Drug product:	CRESTOR™	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
Document No.:			
Edition No.:			
Study code:	D3560C00071		
Date:	11 September 2007		

An 18-Week, Randomized, Multicenter, Phase IIIb, Double-Blind, Crossover Study, Followed by an 18-Week Open-Label Period to Evaluate the Efficacy and Safety of the Lipid-Regulating Agents, Rosuvastatin and Pravastatin in the Treatment of Subjects with Dysbetalipoproteinemia (Fredrickson type III Hyperlipoproteinemia)

Three centers in The Republic of South Africa, the United States of America and Norway.

Publications

None at the time of approval of this report.

Study dates		**Phase of development**
First patient enrolled	14 February 2005	Therapeutic confirmatory (III)
Last patient completed	14 February 2007	

Objectives

The primary objective of this study was to evaluate the efficacy of once daily treatment with rosuvastatin 10 mg, rosuvastatin 20 mg, and pravastatin 40 mg in patients with dysbetalipoproteinemia by assessment of the percentage change from baseline in non-high density lipoprotein cholesterol (non-HDL-C) after 6 weeks of treatment at a given dose during the 18-week randomized crossover period.

Secondary objectives included efficacy and safety evaluations and are presented in Table S1.

Table S1 Secondary objectives

Efficacy:

18-week randomized, crossover phase: to evaluate the efficacy of once daily treatment with rosuvastatin 10 mg, rosuvastatin 20 mg, and pravastatin 40 mg in patients with dysbetalipoproteinemia after 6 weeks of treatment by assessment of:

- The percentage of patients who achieve their National Cholesterol Education Panel (NCEP) Adult Treatment Panel III (ATP III):
  - non-HDL-C goal
  - low-density lipoprotein cholesterol (LDL-C) goal
  - optimal triglycerides (TG) level
  - non-HDL-C goal and optimal TG level
- The percentage change from baseline in:
  - combined intermediate-density lipoprotein cholesterol (IDL-C) and very-low density lipoprotein-cholesterol (VLDL-C) as measured by ultracentrifugation
  - IDL-C, VLDL-C, LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, remnant lipoprotein cholesterol (RLP-C), TG, IDL-TG, VLDL-TG, LDL-TG, HDL-TG, apolipoprotein (Apo) B (total, LDL, and VLDL), ApoCIII, ApoE, ApoA-I, and ApoB/ApoA-I ratio

18-week open-label phase: to evaluate the efficacy of once daily treatment with rosuvastatin (20 mg, 40 mg, or 40 mg plus fibrates [excluding gemfibrozil]) in patients with dysbetalipoproteinemia at Weeks 24, 30, and 36 by assessment of:

- The percentage change from baseline in non-HDL-C
- The percentage of patients who achieve their NCEP ATP III:
  - non-HDL-C goal
  - LDL-C goal
  - optimal TG level
  - non-HDL-C goal and optimal TG level
- The percentage change from baseline in:
  - combined IDL-C and VLDL-C as measured by ultracentrifugation
  - IDL-C, VLDL-C, LDL-C, TC, HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, RLP-C, TG, IDL-TG, VLDL-TG, LDL-TG, HDL-TG, ApoB (total, LDL, and VLDL), ApoCIII, ApoE, ApoA-I, and ApoB/ApoA-I ratio

6-week washout phase: to evaluate the effect of a washout following an 18-week open-label period with once daily treatment with rosuvastatin 10 mg, 20 mg, or 40 mg (plus optional fibrates [excluding gemfibrozil]) in patients with dysbetalipoproteinemia by assessment of the percentage change from baseline in non-HDL-C, IDL-C, VLDL-C, LDL-C, TC, HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, RLP-C, TG, IDL-TG, VLDL-TG, LDL-TG, HDL-TG, ApoB (total, LDL and VLDL), ApoCIII, ApoE, ApoA-I, and ApoB/ApoA-I ratio at Week 42

Safety:

To evaluate the safety of rosuvastatin and pravastatin by assessing the incidence and severity of adverse events (AEs) and abnormal laboratory values in this study population throughout all study periods.

Apo Apolipoprotein; ATP Adult Treatment Panel; HDL-C High-density lipoprotein-cholesterol; IDL-C Intermediate-density lipoprotein cholesterol; LDL-C Low-density lipoprotein-cholesterol; NCEP National Cholesterol Education Program; RLP C Remnant lipoprotein-cholesterol; TC total cholesterol; TG Triglycerides; VLDL-C Very low-density lipoprotein-cholesterol.

Study design

Randomized, double-blind, crossover, multi-center, Phase IIIb study, consisting of a dietary lead-in phase followed by a 3-period randomized crossover phase evaluating the efficacy and safety of rosuvastatin (10 mg and 20 mg per day) and pravastatin (40 mg per day) given to patients with dysbetalipoproteinemia (hereafter referred to as Fredrickson type III hyperlipoproteinemia). The randomized crossover phase of the study was followed by an 18 week open-label phase during which treatments could include rosuvastatin 10 mg, 20 mg, 40 mg, and a combination of rosuvastatin 40 mg with fibrates in a stepwise manner targeting NCEP ATP III (non-HDL-C goal and optimal TG level) as deemed appropriate by investigators. The final 6 weeks of the study were the washout phase, during which no study drug or other lipid-regulating agents were taken and patients continued on the Therapeutic Lifestyle Change diet.

Target patient population and sample size

Thirty male and non-pregnant female patients aged 18 years of age or older, who had a diagnosis of Fredrickson type III hyperlipoproteinemia.

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

Randomized crossover phase—Weeks 0 to 18: Rosuvastatin 10 mg (1 x 10 mg and 1 x placebo), or rosuvastatin 20 mg (2 x 10 mg), or pravastatin 40 mg (2 x 20 mg) once daily in oral encapsulated tablet form. The rosuvastatin 10 mg batch number was ST74024-001FA26 and the pravastatin 40 mg numbers were ST74020-001-FA07 and ST74020-001-FA08.

Open-label phase—

- Weeks 18 to 24: Rosuvastatin 20 mg once daily in oral tablet form.
- Weeks 24 to 30: Rosuvastatin 10 mg, 20 mg or 40 mg once daily in oral tablet form.
- Weeks 30 to 36: Rosuvastatin 10 mg, 20 mg or 40 mg, or at the discretion of the investigator, rosuvastatin 40 mg and additional fibrates (excluding gemfibrozil) once daily in oral tablet form.

Batch numbers for the open-label phase were BN P010040628, TX15034, TX13035, TX13078, TX13034, and TX14049 for rosuvastatin 10 mg; P010040629, TX14050, TX15028, and TX13073 for rosuvastatin 20 mg; and P010040670, TX13074, and TX14006 for rosuvastatin 40 mg.

Duration of treatment

The randomized crossover phase (Weeks 0 to 18) consisted of three 6-week treatment periods. This was followed by an 18-week open-label phase and a 6-week washout phase (no study treatment).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Percentage change from baseline in non-HDL-C with rosuvastatin 10 mg, rosuvastatin 20 mg, and pravastatin 40 mg after 6 weeks of treatment in the crossover phase.
- Secondary variables: Percentage of patients achieving NCEP ATP-III lipid lowering goals and percentage change from baseline of lipids and apolipoproteins in the crossover phase, open-label phase, and final washout phase.

Safety:

The incidence and severity of AEs and abnormal laboratory values in the crossover phase, open-label phase, and final washout phase.

Statistical methods

In the randomized crossover phase of the study (Weeks 0 to 18), efficacy data were evaluated based on intention-to-treat (ITT) [primary analysis] and per-protocol (PP) populations. In the open-label and washout phases, efficacy data were evaluated based on the ITT population only.

The analyses of the primary and secondary efficacy outcome variables are presented by descriptive statistics and graphical displays for the percent change from baseline in lipids and lipoproteins, and summarized the number and percentage of patients achieving the various goals at the different doses and timepoints. For the primary efficacy variable, efficacy was concluded if the 95% confidence interval of the median percentage change from baseline lay entirely below -25%. There was no formal statistical comparison of treatments.

Patient population

Patient disposition is summarized in Table S2. The study population consisted of patients between the ages of 35 and 72 years old (mean age was 54.4 years) with slightly more male than female patients. The baseline lipoprotein profile was typical for the disease, ie, mixed hyperlipidemia with elevated TC and TG levels; elevated cholesterol and TG in VLDL and IDL, RLP-C and ApoE levels; LDL-C, ApoB, ApoCIII, and ApoA-I in the approximate normal range; and HDL-C slightly decreased. All but 1 patient had an ApoE genotype associated with Fredrickson type III hyperlipoproteinemia and all but 3 had a VLDL-C/VLDL-TG mass ratio >0.35. From the perspective of cardiovascular (CV) risk profile, this group of patients presented with multiple CV risk factors, a high prevalence of coronary heart disease (CHD) and other forms of atherosclerosis, as well as type 2 diabetes mellitus. Taking into consideration the accumulation of atherogenic remnant lipoproteins, these patients may all reasonably be considered as high risk for CHD. More than one-third of the group was hypertensive and more than half had a low HDL-C level. Overall, the patient group had demographic characteristics, baseline lipoprotein profile, ApoE genotype, CV risk profile, and atherosclerosis manifestations that were typical of patients with Fredrickson type III hyperlipoproteinemia. It is noted that patients with severe hypertriglyceridemia or history

of pancreatitis were not represented in this study based on study design and patient selection criteria.

Table S2 Patient disposition

	Total (N=32)
Patients randomized	32 (100.0%)
Patients completed randomized phase	31 (96.9%)
Patients discontinued from randomized phase	1 (3.1%)
Patient not willing to continue study	1 (3.1%)
Patients completed open-label phase	31 (96.9%)
Patients discontinued from open-label phase	0
Patients completed washout phase	30 (93.8%)
Patients discontinued from washout phase[a]	1 (3.1%)
Other[b]	1 (3.1%)

[a] Patient E2000005 discontinued study after completing the open-label phase of the study. Investigator decided not to have patient enter the washout phase.

[b] Reason coded as "other." Investigator decided not to enter patient into washout phase, as did not want patient to be without treatment

Efficacy results

Both rosuvastatin 10 mg and 20 mg were effective in reducing non-HDL-C level (the primary variable of the study) in patients with Fredrickson type III hyperlipoproteinemia (median change from baseline was -48.2% (95% CI -56.7, -45.6) for rosuvastatin 10 mg and -56.4% (95% CI -61.4, -48.5) for rosuvastatin 20 mg treatment. Both treatments met the prespecified efficacy criteria with 95% confidence interval of median change from baseline lying entirely below -25% supporting a positive efficacy conclusion.

In this study, the reference treatment pravastatin 40 mg had a median non-HDL-C reduction of -35.1% (95% CI -41.6, -29.6), consistent with its published data; it also met the prespecified efficacy criteria for pravastatin in this study with 95% CI of median change from baseline lying entirely below 0. A numerically greater reduction of non-HDL-C was observed with both rosuvastatin doses compared to pravastatin 40 mg and there was also a numerically greater reduction with rosuvastatin 20 mg compared to 10 mg.

Table S3 Non-HDL-C (mg/dL) percent change from baseline after 6 weeks of treatment (randomized crossover ITT population)

			% change from baseline[a]	
	n	Median	Median	95% CI
Baseline	32	294.50	NA	NA
Rosuvastatin 10 mg	32	144.50	-48.2	-56.7, -45.6
Rosuvastatin 20 mg	31	130.00	-56.4	-61.4, -48.5
Pravastatin 40 mg	32	189.00	-35.1	-41.6, -29.6

CI Confidence interval; ITT Intention-to-treat; NA Not applicable; Non-HDL-C Non-high-density lipoprotein cholesterol; SD Standard deviation.

[a] Baseline value calculated as the average of the available readings at the last 3 consecutive pretreatment visits, including any repeated visits in weeks –2, -1, and 0. That baseline value was used to calculate percent change from baseline for each of the 3 treatments.

The results of secondary variables were consistent with the findings of the primary variable and served to support the effectiveness of rosuvastatin. These included the percentage of patients who met NCEP ATP III lipid-lowering goals and the percentage change from baseline in other lipid and lipoprotein values. Percentage change from baseline for key lipid and lipoprotein values are presented in Table S4.

Treatment effects on total, VLDL, IDL, LDL, and HDL cholesterol, TG, and their corresponding apolipoproteins were observed in a consistent pattern for rosuvastatin 10 mg, rosuvastatin 20 mg and pravastatin 40 mg. The changes were nominally greater with both rosuvastatin doses than with pravastatin 40 mg. In general, the changes were also incrementally greater with rosuvastatin 20 mg compared to rosuvastatin 10 mg. Specifically, TC and TG declined 43.3% and 40.1% with rosuvastatin 10mg and 47.6% and 43.0% with rosuvastatin 20 mg, respectively. HDL-C and ApoA-I levels increased, by 10.2% and 4.0% for rosuvastatin 10mg and 11.2% and 6.6% for rosuvastatin 20 mg, respectively.

There was also a reduction in RLP-C (rosuvastatin 10 mg [-56.4%] and rosuvastatin 20 mg [-64.9%]). The reduction in RLP-C together with the approximate 50% reduction of cholesterol and TG in VLDL and IDL and the reduction in ApoE, are consistent with a substantial reduction in the plasma remnant lipoprotein level.

Table S4 Key lipid and lipoprotein values and percent change from baseline after 6 weeks of treatment (randomized crossover ITT population)

			% change from baseline	
	n	Median	Median	95% CI
TC (mg/dL)				
Baseline[a]	32	342.50	NA	NA
Rosuvastatin 10 mg	32	187.50	-43.3	-46.9, -37.5
Rosuvastatin 20 mg	31	173.00	-47.6	-51.6, -42.8
Pravastatin 40 mg	32	228.00	-31.4	-37.7, -25.5

Table S4 Key lipid and lipoprotein values and percent change from baseline after 6 weeks of treatment (randomized crossover ITT population)

			% change from baseline	
	n	**Median**	**Median**	**95% CI**
TG (mg/dL)				
Baseline[a]	32	503.50	NA	NA
Rosuvastatin 10 mg	32	309.50	-40.1	-44.9, -33.6
Rosuvastatin 20 mg	31	276.00	-43.0	-52.5, -33.1
Pravastatin 40 mg	32	324.00	-28.6	-35.5, -19.1
VLDL-C (mg/dL)				
Baseline[a]	32	180.00	NA	NA
Rosuvastatin 10 mg	32	84.00	-46.6	-55.7, -42.0
Rosuvastatin 20 mg	31	65.00	-55.7	-64.4, -47.2
Pravastatin 40 mg	32	99.00	-34.6	-52.6, -26.6
IDL-C (mg/dL)				
Baseline[a]	32	30.50	NA	NA
Rosuvastatin 10 mg	28	17.00	-56.8	-67.7, -32.1
Rosuvastatin 20 mg	28	13.00	-63.0	-72.0, -56.3
Pravastatin 40 mg	30	17.00	-44.0	-65.3, -32.6
LDL-C (mg/dL)				
Baseline[a]	32	112.50	NA	NA
Rosuvastatin 10 mg	32	55.00	-54.4	-59.1, -47.3
Rosuvastatin 20 mg	31	54.00	-57.3	-59.4, -52.1
Pravastatin 40 mg	32	80.00	-33.8	-43.0, -24.5
HDL-C (mg/dL)				
Baseline[a]	32	35.50	NA	NA
Rosuvastatin 10 mg	32	38.00	10.2	1.9, 12.3
Rosuvastatin 20 mg	31	40.00	11.2	8.3, 20.5
Pravastatin 40 mg	32	36.00	5.6	-2.8, 9.8
RLP-C (mg/dL)				
Baseline[a]	32	82.00	NA	NA
Rosuvastatin 10 mg	32	34.50	-56.4	-67.1, -49.0
Rosuvastatin 20 mg	31	29.00	-64.9	-74.0, -56.6
Pravastatin 40 mg	32	43.00	-47.4	-55.8, -36.2
ApoE (mg/dL)				
Baseline[a]	32	15.95	NA	NA
Rosuvastatin 10 mg	32	9.95	-42.9	-46.3, -33.3
Rosuvastatin 20 mg	30	9.40	-42.5	-47.1, -35.6
Pravastatin 40 mg	32	11.95	-28.1	-37.8, -22.3

Apo Apolipoprotein; HDL-C High-density lipoprotein-cholesterol; IDL-C Intermediate-density lipoprotein cholesterol; ITT Intention-to-treat; LDL-C Low-density lipoprotein-cholesterol; RLP-C Remnant lipoprotein-cholesterol; TC total cholesterol; TG Triglycerides; VLDL-C Very low-density lipoprotein-cholesterol.

[a] Baseline value calculated as the average of the available readings at the last 3 consecutive pretreatment visits, including any repeated visits in weeks –2, -1, and 0. That baseline value was used to calculate percent change from baseline for each of the 3 treatments.

In the follow-on open-label phase, in which the investigator had the option to titrate the rosuvastatin dose and to add on fibrates, maintenance of a treatment effect was apparent as reflected in lipid parameters and achievement of NCEP ATP III goals. There appeared to be an additional complementary treatment effect when a fibrate was added to rosuvastatin 40 mg dose, eg, reduction of TG (mainly VLDL-TG). After the final washout phase, patients' lipid levels essentially returned to baseline status.

Safety results

Treatment-emergent AEs were reported by 25 out of the 32 patients (78.1%) in the randomized crossover phase of this study. The rate of treatment-emergent AEs was comparable for the rosuvastatin 10 mg (37.5%), rosuvastatin 20 mg (34.4%), and pravastatin 40 mg (43.8%) groups during the randomized crossover phase.

During the randomized crossover and open-label study phases combined, treatment-emergent AEs were reported by 29 out of the 32 patients (91%). The most commonly-reported AEs were influenza (5 patients, 15.6%) and rhinitis (4 patients, 12.5%).

There were no deaths during the study. There were 2 patients with 3 treatment-emergent serious adverse events (SAEs) (1 patient with appendicitis [40 mg pravastatin] and 1 with sciatica [10 mg rosuvastatin] during the randomized crossover phase; the former patient also had a SAE of unstable angina during the final washout phase). All SAEs were considered not related to study drug by the investigator. One patient receiving 10 mg rosuvastatin experienced an AE of moderate headache leading to study drug discontinuation, which the investigator considered to be treatment-related. This patient later discontinued the study, with the recorded reason being "not willing to continue on the study," but the event was considered an AE leading to study discontinuation (DAE) due to the timing of the AE before withdrawal. There were no other significant adverse events (OAEs). The review of AEs did not raise any new safety concerns for rosuvastatin.

Changes in clinical laboratory results were generally small and no clinically meaningful patterns were identified, except for 1 patient on pravastatin 40 mg treatment, who had an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation >3 times the upper limit of normal (ULN) for 2 consecutive visits. There were no clinically significant findings from vital signs or physical examinations.