Clinical Study Report Synopsis

Drug Substance	Rosuvastatin
Study Code	D3560L00053
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A 6-week, randomised, open-label, parallel group, multi-centre study to compare the efficacy of rosuvastain 10mg with atorvastatin 10mg in the treatment of non-diabetic metabolic syndrome subjects with raised LDL-C

Study dates:
First healthy volunteer/patient enrolled: 11 August 2005
Last healthy volunteer/patient completed: 29 January 2007

Phase of development:
Therapeutic use (Phase IV)

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

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Study centre(s)

Twenty (20) centers in Korea:

Yeungnam University Medical Center
Daegu Catholic University Medical Center
Kyungpook National Univerisity Hospital
Keimyung University Dongsan Medical Center
Kosin University Gospel Hospital
Dong-A University Medical Center
Meryknoll General Hospital
Pusan National University Hospital
Inje University Pusan Paik Hospital
Gyeongsang National University Hospital
Ulsan University Hospital
Konyang University Hospital
Chonnam National University Hospital
Kwangju Christian Hospital
Seonam University Hospital
Chonbuk National University Hospital
Presbyterian Medical Center
Wonkwang University Hospital
Chungnam National University Hospital
St. Carollo Hospital

Publications

None at the time of writing this report.

Objectives

Primary:

The primary objective of this study is to compare the effect of rosuvastatin 10mg with atorvastatin 10mg in the percentage reduction of LDL-C in Subjects with metabolic syndrome after 6 weeks of treatment.

Secondary:

The secondary objectives of this study are to compare the effects of rosuvastatin 10mg with atorvastatin 10mg in subjects with metabolic syndrome, after 6 weeks of treatment, on:

1. Bringing subjects to their NCEP ATP III target goals for LDL-C.

2. Brining subjects to their nonHDL-C target goal (based on NCEP-ATP III criteria).

3. Modifying other lipids and lipid ratios.

4. Modifying inflammatory markers

5. Glucose and Insulin resistance

6. Safety

Study design

This is a randomised, multi-centre, open-label, parallel-group study to compare the efficacy and safety of rosuvastatin compared with atorvastatin in the treatment of non-diabetic subjects with metabolic syndrome. The study comprises the following 2 periods:

- 6-week dietary run-in period (week –6 to 0)

Subjects entering the run-in will follow the standard diet. At entry to the dietary run-in period (week –6), subjects are required to discontinue any previous lipid lowering therapy. Fasting LDL-C concentration following the dietary lead-in will be required to determine subject eligibility for inclusion in the randomised treatment period.

- 6-week randomised treatment period (week 0 to 6)

Eligible subjects will be randomised to either rosuvastatin 10 mg or atorvastatin 10 mg. Treatment will be administered once daily for 6 weeks. Levels of LDL-C (calculated LDL-C from TG and HDL-C) will be determined at week 0 (baseline) and week 6 (the end of randomised treatment).

Target healthy volunteer population and sample size

Subjects will be male or female, aged 18 years or older, with metabolic syndrome (as defined by the NCEP-ATP III guidelines), plus a raised LDL-C [≥130 mg/dL (3.36 mmol/L)]. Diabetic subjects will be excluded.

This study will be conducted in approximately 360 subjects to as ensure that at least 286 evaluable subjects will complete this study.

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

Rosuvastatin 10 mg once daily in oral tablet form: DB990, CM171, CT706
Atorvastatin 10 mg once daily in oral tablet form: 0618075, 0625084, 0694045

Duration of treatment

Subjects will be randomised and treated for 6 weeks with rosuvastatin 10 mg or atorvastatin 10 mg therapy once daily.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary:

1. Percentage change from baseline in LDL-C at 6 weeks

Secondary:

1. Number and percentage of subjects reaching their NCEP ATP III LDL-C target goal after 6 weeks of treatment.
2. Number and percentage of subjects who achieve their NCEP ATP III non HDL-C target goal after 6 weeks of treatment [subjects with baseline TGs ≥200 mg/dL (2.26 mmol/L) only].
3. Percent change from baseline in TC, HDL-C, TG, Non HDL-C, ApoA1 and ApoB at 6 weeks.
4. Percent change from baseline in C-reactive protein at week 6.
5. Percent change from baseline in glucose and insulin resistance at week 6.

Criteria for evaluation - safety (main variables)

Safety evaluation as determined by the incidence of adverse events and abnormal laboratory data

Statistical methods

The primary analysis population will be the last observation carried forward (LOCF) on the intention to treat (ITT) population. This included all subjects with a baseline and at least one post-baseline lipid measurement.

For the primary objective of comparing Rosuvastatin 10 mg with Atorvastatin 10 mg effects on percentage change in LDL-C, an analysis of variance model with terms for centre and treatment was used. The result was presented as an estimate of the treatment effect (adjusted difference between the treatment groups) together with its 95% confidence intervals. A similar analysis of variance was also used to analyse the % change from baseline in other lipids (secondary endpoint 3).

For secondary endpoints 1 and 2, logistic regression models with effects for baseline LDL-C, centre, NCEP risk group and treatment was used and the results were be presented in terms of odds ratios, associated 95% confidence intervals, and p-values.

The non-parametric Wilcoxon Rank Sum test was used to test for differences between treatments in their effect on inflammatory markers (secondary endpoint 4). Data summaries will also be provided.

Numbers and percentages of subjects experiencing adverse events were summarised for subjects entering the dietary lead-in, and in the randomised safety population. Laboratory safety data was tabulated.

Subject population

A total of 645 subjects were screened for participating in this study. 371 took part in dietary run-in period and finally 351 took at least one dose of study medication. But of them, 1 lost to follow-up and had no safety assessment (350 subjects constituted Safety set) and 5 were dropped out from this study. 346 subjects completed this study and 329 were included in PP set except 17 with the protocol deviations.

Table 1 Analyzed population

	Rosuvastatin group	Atrovastatin group	Total
ITT set	170	176	346
PP set	162	167	329
Safety set	172	178	350

Summary of efficacy results

Efficacy analyses were carried-out on the intent-to-treat (ITT) set defined as all the subjects randomized to treatment who took at least one dose of study medication and had efficacy assessment (N=346).

For percentage change from baseline in LDL-C at 6 weeks, the LDL-C decreased 48.04 ± 14.45 mg/dL from baseline in rosuvastatin group and 39.52 ± 14.42 mg/dL in atorvastatin group. This change was statistically significantly greater in the rosuvastatin group than in atorvastatin ($p<.0001$). Overall, 149(87.64%) subjects in rosuvastatin group reached their NCEP ATP III LDL-C target goal and in atorvastatin group, 123(69.88%), which was statistically significantly different ($p<.0001$).

Overall achievement rate for NCEP non-HDL target goal after 6 weeks of treatment was 76.08% (35 of 46) in rosuvastatin group and 58.92% (33 of 56) in atorvastatin group, thereby rosuvastatin group had higher achievement rate than atorvastatin but this difference was not statistically significant (p=0.0674).

After 6 weeks treatment, among lipid profiles, the change in TC (-35.94 ± 11.38 vs. -30.07 ± 10.46 mg/dL, p<.0001), non-HDL-C (-42.93 ± 13.15 vs. -35.52 ± 11.76 mg/dL, p<.0001) and ApoB (-38.7 ± 18.85 mg/dL vs. -32.57 ± 17.56 mg/dL, p=0.0019) were greater in rosuvastatin group than in atorvastatin group.

For glucose, HOMA-R index and QUICKI index, there was no statistically significant difference in percentage change from baseline after 6 weeks treatment between two groups.

These results show that rosuvastatin 10mg is more effective than atorvastatin 10mg in the percentage reduction of LDL-C in subjects with metabolic syndrome after 6 weeks of treatment

Summary of pharmacokinetic results

Not Applicable

Summary of pharmacodynamic results

Not Applicable

Summary of pharmacokinetic/pharmacodynamic relationships

Not Applicable

Summary of pharmacogenetic results

Not Applicable

Summary of safety results

All the subjects randomized in each group to treatment who received at least one dose of IP and reported their conditions are included in the safety analyses. Twelve (12) AEs during dietary run-in period were reported in 11 subjects (2.97%). Amongst these subjects, 1 (0.27%) had drug-related AE. There was no SAE or AEs leading to discontinuance. Most frequent AE was gastritis in gastrointestinal disorder.

During treatment period, a total of 350 subjects were exposed to IP. Fourteen (14) AEs in 13 of 172(7.56%) subjects in rosuvastatin group and 13 AEs in 9 of 178 (5.06%) subjects in atorvastatin group were reported. A total of 3, of which 1 was from rosuvastatin group and 2 from atorvastatin group, were reported as SAEs during treatment period. Only in atorvastatin

group, 5 AEs resulted in discontinuance from the study. Most frequent AEs in rosuvastatin group were oedema and dizziness, and the incidence of both AE's was 1.16%. Only 5 AEs reported in atorvastatin group were reported as related to study drug.

There was one AE which caused subject to discontinue the study and no such AE was related to rosuvastatin.

This study demonstrated the safety and tolerability of rosuvastatin 10mg as comparable to atorvastatin 10mg when administered in subjects with metabolic syndrome.

Conclusion(s)

This study demonstrated that rosuvastatin 10mg, administered in subjects with metabolic syndrome, is more effective than atorvastatin 10mg and has excellent safety and tolerability profile.

Date of the report

26 March 2008