KARO BIO

CONFIDENTIAL

CLINICAL STUDY REPORT

Study Code: KBT-006
EudraCT No: 2007-007831-24
ClinicalTrials.gov No: NCT00677248

A PHASE II, PLACEBO CONTROLLED, DOUBLE BLIND, RANDOMIZED, 10-WEEK, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY OF DIFFERENT DOSES OF EPROTIROME (KB2115) AS ADD-ON TO EZETIMIBE TREATMENT IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA

Name of investigational product:	Eprotirome (KB2115)
Development phase:	Phase II
Date of study initiation:	25 March 2008
Date of study completion:	24 September 2008
Study Coordinating Investigator:	Dr. Carl-Peter Anderberg Me3+ AB, Gothenburg, Sweden Tel: +46 31 81 72 75 Fax: +46 31 16 34 26
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Version and Date of Report:	Final, 29 October 2010

This study was performed in compliance with Good Clinical Practice (GCP).

2. SYNOPSIS

Name of the Sponsor/Company: Karo Bio AB	**Individual Study Table Referring to Part 5 of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: To be determined		
Name of Active Ingredient: Eprotirome		

STUDY CODE: KBT-006

TITLE OF STUDY: A phase II, placebo controlled, double blind, randomized, 10-week, parallel-group study to assess the efficacy of Eprotirome (KB2115) as add-on to Ezetimibe treatment in patients with primary hypercholesterolemia.

INVESTIGATORS:

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STUDY CENTER(S):

This was a multi-center study conducted in Sweden (11 centers).

PUBLICATION (REFERENCE): None

STUDY PERIOD (YEARS):

Date of first enrolment 25 March 2008

Date of last completed 24 September 2008

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PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

Primary objective:

- To assess the efficacy of different doses of Eprotirome as add-on to Ezetimibe treatment on low-density lipoprotein (LDL) cholesterol in subjects with primary hypercholesterolemia.

Secondary objectives:

- To assess safety and tolerability of different doses of Eprotirome as add-on to Ezetimibe treatment in subjects with primary hypercholesterolemia.
- To assess plasma concentration time relationship and exposure of Eprotirome and KB42899 in terms of AUC and C_{max} in a subset of approximately 24 subjects.
- To assess the influence of Eprotirome as add-on to Ezetimibe treatment on blood lipids including total and high-density lipoprotein (HDL) cholesterol, triglycerides, free fatty acids, apolipoprotein (apo) A-1, apo B and apo B/A-1 ratio, and lipoprotein (a) [Lp(a)].
- To assess the influence of Eprotirome as add-on to Ezetimibe treatment on the pituitary-thyroid axis by determination of biomarkers of thyroid activity.
- To assess potential effects on heart rate and QT/QTc interval.

METHODOLOGY:
This was a phase II, double-blind, randomized, placebo-controlled, parallel-group, multi-center study.

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NUMBER OF SUBJECTS (planned and analyzed):

	Placebo	Eprotirome			Total
		25 mcg	50 mcg	100 mcg	
	+ Ezetimibe treatment				
No. planned to be screened					200
No. screened					222
No. planned to be randomized	25	25	25	25	100
No. randomized and treated	28	28	28	29	113
No. completed	26	25	25	25	101
No. analyzed (Safety)	28	28	28	29	113
No. analyzed (FAS)	28	26	27	28	109
No. analyzed (PPAS)	24	21	22	21	88

FAS, Full Analysis Set; PPAS, Per Protocol Analysis Set

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects had to be/have:

1. Signed informed consent
2. Males or females aged ≥ 18 to ≤ 75 years. Female subjects had to be non-fertile. To be considered as non-fertile, females had to fulfill the following:
   a. Non-nursing and non-pregnant 12 months prior to enrolment
   b. Not of child bearing potential i.e., either documented irreversible surgically sterile (bilateral oophorectomy or hysterectomy was acceptable, but not tubal ligation) or post-menopausal. Post-menopausal was defined as serum follicle-stimulating hormone levels in the post-menopausal range combined with amenorrhea for more than one year in a woman above 50 years of age, or amenorrhea for more than two years below 50 years of age
3. Subjects with primary hypercholesterolemia with an LDL-cholesterol >3.0 mmol/L (>116 mg/dL) at Enrolment (Week -4) and at Week -1
4. Subject able and willing to comply with all study requirements
5. At randomization, diet as instructed by the investigator during the last 4 weeks prior to randomization and willingness to follow these instructions throughout the study.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER :

Eprotirome tablets, 25 mcg (batch number RF 1651)

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Eprotirome tablets, 50 mcg (batch number RF 1652)

Dose: Two enteric coated tablets daily, oral administration. Three dose levels were administered 25, 50 and 100 mcg/day, besides Placebo.

Subjects randomized to 50 mcg/day received 25 mcg/day during the first two weeks and then 50 mcg/day. Subjects randomized to 100 mcg/day received 25 mcg/day during the first two weeks, 50 mcg/day during the following two weeks, and then 100 mcg/day.

To preserve the double-blind nature of the study, each subject received two containers of study medication for each treatment period (Baseline – Week 2; Week 2 – Week 4, and Week 4 – Week 10) and was instructed to take one tablet from each container in the morning of each day.

Throughout the study, from Enrolment (Week -4) to Follow-up (Week 14), all subjects received Ezetimibe treatment at 10 mg/day.

DURATION OF TREATMENT:

The study period began with an enrolment visit, followed by a 4-week dietary lead-in period according to the National Cholesterol Education Program (NCEP) Step 1 diet or a country specific NCEP Step 1 diet guide), a 10-week treatment period (including a 4-week period with step-wise dose increases of Eprotirome; for details, see Test Products above), and a follow-up visit four weeks after the last administration of study drug.

The maximum study duration for an individual subject was 18 weeks (10 weeks on Eprotirome treatment).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo tablets (batch number RF 1650)

Dose: Two enteric coated tablets daily, oral administration. For details, see Test Products above.

Throughout the study, from Enrolment (Week -4) to Follow-up (Week 14), all subjects received Ezetimibe treatment at 10 mg/day.

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CRITERIA FOR EVALUATION

EFFICACY:

The primary efficacy endpoint was the absolute change in LDL-cholesterol from Baseline to Week 10.

Secondary efficacy evaluations were:

- Relative change in LDL-cholesterol from Baseline to Week 10
- Percentage responders in each group (with 15% lowering of LDL-cholesterol level at Week 10 versus Baseline)
- Absolute and relative change from Baseline to Week 10 in total cholesterol, HDL-cholesterol, triglycerides, free fatty acids, apo A-1, apo B, apo B/A-1 ratio, and Lp(a). The analyses of triglycerides also included a subgroup analysis of subjects with Baseline levels >1.70 mmol/L and the analyses of Lp(a) also included subgroup analyses of subjects with Baseline levels >300 mg/L, >200 mg/L and >100 mg/L, respectively.

SAFETY: The safety evaluations comprised:

- Adverse events (AEs)
- Concomitant medications
- Safety laboratory tests – hematology, serum chemistry and urinalysis
- Thyroid function – biomarkers of thyroid activity [thyroid stimulating hormone (TSH), total and free triiodothyronine (T3), total and free thyroxine (T4), and thyroid-binding globulin (TBG)]
- Muscle effects – creatine kinase (CK)
- Bone effects – bone specific biomarker activity (serum levels of C-terminal teleopeptide of type I collagen (CTX), bone specific alkaline phosphatase (ALP), and N-terminal propeptide of type I procollagen (S-PINP)
- Vital signs - blood pressure, pulse and body temperature
- 12-lead Electrocardiogram (ECG)
- Body weight

STATISTICAL METHODS:

Analysis of all efficacy variables was performed on a Full-Analysis-Set (FAS) and on the Per-Protocol-Analysis-Set (PPAS). At the clean file meeting and before code-breaking it was

decided whether a subject was to be included in the PPAS and FAS population, respectively.

The full analysis set (FAS) included all subjects who had been randomized, had taken at least one dose of Eprotirome/Placebo, had been compliant to treatment with Ezetimibe tablets during the lead-in period, and who had evaluable data for the primary variable, LDL-cholesterol, at Baseline and at least one measure on treatment.

The per-protocol analysis set (PPAS) is a subset of the FAS as defined above including subjects who also had an LDL-cholesterol measure at Week 10. Subjects in the PPAS also had to be compliant (80 – 120%) to Eprotirome/Placebo and Ezetimibe treatment during the treatment period. Subjects who were considered to be major protocol violators at the clean file meeting were also excluded from the PPAS.

All subjects who received one dose or more of Eprotirome/Placebo were included in the safety evaluation (Safety Set).

All statistical analyses were performed using SAS, version 9.1 or higher. All tests were two-sided at a 5% significance level and all confidence intervals were two-sided at a 95% confidence level. Sequential testing with fixed sequences was employed when testing each of the Eprotirome doses against Placebo in the primary analysis. No adjustment for multiplicity of secondary efficacy variables was done. All continuous variables were summarized per treatment group with standard statistical measures, i.e., number of observations (n), number of missing observations (missing), mean, median, standard deviation (SD), minimum (min), 1st (Q1) and 3rd (Q3) quartile and maximum (max) value. All categorical variables were summarized by absolute and relative frequencies.

The null hypothesis for the primary efficacy variable, absolute change in LDL-cholesterol from Baseline to Week 10, was tested with an analysis of covariance (ANCOVA). The null hypothesis was that the active treatment dose was equal to Placebo, and the alternative hypothesis was that the active treatment dose was different from Placebo. Baseline LDL-cholesterol level was included as a covariate and treatment as a factor in the model. Comparisons between Placebo versus Eprotirome doses were made in terms of absolute changes in LDL and the 95% confidence intervals were derived. The 25 mcg, 50 mcg and 100 mcg doses were compared to Placebo. Sequential testing with fixed sequences was employed when testing the dose groups against Placebo. The doses were tested in the following order: 100 mcg versus Placebo, 50 mcg versus Placebo and 25 mcg versus Placebo. Model adequacy checks were carried out (normally distributed errors, heteroscedasticity etc.). For assessment of the dose response, a Williams Test or the non parametric Jonkheere Terpstra test, depending on if the distributional assumptions were fulfilled, was carried out.

The null hypothesis for the secondary efficacy variables, the change from Baseline to Week

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10 in total cholesterol, LDL-cholesterol expressed as percent, responders for LDL-cholesterol, HDL-cholesterol, triglycerides, free fatty acids, apo A-1, apo B, apo B/ A-1 ratio and Lp(a) were tested with an analysis of covariance with adjustment for the Baseline value of the respective variables. The null hypothesis was that the active treatment dose was equal to Placebo, and the alternative hypothesis was that the active treatment dose was different from Placebo.

In the analysis of efficacy variables, the last observation on therapy was carried forward if the last visit value was missing. Baseline values were not imputed.

Percentage of responders, defined as a 15% lowering of LDL-cholesterol at Week 10 versus Baseline, was analyzed. Exact 95% confidence intervals based on binominal distribution were calculated. For Lp(a) and triglycerides, dose responses were assessed as for the primary variable.

The secondary safety and tolerability variables [TSH, total and free T3, total and free T4, TBG, S-CTX, bone specific ALP, S-PINP, body weight and heart rate and QTcF (corrected QT interval by Fridericia's formula)] were tested with an analysis of covariance with adjustment for the Baseline value of the respective variables. Adjustments for multiplicity were made with the method of Bonferroni for the thyroid and bone metabolism variables.

For subjects with blood sampling for PK evaluation, C_{max}, t_{max} and t_{lag}, AUC, CL/F, and $t_{½}$ were listed and summarized using descriptive statistics and compared by treatment groups.

SUMMARY AND CONCLUSION(S):

EFFICACY RESULTS (FAS):

The change in LDL-cholesterol from Baseline to Week 10, the primary efficacy variable, was highly statistically significant in all Eprotirome treatment groups compared to Placebo ($p<0.0001$). There was a decrease in LDL-cholesterol by 10.0%, 18.1% and 20.3% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 5.1%). Mean LDL-cholesterol levels decreased by 0.43, 0.87 and 0.95 mmol/L in the 25, 50 and 100 mcg group, respectively, compared with an increase by 0.18 mmol/L in the Placebo group.

The proportion of responders (subjects with a 15% decrease in LDL-cholesterol from Baseline to Week 10) was 42.3%, 66.7% and 75.0% in the 25, 50 and 100 mcg group, respectively, compared with 0% in the Placebo group.

Statistically significant differences in the Eprotirome treatment groups relative to Placebo for the change from Baseline to Week 10 were also observed for the secondary efficacy variables total cholesterol (overall $p<0.0001$), apo A-1 ($p<0.0001$), apo B ($p<0.0001$), apo B/

A-1 ratio (p=0.0007), and Lp(a) (p=0.0002), as well as for the individual Eprotirome groups relative to Placebo. For triglycerides, there was an overall statistically significant difference between Eprotirome and Placebo (p=0.0497), and significant changes for the 25 and 100 mcg groups, and a trend towards significance for the 50 mcg group. There were no statistically significant changes for triglycerides in the subgroup of subjects with Baseline triglycerides >1.70 mmol/L. There were no statistically significant changes for HDL-cholesterol.

Total cholesterol decreased by 9.5%, 15.0% and 17.6% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 1.9%). Mean total cholesterol levels decreased by 0.63, 1.06 and 1.17 mmol/L in the 25, 50 and 100 mcg group, respectively, compared with an increase by 0.09 mmol/L in the Placebo group.

Triglyceride levels decreased by 17.4%, 16.4% and 20.8% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 1.9%). Mean triglyceride levels decreased by 0.45, 0.39 and 0.24 mmol/L in the 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.03 mmol/L in the Placebo group.

Apo A-1 decreased by 4.4%, 6.8% and 7.7% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 2.2%). Mean apo A-1 levels decreased by 0.08, 0.13 and 0.13 g/L in the 25, 50 and 100 mcg group, respectively, compared with an increase by 0.03 g/L in the Placebo group.

Apo B decreased by 11.4%, 16.9% and 19.0% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 2.0%). Mean apo B levels decreased by 0.14, 0.24 and 0.26 g/L in the 25, 50 and 100 mcg group, respectively, compared with an increase by 0.02 g/L in the Placebo group.

The apo B/ A-1 ratio decreased by 7.3%, 10.5% and 12.1% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 0.3%). Mean apo B/ A-1 ratios decreased by 0.06, 0.10 and 0.10 in the 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.003 in the Placebo group.

Lp(a) decreased by 18.6%, 24.4% and 32.3% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 3.8%). Mean Lp(a) levels decreased by 67, 153 and 147 mg/L in the 25, 50 and 100 mcg group, respectively, compared with a decrease by 23 mg/L in the Placebo group.

In the subset of subjects with Baseline Lp(a) levels >100 mg/L, Lp(a) levels decreased by 23.6%, 27.0% and 35.0% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 5.9%). In this subgroup, mean Lp(a) levels decreased by 93, 185 and 169 mg/L in the 25, 50 and 100 mcg group, respectively, compared with a

decrease by 28 mg/L in the Placebo group.

In the subset of subjects with Baseline Lp(a) levels >200 mg/L, Lp(a) levels decreased by 26.8%, 27.4% and 32.6% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 4.6%). In this subgroup, mean Lp(a) levels decreased by 114, 219 and 195 mg/L in the 25, 50 and 100 mcg group, respectively, compared with a decrease by 29 mg/L in the Placebo group.

In the subset of subjects with Baseline Lp(a) levels >300 mg/L, Lp(a) levels decreased by 28.9%, 22.8% and 27.1% in the 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 9.9%). In this subgroup, mean Lp(a) levels decreased by 151, 250 and 195 mg/L in the 25, 50 and 100 mcg group, respectively, compared with a decrease by 47 mg/L in the Placebo group.

There were no statistically significant changes in FFA levels in any of the Eprotirome dose groups relative to Placebo.

The systemic exposure of Eprotirome appeared to be roughly proportional to dose, and the absorption typically started after a lag time of approximately one hour. There were no measurable amounts of KB42899.

SAFETY RESULTS:

In total, 154 AEs were reported by 70 subjects. AEs reported in more than two subjects in a treatment group were diarrhea, nasopharyngitis, back pain, and hyperhidrosis in the Placebo group; diarrhea, nasopharyngitis, pain in extremity, and headache in the 25 mcg group; nasopharyngitis in the 50 mcg group; and nasopharyngitis and headache in the 100 mcg group. The majority of the AEs were mild or moderate. Three subjects experienced severe AEs [one each in the Placebo group (nausea), 50 mcg group (depression) and 100 mcg group (osteoarthritis). There were no serious adverse events (SAEs).

Out of the 154 AEs, 36 were adverse drug reactions (ADRs) to Eprotirome, i.e., judged by the investigator to be possibly or probably related to Eprotirome, and 34 were ADRs judged as related to Ezetimibe treatment. ADRs to Eprotirome in more than one subject per treatment group were nausea and hyperhidrosis in the placebo group, headache in the 25 mcg group, and depression in the 50 mcg group. ADRs as judged related to Ezetimibe treatment in more than one subject per treatment group were nausea, pain in extremity and headache in the 25 mcg group, and nausea, upper abdominal pain and pruritus in the 50 mcg group.

Twelve subjects withdrew prematurely from the study. The reasons for premature withdrawal were safety reason/AE [three subjects, one each in the Placebo group (nausea), 50 mcg group (nausea), and 100 mcg group (increased liver function test)], consent withdrawal (two

subjects, one each in the 25 and 50 mcg groups), incorrect enrolment (three subjects, one in the 50 mcg group and two in the 100 mcg group), inclusion/exclusion criteria not met (one subject in the 25 mcg group), protocol violation (one subject in the 25 mcg group), lost to follow-up (one subject in the Placebo group) and other reasons (one subject in the 100 mcg group).

Transient and apparently dose dependent increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) were observed. Four subjects, all women, had transient increases in ALT >3x the upper limit of normal (ULN) during the study (two each in the 50 and 100 mcg groups). One of these (100 mcg group) was consecutive following re-test (at Week 6 and three days later when the subject was withdrawn from the study). She also had concomitant increases in AST, GGT and ALP but normal total and conjugated bilirubin levels.

Mean values remained within the normal range for all thyroid variables. There were no statistically significant changes in TSH, total T3 or free T3 (fT3), whereas moderate reductions in total T4 (T4) and free T4 (fT4) ($p<0.0006$) were observed in a dose dependent fashion. The changes were reversible and returned to baseline levels at the follow up visit. No single value below the respective lower limit of normal (LLN) was seen in any subject at any time point for TSH and T3. Occasional TSH values above ULN were observed for three subjects in the Placebo group, three subjects in the 25 mcg group, six subjects in the 50 mcg group, and three subjects in the 100 mcg group. Single T3 values above ULN were observed for one subject in the 25 mcg group and one subject in the 50 mcg group. Single fT3 values below LLN were observed in two subjects in the Placebo group (Week -4 and Week 4, respectively), one subject in the 25 mcg group (Week 4), two subjects in the 50 mcg group (Week -4 and Week 4, respectively), and one subject in the 100 mcg group (Week 10). Values above ULN for fT3 were observed occasionally in eight subjects in the Placebo group, four subjects in the 25 mcg group, six subjects in the 50 mcg group, and seven subjects in the 100 mcg group.

No apparent trends were observed for the other laboratory evaluations except for SHBG in both male and female subjects, and for LH and estradiol in male subjects. In males, apparently dose dependent increases were observed for SHBG ($p<0.001$ for each Eprotirome group relative to Placebo), LH ($p<0.01$ for the 100 mcg group relative to Placebo) and estradiol ($p<0.05$ and <0.001 for the 50 and 100 mcg group, respectively). There was no change in FSH in males. In females, the increase in SHBG was also dose dependent ($p<0.001$ for each Eprotirome group relative to Placebo). There were no changes in FSH, LH or estradiol in females.

There were no apparent changes in vital signs during the study. ECG's with central manual reading were performed at each of the eight visits (three before, four during and one after the

dosing period). There were no clinically significant ECG abnormalities in any of the subjects during the study. There were no statistically significant differences in heart rate or QTcF between the treatment groups. The maximum change from Baseline in mean heart rate at any visit during treatment were 2.3 beats/min (Week 4) in the Placebo group, 1.3 beats/min (Week 10) in the 25 mcg group, 2.3 beats/min (Week 2) in the 50 mcg group and 0.9 beats/min (Week 10) in the 100 mcg group. There were no QTcF values above 480 ms, except for one subject in the 25 mcg group. This subject had a QTcF value of 491 ms at Enrolment (Week -4), 484 ms at Baseline, 493 ms at Week 4, 479 ms at Week 10, and 492 ms at Week 14. There was no change in QTcF from baseline of ≥60 ms in any subject at any time point.

CONCLUSIONS:

In conclusion, pronounced and clinically relevant reduction in risk factors [LDL-cholesterol, total cholesterol, triglycerides, apo B, apo B/ apo A-1 ratio, and Lp(a)] for the development of atherosclerotic cardiovascular disease were documented during Eprotirome as add-on to Ezetimibe treatment in subjects with primary hypercholesterolemia at doses where extra-hepatic thyroid homeostasis was preserved. The addition of Eprotirome at doses ranging from 25 to 100 µg to ongoing ezetimibe therapy reduced the serum concentrations of LDL cholesterol (-15% to -25%), apo B (-13% to -21%), triglycerides (-19% to -23%) and Lp(a) (-15% to -29%), when adjusted for Placebo.