CLINICAL STUDY REPORT

A Placebo-controlled, Double-blind, Randomised, Parallel-group, Long-term Phase III Trial Assessing the Safety and Efficacy of 50 μg and 100 μg/day of eprotirome in Patients with Heterozygous Familial Hypercholesterolaemia who are on Optimal Standard of Care

Investigational Product: eprotirome

Indication Studied: heterozygous familial hypercholesterolaemia

Protocol Number: KBT009

Development Phase: III

Initiation Date: 03 October 2011

Completion Date: 11 July 2012

Early Termination Date: 14 February 2012

Sponsor:
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1 SIGNATURE PAGE

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We, the undersigned, have read this report and confirmed to the best of our knowledge it accurately describes the conduct and results of the study.

Signature	Date

Per Bengtsson, MD, PhD
President and CEO
Chief Medical Officer
Karo Bio AB
Novum

	20 Sept 2012

David G. Orloff, MD
Vice President, Medical and Regulatory Affairs
Medpace, Inc.

2 SYNOPSIS

Name of Sponsor: Karo Bio AB

Name of Finished Product: eprotirome

Name of Active Ingredient: eprotirome

Title of Study: A Placebo-controlled, Double-blind, Randomised, Parallel-group, Long-term Phase III Trial Assessing the Safety and Efficacy of 50 μg and 100 μg/day of eprotirome in Patients with Heterozygous Familial Hypercholesterolaemia who are on Optimal Standard of Care

Investigators: For the list of investigators, see Appendix 16.1.4.

Study Sites: 13 sites in Netherlands, 9 sites in South Africa, 8 sites in Spain, 7 sites in Israel, 5 sites in the Czech Republic, 3 sites in the United Kingdom, 3 sites in Sweden, 3 sites in Denmark, 2 sites in Austria, 1 site in India, and 1 site in Norway

Publication (reference): none

Study Period:

Initiation Date: 03 October 2011

Completion Date: 11 July 2012

The study was terminated early on 14 February 2012 due to safety findings of a preclinical toxicology study in dogs treated with eprotirome. Damage to cartilage was seen in dogs that were given eprotirome for up to 12 months. The cartilage damage was apparent only after 12 months exposure and occurred not only in all animals treated with high doses but was also seen in the lower dose groups. The control animals displayed no damage. In a 6-month toxicology study in dogs, these findings were not observed.

Phase of Development: III

Study Objectives:

Primary: The primary objective of this study was to compare the efficacy of eprotirome 50 μg and eprotirome 100 μg versus placebo in terms of the percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to Week 12 in heterozygous familial hypercholesterolaemia (HeFH) subjects with coronary artery disease (CAD), or who were at high risk for CAD, and who were on optimal standard of care consisting of a statin with or without ezetimibe.

Secondary: The secondary objectives of this study were the following:

- To compare the efficacy of eprotirome 50 μg and eprotirome 100 μg versus placebo in terms of the percent change in LDL-C from baseline to Week 28, Week 52, Week 76, and Week 100;

- To compare the efficacy of eprotirome 50 μg and eprotirome 100 μg versus placebo in terms of the percent change in triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein (apo) A-I, apo B, lipoprotein (a) (Lp[a]), and markers for inflammation (eg, high-sensitivity C-reactive protein [hsCRP]) from baseline to Week 12, Week 28, Week 52, Week 76, and Week 100;
- To compare the efficacy of eprotirome 50 μg and eprotirome 100 μg versus placebo in terms of the proportion of subjects who have a reduction in LDL-C of >15% from baseline to Week 12;
- To monitor the systemic exposure to the nitrated reaction product KB42899 in the population through sparse sampling and explore the pharmacokinetics (PK) of KB42899 and eprotirome through rich sampling in selected cases;
- To assess the effects of eprotirome on skeleton by bone mineral density (BMD) using dual-emission x-ray absorptiometry (DXA) scans of the lumbar spine in a subset of subjects;
- To assess the cardiovascular safety of eprotirome in a subset of subjects using echocardiography and Holter monitoring to evaluate cardiac structure and function;
- Subjects were evaluated for knee-joint function and symptoms using a Patient Reported Outcome (PRO) questionnaire (Knee injury and Osteoarthritis Outcome Score [KOOS]); and
- To assess the long-term safety and tolerability of eprotirome.

The exploratory objectives of this study included the following:

- The cardiovascular safety of eprotirome was assessed through the adjudication of the following events:
  - All cause mortality,
  - Fatal myocardial infarction,
  - Non-fatal myocardial infarction,
  - Stroke,
  - Unstable angina requiring hospitalisation,
  - Coronary and peripheral arterial revascularisation,
  - Supraventricular arrhythmia requiring intervention and/or hospitalisation,
  - Atrial fibrillation confirmed by 12-lead electrocardiogram (ECG), and
  - Congestive heart failure requiring hospitalisation.
- To investigate the safety of eprotirome with regards to potential skeletal effects, fractures were to be adjudicated.

Further analysis of carbohydrate and lipid metabolism was to be performed to investigate the effects of eprotirome. This could have involved assessments including, but not limited to: 7-alphahydroxycholestenone (C4), lathosterol, lanosterol, plant sterols, lipoprotein particle size, oxidized cholesterol, apolipoproteins by gel electrophoresis, fibroblast growth factor 21 (FGF21), fibroblast growth factor 19 (FGF19), adiponectin, leptin, resistin, betahydroxybutyrate, proprotein convertase subtilisin/kexin type 9 (PCSK-9), glycerol, and glucagon.

An optional blood sample for genotyping was to be collected and could have been used to confirm the diagnosis of HeFH or to identify/explore genetic variations that may affect PK, pharmacodynamics (PD), safety, and tolerability related to eprotirome treatment.

Methodology: This was planned to be a multi-centre, randomised, double-blind, parallel-group study consisting of an up to 10-week run-in period, 100-week randomised treatment period (consisting of 52-76 weeks of double-blind treatment and 24-48 weeks of open-label treatment), and 12-week post-treatment follow-up period.

At the completion of the screening period, subjects who met the eligibility criteria were assigned randomly in a 1:1:1 ratio to placebo, eprotirome 50 μg, or eprotirome 100 μg. Subjects who were randomised to eprotirome 100 μg received 2 eprotirome 50 μg tablets per day, except during the first 2 weeks of the double-blind treatment period when they received 1 eprotirome 50 μg tablet and 1 placebo tablet per day.

Duration of Treatment: 100 weeks of randomised treatment with placebo, eprotirome 50 μg, or eprotirome 100 μg was planned; subjects received up to 6 weeks of randomised treatment due to early study termination. Some subjects were still in the screening period at the time of termination.

Number of Subjects:

Planned: 630 randomised subjects

Screened: 564 subjects

Randomised: 236 subjects

Completed: 0 subjects

Discontinued: 236 subjects

Diagnosis and Main Criteria for Inclusion: The study population included adult male or female subjects ≥18 years of age, with established HeFH and CAD, or at high risk for CAD, who had not met LDL-C treatment goals while on optimal standard of care consisting of a statin with or without ezetimibe. At least 55% of subjects were to be on a maximum dose of statin.

Investigational Product and Comparator Information: The investigational product was eprotirome 50 μg; the comparator was placebo. For the study drug lot numbers, see Appendix 16.1.6.

Criteria for Evaluation: Subjects were adult men and women, ≥18 years of age, with established HeFH who had not met LDL-C treatment goals while on optimal standard of care consisting of a statin with or without ezetimibe. At least 55% of subjects were to be on a maximum dose of statin and at least 40% of the subjects were to have CAD as specified in inclusion criteria 2a (see Protocol, Appendix 16.1.1). Subjects had to meet all of the inclusion criteria and none of the exclusion criteria in order to be randomised in the study.

Statistical Methods: Approximately 1050 subjects were planned to be enrolled in order to obtain 630 randomised subjects (assuming an approximately 40% screen failure rate) at approximately 70 clinical sites. A total sample size of 630 randomised subjects (210 subjects per treatment group) was planned.

Efficacy, PK, and pharmacogenetic analyses were not conducted as planned due to early study termination.

All safety analyses were conducted on the Safety Set, defined as all randomised subjects who took at least 1 dose of randomised study drug. The primary safety assessment was evaluation of the incidence of adverse events between placebo and eprotirome treatment groups. Adverse events were coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) were defined as adverse events with a start date on or after the first dose of study drug and up to 14 days after the last dose of study drug. A general summary of the TEAEs and serious adverse events (SAEs) was presented by overall number of adverse events, severity, and relationship to study drug per treatment group. The number of TEAEs leading to withdrawal and SAEs was also summarized. The incidence of adverse events was summarized by system organ class, preferred term, and treatment group.

Changes in safety laboratory parameters from baseline were summarized for all relevant chemistry, haematology, urinalysis, and thyroid function. Shift tables for the change from baseline to the most severe value post-baseline were presented for selected laboratory parameters. Summaries were provided for the number and percentage of subjects experiencing elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or bilirubin according to thresholds specified in the FDA guidance relative to drug-induced liver injury. Subjects with any post-baseline ALT or AST >3 × the upper limit of normal were listed.

Changes from baseline in vital signs (blood pressure, heart rate, and body temperature), weight, ECG parameters, echocardiography variables, and lumbar spine BMD from DXA scans over time were summarized. The frequency of subjects with abnormal post-baseline QRS and QTc intervals were tabulated by treatment group. The QT intervals were corrected for heart rate using the default regression method during the ECG reading (QTc) and Bazett's (QTcB) and Fridericia's (QTcF) correction formulas. Changes in knee-joint symptoms and function were the change from baseline to last visit on study drug in the average scores on the subscales of the KOOS questionnaire.

Summary of Results: Efficacy analyses were not performed due to early study termination. Pharmacokinetic and pharmacogenetic data were not collected due to early study termination.

Of 564 screened subjects, 236 subjects were randomised to receive treatment with eprotirome 50 μg, eprotirome 100 μg, or placebo in a 1:1:1 ratio and 234 subjects were withdrawn due to early study termination. Two subjects were withdrawn due to increased liver enzymes.

Overall, there were a similar number of male and female subjects and the mean age of subjects was 56.1 years. The treatment groups were generally comparable with respect to demographic and baseline characteristics. Study drug exposure was similar across placebo (34.6 days), eprotirome 50 μg (33.7 days), and eprotirome 100 μg (35.1 days) treatment groups.

Overall, administration of eprotirome 50 μg and 100 μg was well tolerated compared to placebo. In total, 87 (36.9%) subjects had at least 1 TEAE. While taking placebo, 23 (28.8%) subjects had a TEAE; while taking eprotirome 50 μg, 34 (43.0%) subjects had a TEAE; and while taking eprotirome 100 μg, 30 (39.0%) subjects had a TEAE. Twenty-four (10.2%) subjects had a drug-related TEAE. No subjects had a severe TEAE; 36 (15.3%) subjects had at least 1 moderate TEAE, and 51 (21.6%) subjects had at least 1 mild TEAE.

No deaths occurred during the study. Nine (3.8%) subjects had an SAE during the study. Five subjects discontinued the study drug due to TEAEs.

The system organ classes with the highest incidence of TEAEs were musculoskeletal and connective tissue disorders (29 [12.3%] subjects) and infections and infestations (25 [10.6%] subjects). Overall, the incidence of TEAEs was comparable between placebo and eprotirome treatments and no dose-related trends were observed.

Mean changes in hematology, chemistry, and urinalysis parameters were generally comparable between the eprotirome and placebo groups. Increases from baseline to Week 14/Early Termination (ET) were observed for gamma-glutamyltransferase (GGT) in both eprotirome groups. Decreases from baseline to Visit 4 and Visit 5 were observed for free thyroxine (T4), T4, and thyroid-stimulating hormone (TSH) in both eprotirome groups. These changes reversed after withdrawal of study drug.

No laboratory abnormalities were considered SAEs. Three subjects had laboratory abnormalities that resulted in withdrawal of study drug. Subject 107-005 in the eprotirome 50 μg group had TEAEs of ALT increased, AST increased, and blood thyroid stimulating hormone decreased. These events were all considered moderate in severity and related to study drug. Subject 151-013 in the eprotirome 50 μg group had a TEAE of transaminases increased that was considered moderate in severity and related to study drug. Subject 552-008 in the eprotirome 100 μg group had study drug stopped due to increased ALT/AST values; treatment with study drug was not resumed and the study was subsequently terminated. Abnormalities reversed after withdrawal of study drug.

In addition, there were no clinically significant treatment differences observed in vital signs, ECG, DXA scan, PRO, or echocardiography findings.

Conclusions: The study objectives were not fulfilled due to early study termination. Overall, up to 6 weeks administration of eprotirome 50 μg or 100 μg was well tolerated compared to placebo.

Date of the Report: 20 September 2012