KARO BIO

CONFIDENTIAL

CLINICAL STUDY REPORT

Study Code: KBT-003
EudraCT No: 2006-003191-35

A PLACEBO CONTROLLED, DOUBLE BLIND, RANDOMISED, 12-WEEK, PHASE II STUDY TO ASSESS THE SAFETY AND EFFICACY OF EPROTIROME (KB2115) IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA

Name of investigational product:	Eprotirome (KB2115)
Development phase:	Phase II
Date of study initiation:	October 24, 2006
Date of study completion:	April 20, 2007
Principal Investigators:	Dr. Jorma Strand Oulun Diakonissalaitos, Oulu, Finland Tel: +358 8 313 2011 Fax: +358 400 686 026 Dr. Mats Eriksson Karolinska Universitetssjukhuset, Stockholm Sweden Tel: +46 8 5858 2094
Company/sponsor signatory:	Karo Bio AB Novum S-141 57 Huddinge Sweden
Company/sponsor contact person:	Dr Jens Kristensen Vice President of Clinical Development Karo Bio AB Tel: +46 8 608 6005 Fax: +46 8 774 8261
Version and Date of Report:	Final, 20 October 2008

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

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2. SYNOPSIS

Name of the Sponsor/Company: Karo Bio AB	**Individual Study Table Referring to Part 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Eprotirome	**Volume:**	
Name of Active Ingredient: 3-[[3,5-Dibromo-4-[4-hydroxy-3-(1-methylethyl)-phenoxy]-phenyl]-amino]-3-oxopropanoic acid	**Page:**	
STUDY CODE: KBT-003		
TITLE OF STUDY: A placebo controlled, double blind, randomised, 12-week, phase II study to assess the safety and efficacy of KB2115 in patients with primary hypercholesterolemia		
INVESTIGATORS: Dr. Jorma Strand, Oulu, Finland Dr. Mats Eriksson, Stockholm, Sweden Dr. Pertti Ebeling, Hus, Finland Dr. Hannu Haapamäki, Lahti, Finland Dr. Pertti Himanen, Turku, Finland Dr. Matti Kuusela, Kokkola, Finland Dr. Toivo Piippo, Tampere, Finland Dr. Juha Tervo, Tampere, Finland Dr. Carl-Peter Anderberg, Gothenburg, Sweden Dr. Christer Höglund, Stockholm, Sweden Dr. Anders Olsson, Stockholm, Sweden Dr. Gisela Rose, Gothenburg, Sweden		
STUDY CENTRE(S): This was a multi-centre study conducted in Finland (7 centres) and Sweden (5 centres).		
PUBLICATION (REFERENCE): Drugs Affecting Lipid Metabolism, 16th International Symposium, New York USA, Oct. 2007. American Thyroid Association 78th annual meeting. New York, USA, Oct. 2007		
STUDY PERIOD (YEARS):		

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Date of first enrolment 2006-10-24

Date of last completed 2007-04-20

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

The primary objective was to determine the efficacy of KB2115 in lowering low-density lipoprotein (LDL-cholesterol) and to assess safety of KB2115 in patients with primary hypercholesterolemia.

The secondary objective was to identify the lipid efficacy profile of KB2115 in relation to risk markers for heart, bone, liver and muscle and to assess the kinetics of KB2115.

METHODOLOGY:
This was a phase II, double-blind, randomised, placebo-controlled, multi-centre study.

NUMBER OF SUBJECTS (planned and analysed):

Planned: A total of 100 subjects: 40 subjects per active treatment arm, 20 subjects in placebo.

	Placebo	**KB2115** 100 µg	**KB2115** 200 µg	**Total**
No. planned to be screened				130
No. screened				142
No. planned to be randomised	20	40	40	100
No. randomised and treated	20	38	40	98
No. completed	19	35	37	91
No. analysed (Safety)	20	38	40	98
No. analysed (FAS)	20	38	40	98
No. analysed (PPS)	19	33	37	89

FAS, Full Analysis Set; PPS, Per Protocol Set

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects had to be/have:

- Primary hypercholesterolemia

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- Between 18 to 65 years of age
- Males or females. If female - non-nursing, non-pregnant, not of childbearing potential, i.e., either surgically sterile or post-menopausal for >1 year.
- LDL-cholesterol > 4 mmol/L at Screening and Week -1 Visit or statin treatment at Screening and LDL-cholesterol > 4mmol/L at Week -1 Visit.
- National Cholesterol Education Program (NCEP) Step 1 diet during the last 4 weeks prior to randomisation.
- Adequate wash-out of present lipid lowering treatment

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

KB2115 tablets, 100 µg (batch number 94301-0608-04)

KB2115 tablets, 200 µg (batch number 94301-0608-06)

Dose: 1 tablet daily, oral administration

DURATION OF TREATMENT:

Before treatment, each subject eligible for this study had a 4 weeks dietary lead-in period, and, if applicable, an appropriate wash-out of present lipid lowering therapy. Subject received study medication for 12 weeks. The follow-up visit was scheduled 4 weeks after the last dose.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:
Placebo tablets (batch number 94301-0608-02)

Dose : 1 tablet daily, oral administration

CRITERIA FOR EVALUATION

EFFICACY:

The primary efficacy endpoint was the change in LDL-cholesterol from baseline to Week 12.

Secondary efficacy evaluations were:

- Percentage of subjects in each group with 20% lowering of LDL-cholesterol; Week 12 versus baseline.
- Percentage of subjects in each group that at Week 12 fulfil the treatment goals

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described in the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

and change from baseline to each follow-up visit (i.e., Week 2, 4, 8, 12 and 16) of the following variables:

- LDL-Cholesterol (except Week 12)
- Total cholesterol
- HDL-cholesterol
- Triglycerides
- Free fatty acids
- Lipoprotein a [Lp(a)]
- Apolipoprotein A-1 and B

Exploratory assessments

- 7-alpha-hydroxy-cholest-4-en-3-one (Cholestan C4)
- Lathosterol
- Plant sterol

SAFETY: The safety evaluations comprised:

- Adverse events
- Safety laboratory tests
- 12-lead Electrocardiogram (ECG) and Echocardiography (ECHO)
- Thyroid function – biochemistry and clinical signs
- Muscle effects – biochemistry and functional muscle strength (where the test was available)
- Bone effects – biochemistry and bone mineral density (BMD)
- Blood pressure and pulse
- Change in body weight

STATISTICAL METHODS:

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All subjects who had received study medication were included in the analysis of safety. Statistical analyses of efficacy performed on the Full Analysis Set (FAS), which is as close as possible to the "intention-to-treat" principle, were considered as the primary analyses (The FAS included as all randomised subjects who received any amount of the study medication and had baseline assessment of the efficacy variables and at least one post baseline assessment of the efficacy variables).

The primary endpoint was the change in LDL-cholesterol from baseline to Week 12. The primary analysis compared that change in the KB2115 200 and 100 µg groups with the corresponding change in the Placebo group. A step down statistical testing procedure designed in such a way that the overall statistical significance level is retained at 5% (i.e., α=0.05) was used.

The analysis of the primary endpoint was performed using analysis of covariance (ANCOVA) with treatment as explanatory variable and LDL-cholesterol at baseline as covariate. Point estimates, standard errors, 95% confidence intervals (95% CI) and p-values from these analyses were presented. The use of the step down procedure implies the 95% confidence intervals are approximate. The hypotheses testing procedure was repeated using the non-parametric Wilcoxon rank sum test and additional ANCOVA analyses that assessed the sensitivity of the results in the primary analysis were performed.

For the secondary endpoints total LDL-cholesterol at assessments other than Week 12, Total cholesterol, HDL-cholesterol, Triglycerides, Free fatty acids, Apoliprotein A-1 and B and Lp(a) were analysed. Of exploratory endpoints, Lathosterol and Plant sterols as a fraction of total cholesterol were analysed. For secondary and exploratory endpoints, the change from baseline to each follow-up visit (i.e., Week 2, 4, 8, 12 and 16), statistical analysis was performed by means of an ANCOVA including treatment as explanatory variable and the endpoint in question at baseline as covariate. In these analyses all three treatment groups were analysed within the same ANCOVA and overall F-statistic for test of difference between treatments.

Also, the percentage of responders, defined as a 20 % lowering of LDL-cholesterol; Week 12 versus baseline and the percentage of subjects in each group that at Week 12 fulfilled the treatment goals described in the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) was calculated.

SUMMARY AND CONCLUSION(S):

EFFICACY RESULTS:

From baseline to Week 12, the average change in LDL-cholesterol was an increase of 0.08 mmol/L in the Placebo group and a decrease of 1.11 and 1.49 mmol/L in the KB2115 100 µg

and 200 µg groups, respectively. When adjusted for baseline LDL-cholesterol level, the difference in change in LDL-cholesterol was 1.54 (95% CI: 1.14: 1.93) mmol/L in favour of the KB2115 200 µg group as compared with the Placebo group (p<0.0001). The corresponding difference between the KB2115 100 µg and the Placebo groups was 1.18 (95% CI: 0.76: 1.59) mmol/L in favour of the KB2115 200 µg group (p<0.0001).

This finding was robust in terms of analysis approach used, i.e., both the ANCOVA and the non-parametric Wilcoxon test p-values were below 0.0001. Adjustment for centre, age, gender or baseline Lp(a) did not affect the outcome more than marginally. Furthermore, the finding at Week 12, was supported by findings at the intermediate visits (i.e., Week 2, 4 and 8) at which all comparisons between the two doses of KB2115 and Placebo were statistically significant at the 0.0001 level.

The proportion of responders (subjects with a 20% decrease in LDL-Cholesterol at Week 12) was 60.5% in the KB2115 100 µg group and 72.5% in the KB2115 200 µg group (p<0.0001). Also, 5.0%, 37.5% and 57.5% reached the treatment goals of the Adult Treatment Panel III in the Placebo, the KB2115 100 and 200 µg groups, respectively (p<0.01).

Total cholesterol decreased from baseline to Week 12 with 0.02, 1.13 and 1.71 mmol/L in the Placebo group, the KB2115 100 and 200 µg groups, respectively (p<0.0001). Apolipoprotein B decreased from baseline to Week 12 with 0.004, 0.284 and 0.390 g/L in the Placebo group, the KB2115 100 and 200 µg groups, respectively (p<0.0001). Triglycerides were unchanged in the Placebo group and decreased from baseline to Week 12 with 0.21 and 0.65 mmol/L in the KB2115 100 and KB2115 200 µg groups, respectively (p=0.0003). Lp(a) decreased from baseline to Week 12 with 4.4, 121.9 and 173.3 mg/L in the Placebo group, the KB2115 100 and 200 µg groups, respectively (p<0.0001). From baseline to Week 12, the change in the ratio of Apolipoprotein B/apolipoprotein A-1 increased by 0.038 in the Placebo group and decreased by 0.139 and 0.191 in the KB2115 100 and 200 µg groups, respectively (p<0.0001). Also, statistically significant (p<0.0001) differences between the treatment groups were observed for camposterol and sitosterol measured as fractions of total cholesterol.

For HDL-cholesterol, apolipoprotein A-1, free fatty acids, lathosterol (fraction of total cholesterol) or C4 cholestan, there were no statistically significant differences between the treatment groups.

The PK evaluation showed that plasma levels of KB2115 exhibited a lag time of about 1 hour after dosing and that peak concentrations occurred at about 2 – 3 hours after dose but with large variability. The systemic exposure to KB2115 increased with dose and was approximately 45 % to 109 % higher after the 200-µg tablet as compared to the 100-µg tablet. There were no measurable amounts of the nitrated reaction product KB42899 in any

subject.

SAFETY RESULTS:

In total, 183 unique AEs (i.e., unique preferred AE term within a subject) were reported by 70 subjects out of 98 subjects (71.4%) in the safety population. There were 29 unique AEs in 14 (70.0%) placebo-treated subjects, 72 unique AEs in 38 (71.1%) subjects in the KB2115 100 μg group and 82 unique AEs in 29 (72.5%) of subjects in the KB2115 200 μg group.

AEs that occurred to more than 1 subject were influenza (3 subjects) and fatigue (2 subjects) in the Placebo group, nasopharyngitis (9 subjects), hyperhidrosis (4 subjects), influenza (3 subjects), dry skin (3 subjects), diarrhoea, dyspepsia, nausea, fatigue, arthralgia, and muscle spasm (2 subjects each) in the KB2115 100 μg group, and fatigue (5 subjects), nasopharyngitis (5 subjects), headache (4 subjects), pruritus (4 subjects), feeling cold (3 subjects), eye swelling, constipation, diarrhoea, temperature intolerance, anorexia, increased apetite, dysphonia and dry skin (2 subjects each) in the KB2115 200 μg group. Importantly, when comparing AEs across the treatment groups, there were 20 subjects in the Placebo group, 38 subjects in the KB2115 100 μg group and 40 subjects in the KB2115 200 μg group. Overall, the most commonly reported AEs were nasopharyngitis (15.3% of the subjects), fatigue (9.2%), influenza (7.1%), dry skin (6.1%), pruritus (5.1%) and headache (5.1%).

Out of the 183 AEs there were 85 ADRs. ADRs reported in more than one subject were fatigue (2 subjects) in the Placebo group, hyperhidrosis (4 subjects), fatigue, diarrhoea, dry skin, dyspepsia and nausea (2 subjects each) in the KB2115 100 μg group, and pruritus (4 subjects), fatigue (3 subjects), diarrhoea, feeling cold, headache, increased appetite (2 subjects each) in the KB2115 200 μg group.

The majority of the AEs were mild or moderate. Three subjects experienced AEs of severe intensity [1 in the 100 μg group (abnormal hepatic enzymes) and 2 in the 200 μg group (tremor/nervousness, and ankle fracture, respectively)].

One SAE occurred during the study, a case of ankle fracture (KB2115 200 μg/day), which was assessed as not related to study medication.

Seven subjects withdrew from the study. The reasons for withdrawal were AEs in 4 subjects (one in the 100 μg/day group and 2 in the 200 μg/day group were redrawn according to ALAT levels exceeding predefined levels set by the Safety Monitoring Board and a fourth subject was withdrawn on sponsor request due to an ALAT level close to the predefined level for withdrawal). Another 3 withdrawals were due to subject request in 2 subjects (one in the

placebo group and one in the 100 µg group and lack of compliance in 1 subject (100 µg).

Mean levels of ALAT, GGT, ALP and SHBG increased from baseline to Week 12 in both KB2115 dose groups relative to placebo whereas the increase in mean ASAT levels was statistically significant for the 200 µg dose only. Dose dependent increases in ALAT, ASAT, GGT and SHBG were observed with the most marked increases at Week 2 for ALAT and ASAT. There were no subject with consecutive ALT levels above 3-fold ULN.

There were statistically significant reductions from baseline to Week 12 in T4, free T4 and TBG in both KB2115 dose groups ($p<0.001$) and reduction in T3 in the KB2115 200 µg group ($p<0.001$) relative to the Placebo group. The magnitude of the reduction in T3 paralleled the reduction in TBG. There were no changes in TSH, free T3 or clinical scales for hypo- or hyperthyroid function or in muscle strength.

Markers to assess bone formation and bone resorption were mainly unchanged (osteocalcin, bone specific ALP, CTX and U-NTX), whereas minor increases were seen in PINP and U-NTX/Creatinine. BMD was unchanged.

Post hoc statistical testing of the change in laboratory parameters from baseline to Week 12 without multiplicity corrections yielded statistically significant differences between the treatment groups for WBC, neutrophil counts, calcium, phosphate, PTH, and creatinine, and none of these differences were judged as clinically meaningful.

There were no apparent changes in vital signs during the study or in QTcF within individual subjects or between the treatment groups. Further, no changes in any of the variables obtained from the echocardiography were seen between the treatment groups.

CONCLUSION(S):

Pronounced and clinically relevant reduction in independent risk factors (LDL-cholesterol, total cholesterol, apolipoprotein B/apolipoprotein A-1 ratio, Lp(a) and triglycerides) for the development of Coronary Heart Disease (CHD) were documented in subjects with primary hypercholesterolemia, at doses where a clinical euthyroid state was maintained.

For the primary endpoint, change in LDL-Cholesterol from baseline to Week 12, there were statistically significant ($p<0.0001$) differences between the both active treatment groups (KB2115 100 µg and 200 µg) and the placebo group. Moreover, treatment with KB2115 resulted in marked lowering of total cholesterol, triglycerides, apolipoprotein B, apolipoprotein B/apolipoprotein A-1 ratio ,and Lp(a) at 100 and 200 µg/day. There were no changes in HDL-cholesterol or apolipoprotein A-1 levels in KB2115 treated subjects relative to placebo treated subjects. The proportion responders, i.e., the percentage of subjects reaching a 20% lowering of LDL-cholesterol at week 12 compared to baseline level, was 60.5% and 72.5% in

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the 100 and 200 µg/day group, respectively, compared with 5.0% in the placebo group. The proportion of subjects fulfilling the ATP III treatment goals was 39.5% and 57.5% in the 100 and 200 µg/day group compared with 5.0% in the placebo group.

Treatment with KB2115 was well tolerated and there were few withdrawals. The systemic exposure of KB2115 increased with dose and the gastro-resistant tablet formulation protected against formation of the nitrated reaction product KB42899.

Preservation of extra-hepatic thyroid homeostasis is supported by lack of clinically relevant changes in THS, fT3, total T3, clinical thyroid rating scales, heart rate, ECG, echocardiography, or biomarkers for bone turnover, after administration of KB2115 in daily doses of up to 200 µg over 12 weeks.