PROTOCOL SYNOPSIS

An open-label, randomised, multi-centre, phase IIIb, parallel group study to compare the efficacy and safety of 10mg and 40mg rosuvastatin (CRESTOR)

Investigators

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Study centre(s) and number of patients planned

This study will be conducted in 200 patients recruited from 25 centres in Austria. It is planned that each centre will recruit approximately 8 patients.

Study period		Phase of development
Estimated date of first patient enrolled	02 September 2002	IIIb
Estimated date of last patient enrolled	20 December 2002	
Estimated date of last patient completed	06 June 2003	

Objectives

Primary objective

The primary objective of the study is to compare the efficacy of rosuvastatin 10mg once daily with rosuvastatin 40mg once daily by assessment of the number of patients with hypercholesterolaemia reaching the LDL-C target goal of <100mg/dL after 12 weeks of therapy.

Secondary objectives

1. To compare the effect of 10mg / 40mg rosuvastatin by assessment of the number of patients reaching LDL-C target goal after 24 weeks of therapy.
2. To compare the effect of 12 weeks therapy with 10mg / 40mg rosuvastatin on change in LDL-C (compare change from baseline).
3. To investigate the effect of 12 weeks therapy with 10 mg rosuvastatin on change in LDL-C (compare values week 0 vs. week 12).
4. To investigate the effect of 12 weeks therapy with 40 mg rosuvastatin on change in LDL-C (compare values week 0 vs. week 12).
5. To compare the effect of 12 weeks therapy with 10mg / 40mg rosuvastatin on change in TC, HDL-C, TG, LDL-density, SAA, ICAM-1, VCAM-1, CRP, high-sensitive CRP, ferritine, D-dimer, fibrinogen and HbA1c (compare change from baseline).
6. To investigate the effect of 12 weeks therapy with 10mg rosuvastatin on change in TC, HDL-C, TG, LDL-density, SAA, ICAM-1, VCAM-1, CRP, high-sensitive CRP, ferritine, D-dimer, fibrinogen and HbA1c (compare values week 0 vs. week 12).
7. To investigate the effect of 12 weeks therapy with 40mg rosuvastatin on change in TC, HDL-C, TG, LDL-density, SAA, ICAM-1, VCAM-1, CRP, high-sensitive CRP, ferritine, D-dimer, fibrinogen and HbA1c (compare values week 0 vs. week 12).
8. To investigate the effect of 12 weeks therapy on change in microalbuminuria in each treatment group (compare change from baseline).
9. To investigate the effect of 12 weeks therapy on change in waist circumference and body fat (compare change from baseline).

The effects of the dose increase and the dose decrease from weeks 12 to 24 will be evaluated as follows:

10. To investigate the change in LDL-C by increasing the dose from 10mg to 40mg (compare values week 12 vs. 24).

11. To investigate the change in LDL-C by decreasing the dose from 40mg to 10mg (compare values week 12 vs. 24).

12. To investigate the change in TC, HDL-C, TG, LDL-density, SAA, ICAM-1, VCAM-1, CRP, high-sensitive CRP, ferritine, D-dimer, fibrinogen and HbA1c by increasing the dose from 10mg to 40mg (compare values week 12 vs. 24).

13. To investigate the change in TC, HDL-C, TG, LDL-density, SAA, ICAM-1, VCAM-1, CRP, high-sensitive CRP, ferritine, D-dimer, fibrinogen and HbA1c by decreasing the dose from 40mg to 10mg (compare values week 12 vs. 24).

The following safety examinations will be performed:
Number of withdrawals from each treatment group.
Assessment of adverse events and safety laboratory monitoring. The following safety laboratory parameters will be evaluated: Creatinine, creatine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Compliance with drug therapy will be assessed by tablet count data (i.e. number of tablets returned).

Study design

This is a randomised, multi-centre, open-label, 2- arm, parallel group study.

Following randomisation at visit 1 (week 0) the patients will receive 12 weeks of open-label treatment with either rosuvastatin 10mg or 40mg od.

At 12 weeks (visit 2) the 10mg dosage group will be switched to 40mg and the 40mg dosage group to 10mg for further 12 weeks (see Figure 1 - study flow chart in section 3.1).

The patients will be assessed for their LDL-cholesterol (LDL-C), LDL-density, total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides (TG), CRP, high-sensitive CRP, ferritin, D-dimer, fibrinogen, haemoglobin adult (HbA1c), SAA, ICAM-1, VCAM-1 and microalbuminuria at study entry (visit 1), week 12 (visit 2) and week 24 (visit 3). Adverse events and safety laboratory parameters will be assessed at week 12 and week 24.

Target patient population

Statin naïve patients or patients who have not been treated with a statin for at least the preceding 4 weeks will be selected. A dietary run-in period for 2 to 4 weeks is necessary before the patients can enter the study. The patients will be male or female, with primary hypercholesterolaemia and with the following characteristics:

Key inclusion criteria:

- Age 45 - 75 years
- LDL-C between130mg/dL and 250mg/dL
- TG $\leq$ 400mg/dL
- HbA1c < 7%
- Waist circumference: female > 85cm; male > 95cm
- Written informed consent to participate in the trial

Key exclusion criteria:

- Known hypersensitivity or history of SAE with another HMG-CoA reductase inhibitor, in particular any history of myopathy
- Active liver disease/severe hepatic impairment
- Treatment with cyclosporin or any disallowed drug
- Treatment with medication for diabetes
- Patients with unstable angina pectoris

Investigational product, dosage and mode of administration

Rosuvastatin, 10mg and 40mg tablets. The patients take one 10mg tablet once daily (10mg od) or one 40mg tablet once daily (40mg od).

Comparator, dosage and mode of administration

NA

Duration of treatment

24 weeks.

Endpoints

- Efficacy

The primary endpoint will be the number of patients from each group (rosuvastatin 10mg or rosuvastatin 40mg) who reach the LDL-C target goal of <100mg/dL after 12 weeks therapy.

For a definition of the secondary endpoints see section 2.2 Secondary objectives.

- Safety

Safety will be assessed by adverse events and safety laboratory monitoring. The following safety laboratory parameters will be evaluated: Creatinine, creatine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

In addition the number of withdrawals from each treatment group will be evaluated.

- Compliance

Compliance with drug therapy will be assessed by tablet count data (i.e. number of tablets returned).

Statistical methods

All statistical evaluations and analyses will be performed using TESTIMATE software package (Test & Estimation, IDV, Gauting).

Patients will be evaluated for all analyses based on an intention to treat (ITT) population. The ITT population will consist of patients who have a pre-dosing reading (the reading taken prior to randomisation), one post-baseline reading (either a week 12 or week 24 reading) and have received at least one dose of trial medication.

All hypothesis testing will be done using two sided alternatives. P-values less than 5% will be considered statistically significant.

Evaluation of the primary objective:
The primary objective of the trial is to investigate the number of patients reaching and not reaching target goal (LDL-C <100mg/dL) on rosuvastatin 10mg and 40mg at week 12.
The statistical comparison of the dosage groups at week 12 will be performed using the 2x2 contingency tables. The results will be presented with associated 95% confidence intervals and p-values.

Nonparametric analysis of covariance (ANCOVA) will be used to examine group differences on the target goal (LDL-C <100mg/dL), adjusting for the baseline variables age, body fat and BMI. If the nonparametric ANCOVA is not powerful enough to detect significant differences, the parametric analysis of covariance (ANCOVA) will be used to examine group differences in changes of LDL-C, also adjusting for the baseline variables age, body fat and BMI.

Evaluation of the secondary objectives:
The comparisons over time will be performed using the Wilcoxon test for continuous data.

The comparisons between treatment groups will be performed using the 2x2 contingency tables for binary data and the Wilcoxon Mann Whitney U test for continuous data. The results will be presented with associated 95% confidence intervals and p-values.

Descriptive evaluation of data:
Descriptive statistics (mean ± standard deviation, median, minimum and maximum value) are used for all values.

The demographic characteristics of height, weight, body mass index, blood pressure and smoking status, along with Coronary Heart Disease risk factors will be summarized by dosage group. Data regarding medical history, physical examination findings, concomitant medications will also be recorded.

Tablet count data will be summarized, but will not be formally analysed statistically.

Mean value of microalbuminuria, the number of withdrawals and the incidence of adverse events will be summarized by treatment dose. With regard to laboratory safety data values out of range will be described over time.

10. REFERENCES

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