)
Discontinued	25 (21.2)	23 (18.5)	29 (26.1)	77 (21.8)
Adverse event	14 (11.9)	10 (8.1)	7 (6.3)	31 (8.8)
Voluntary discontinuation	3 (2.5)	5 (4.0)	11 (9.9)	19 (5.4)
Incorrect enrollment	3 (2.5)	3 (2.4)`	4 (3.6)	10 (2.8)
Severe protocol non-compliance	1 (0.8)	2 (1.6)	3 (2.7)	6 (1.7)
Lost to follow-up	3 (2.5)	1 (0.8)	1 (0.9)	5 (1.4)
Development of study-specific discontinuation criteria	0	0	0	0
Other	1 (0.8)	2 (1.6)	3 (2.7)	6 (1.7)

[a] 24 patients were excluded from the safety population to create the ITT population; the primary reason for exclusion was the lack of a result for post-baseline urinary protein/creatinine ratio.

[b] 65 patients were excluded from the ITT population to create the PP population because they had important protocol deviations/violations that could possibly affect the efficacy outcomes; the most common reasons for exclusion were taking disallowed cholesterol-lowering drugs (35 patients) and taking or adjusting medications with a potential for affecting proteinuria (22 patients).

The majorities of patients in all 3 treatment groups were Caucasian (84.7%) and male (69.4%). The overall mean age was 57.4 years; half (49.6%) of the patients were between 50 and 64 years of age. Patients had a mean height of 169.3 cm, a mean weight of 92.3 kg, and a mean BMI of 32.14 kg/m^2. The mean waist circumference was 108.3 cm; the majority of patients (62.3%) had a waist circumference >102 cm. The treatment groups were comparable for all demographic and key baseline characteristics.

The majority of patients (85.8%) had Type 2 diabetes and the remainder (14.2%) had Type 1 diabetes. At the time of entry into the study, the mean time since diagnosis of diabetes was 14.5 years. The percentage of patients with Type 1 diabetes was higher in the rosuvastatin 20/40 mg group (18.5%) than in the rosuvastatin 10 mg (13.6%) or the atorvastatin 40/80 mg groups (9.9%). The treatment groups were comparable for other baseline diabetes history.

All patients in the study were required to have documented proteinuria. Summaries of quantitative analyses of baseline proteinuria were incorporated in the analyses of key efficacy endpoints. The mean creatinine clearance (CrCL) at baseline was 95.8 mL/min, with most patients having normal (55.0%) or mildly impaired (37.1%) renal function on the basis of CrCL assessment. The mean eGFR at baseline was 70.9 $mL/min/1.73m^2$, with most patients having mild (41.6%) or moderate (39.4%) renal impairment. All the treatment groups were comparable for baseline renal function, with the following exceptions: there was 1 patient (0.3%) with severe renal function impairment in the rovastatin 10 mg treatment group, and the percentage of patients with a normal eGFR (≥90 ml/min/1.73m2) was higher in the rosuvastatin 40/80 mg group (22.6%) than in the rosuvastatin 10 mg (15.3%) or the atorvastatin 40/80 mg (18.7%) treatment groups.

Summary of efficacy results

Patients treated with rosuvastatin 10/10 mg and rosuvastatin 20/40 mg experienced small mean changes (<5%) in urinary protein excretion, evaluated by change in urinary protein/creatinine ratio from baseline to Week 52, that were not statistically significant.

Patients treated with atorvastatin 40/80 mg experienced a mean 12.6% decrease in urinary protein excretion at Week 52 (post:pre geometric mean for urinary protein/creatinine ratio, 0.874; p=0.0332).

Although the study was not designed or powered to demonstrate differences among treatments, a secondary analysis by ANCOVA comparing the change in urinary protein/creatinine ratio at Week 52 was performed. No statistically significant differences between treatment arms were observed.

The effects of rosuvastatin and atorvastatin on urinary protein excretion, evaluated by change in urinary protein/creatinine ratio from baseline to Week 26, were similar to the effects observed at Week 52. Patients treated with rosuvastation 10/10 mg or rosuvastatin 20/40 mg showed small mean changes that were not statistically significant; patients treated with atorvastatin 40/80 mg showed a mean 12.4% decrease (post:pre geometric mean for urinary

protein/creatinine ratio, 0.876; p=0.0197). Exploratory analyses show no statistically significant between-group treatment effects.

Patients treated with rosuvastatin 10/10 mg experienced small mean changes in urinary albumin excretion, evaluated by change in urinary albumin/creatinine ratio from baseline to Week 26 or Week 52, that were not statistically significant. The ratio of geometric means, baseline to Week 52 (LOCF), for urinary albumin/creatinine ratios in patients who received rosuvastatin 20/40 mg was 0.836 (16.4% decrease; p=0.0412), indicating a statistically significant improvement from baseline (ie, decreased albuminuria). The ratio of geometric means, baseline to Week 52 (LOCF), for urinary albumin/creatinine ratios in patients who received atorvastatin 40/80 mg was 0.823 (17.7% decrease; p=0.0105), indicating a statistically significant improvement from baseline (ie, decreased albuminuria); similar results were seen at Week 26. No statistically significant between-group treatment effects were observed at Week 26 or Week 52 (LOCF).

At Week 26 and Week 52, patients treated with rosuvastatin 10/10 mg, rosuvastatin 20/40 mg, and atorvastatin 40/80 mg experienced similar mean decreases in LDL-C, TC, TG, nonHDL-C, ApoA-1, ApoB, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, and ApoB/ApoA-1. At Week 26 and Week 52, patients treated with rosuvastatin 10/10 mg and rosuvastatin 20/40 mg, experienced mean increases HDL-C (4.94 mg/dL and 2.82 mg/dL at Week 52, respectively), and patients treated with atorvastatin 40/80 mg experienced mean decreases in HDL-C (-2.41 mg/dL at Week 52). Among the seven lipid and lipoprotein parameters and four lipid or lipoprotein ratios examined, the percent changes from Baseline to Week 52 for three values were statistically significantly different between the rosuvastatin 20/40 mg group and the atorvastatin 40/80 mg group: LDL-C, the ratio LDL-C/HDL-C, and ApoA-1.

The relationship between renal effects and lipid changes at Weeks 26 and 52, evaluated by correlation coefficients between the changes in urinary protein/creatinine, albumin/creatinine, and eGFR and the lipid parameters, showed no consistent relationships in any treatment group.

Statistically significant mean decreases in eGFR were observed at Week 26 and Week 52 in the 2 rosuvastatin treatment groups, but not in the atorvastatin treatment group. The mean change at Week 26 was -2.73 mL/min (p=0.0334) for the rosuvastatin 10/10 mg group and -5.46 mL/min (p=0.0001) for the rosuvastatin 20/40 mg group. The mean change at Week 52 was -3.70 mL/min (p=0.0098) for the rosuvastatin 10/10 mg group and -7.29 mL/min (p=0.0002) the rosuvastatin 20/40 mg group. Exploratory analyses show a statistically significant difference for mean change in eGFR between the rosuvastatin 20/40 mg treatment group and the atorvastatin 40/80 mg treatment group at both Week 26 (p=0.0441) and Week 52 (p=0.0095). The reductions in eGFR observed with rosuvastatin were greater in patients with normal rather than impaired renal function. Most of the change in eGFR occurred within the first 8 weeks of treatment.

Summary of safety results

Overall, rosuvastatin 10/10 mg, rosuvastatin 20/40 mg, and atorvastatin 40/80 mg were well-tolerated. The AEs that occurred in this study were consistent with the age and underlying medical conditions of the patient population and the known safety profile of statins.

The mean change from baseline (at final visit) in serum creatinine for rosuvastatin 20/40 mg was 0.09 mg/dL higher than for atorvastatin 40/80 mg and 0.08 mg/dL higher than for rosuvastatin 10/10 mg. A doubling of serum creatinine from baseline at any time during the period of follow-up was observed in 6 patients in the rosuvastatin 20/40 mg group but in no patients in the rosuvastatin 10/10 mg or atorvastatin 40/80 mg groups. Alternative explanations for the serum creatinine elevations were apparent in 5 of the 6 patients with a doubling of serum creatinine in the rosuvastatin 20/40 mg group. Acute renal failure was reported as an adverse event in 5 patients in the rosuvastatin 20/40 mg group, 1 patient in the atorvastatin 40/80 mg group and no patients in the rosuvastatin 10/10 mg group. None of the reported acute renal failure events was considered by the investigator to be treatment related. There were no renal deaths or cases of permanent renal failure reported in the rosuvastatin or the atorvastatin groups.

For other safety parameters, no clinically meaningful differences between the 3 treatment groups were observed for changes in hematology, clinical chemistry, and urinalysis variables or for the numbers of patients with laboratory values above or below the reference ranges anytime during the study, except for: (1) mean change in alkaline phosphatase at Week 52, where values were higher in the atorvastatin 40/80 mg treatment group than in the rosuvastatin 10/10 mg and rosuvastatin 20/40 mg treatment groups; (2) median urine protein and albumin at Week 52, where values were higher in the rosuvastatin 20/40 mg treatment group than in the atorvastatin 40/80 mg treatment group; and (3) mean and median urinary RBP/creatinine ratios, where increases over time were greater in the rosuvastatin 20/40 mg treatment group than in the other treatment groups.

Changes in vital signs were small and showed no treatment-related effects. The mean increase from baseline in systolic blood pressure was approximately 3 mmHg higher for the atorvastatin 40/80 mg treatment group than for the 2 rosuvastatin treatment groups.

A Safety Committee, which met 8 times during the trial, performed ongoing reviews of the safety observations; on each occasion, the committee recommended continuation without modification (see Appendix 12.1.4.3).