KARO BIO

CONFIDENTIAL

CLINICAL STUDY REPORT

Study Code: KBT-004
EudraCT No: 2007-004413-33
ClinicalTrials.gov No: NCT00593047

A PHASE II, PLACEBO CONTROLLED, DOUBLE BLIND, RANDOMIZED, 12-WEEK, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY OF DIFFERENT DOSES OF EPROTIROME (KB2115) AS ADD ON TO STATIN TREATMENT IN PATIENTS WITH DYSLIPIDEMIA

Name of investigational product:	Eprotirome (KB2115)
Development phase:	Phase II
Date of study initiation:	12 November 2007
Date of study completion:	23 June 2008
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Version and Date of Report:	Final, 1 September 2009

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-004		
TITLE OF STUDY: A phase II, Placebo controlled, double blind, randomized, 12-week, parallel-group study to assess the efficacy of Eprotirome (KB2115) as add on to statin treatment in patients with dyslipidemia.		
INVESTIGATORS: Dr. Carl-Peter Anderberg, Gothenburg, Sweden Dr. Katarina Berndtsson-Blom, Skene, Sweden Dr. Jan Eskilsson, Helsingborg, Sweden Dr. Lars Haglund, Kristianstad, Sweden Dr. Hans-Erik Johansson, Uppsala, Sweden Dr. Pekka Koskinen, Malmö, Sweden Dr. Carl-Johan Lindholm, Lund, Sweden Dr. Per Eric Lins, Stockholm, Sweden Dr. Ulrik Mathiesen, Oskarshamn, Sweden Dr. Anders G Olsson, Stockholm, Sweden Dr. Aslak Rautio, Luleå, Sweden Dr. Folke Sjöberg, Linköping, Sweden Dr. Jorma Strand, Oulu, Finland Dr. Matti Kuusela, Karleby, Finland Dr. Toivo Piippo, Tampere, Finland		
STUDY CENTER(S): This was a multi-center study conducted in Sweden (12 centers) and Finland (3 centers).		
PUBLICATION (REFERENCE): None		

Clinical Study Report Version: Final Date: 1 September 2009	Study Code: KBT-004 Eudract No: 2007-004413-33 ClinicalTrials.gov No: NCT00593047

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 PERIOD (YEARS):

Date of first enrolment 12 November 2007

Date of last completed 2 June 2008

PHASE OF DEVELOPMENT: Phase II

OBJECTIVES:

Primary objective:

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

Secondary objectives:

- To assess safety and tolerability of different doses of Eprotirome as add-on to statin treatment in subjects with hypercholesteremia.
- To assess systemic exposure of Eprotirome and KB42899 in terms of C_{max} at different doses of Eprotirome and to assess plasma concentration time relationship and exposure in terms of AUC and C_{max} in a subset of approximately 24 subjects. In addition, assessment of Atorvastatin concentrations at Baseline, Week 4 and Week 12.
- To assess the influence of Eprotirome as add-on to statin 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, lipoprotein (a) [Lp(a)], and bone specific biomarker activities (S-CTX, bone specific alkaline phosphatase (ALP), and S-P1NP.
- To assess the influence of Eprotirome as add-on to statin 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.

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: To be determined	**Volume:**	
Name of Active Ingredient: Eprotirome	**Page:**	

NUMBER OF SUBJECTS (planned and analyzed):

	Placebo	Eprotirome			Total
		25 mcg	50 mcg	100 mcg	
	+ statin treatment				
No. planned to be screened					245
No. screened					329
No. planned to be randomized	43	43	43	43	172
No. randomized and treated	49	48	48	44	189
No. completed	43	43	42	40	168
No. analyzed (Safety)	49	48	48	44	189
No. analyzed (FAS)	47	47	46	44	184
No. analyzed (PPAS)	40	38	36	34	148

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 1 year in a woman above 50 years of age, or amenorrhea for more than 2 years below 50 years of age
3. Subjects with hypercholesterolemia treated with stable doses of one of the below listed lipid lowering medication for at least 3 months prior to randomization
   a. Atorvastatin ≤ 20 mg/day or
   b. Simvastatin ≤ 40 mg/day
4. LDL-cholesterol > 3.0 mmol/L (Week –1)
5. Subject able and willing to comply with all study requirements
6. 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.

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		

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

Eprotirome tablets, 25 mcg (batch number RF 1651)

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 bottles of study medication for each treatment period (Baseline – Week 2; Week 2 – Week 4, and Week 4 – Week 12) and was instructed to take one tablet from each bottle in the morning of each day.

DURATION OF TREATMENT:

The study period began with an enrolment visit, followed by a 4-week dietary lead-in period (six weeks if on fibrates) according to the National Cholesterol Education Program (NCEP) Step 1 diet or a country specific NCEP Step 1 diet guide), a 12-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 20 weeks (12 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.

CRITERIA FOR EVALUATION

EFFICACY:

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

Secondary efficacy evaluations were:

- Percentage responders in each group (with 15% lowering of LDL-cholesterol level at Week 12 versus Baseline)

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		

- Relative change in LDL-cholesterol from Baseline to Week 12
- Absolute and relative change from Baseline to Week 12 in total cholesterol, HDL-cholesterol, triglycerides, 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
- Concomitant medications
- Safety laboratory tests – hematology, serum chemistry and urinalysis
- Thyroid function – biomarkers of thyroid activity [TSH, free T3, total T3, free T4, total T4, and thyroid-binding globulin (TBG)]
- Muscle effects – creatine kinase
- Bone effects – bone specific biomarker activity (S-CTX, bone specific ALP, and S-P1NP)
- 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 statin 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 12. Subjects in the PPAS also had to be compliant (80 – 120%) to Eprotirome/Placebo and statin 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

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: To be determined	**Volume:**	
Name of Active Ingredient: Eprotirome	**Page:**	

safety evaluation (Safety Set).

All statistical analyses were performed using SAS, version 8.1 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 12, was tested with an analysis of covariance. 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 Eprotirome 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 12 in total cholesterol, LDL-cholesterol expressed as percent, responders for LDL-cholesterol, HDL-cholesterol, triglycerides, 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 imputed.

Percentage of responders, defined as a 15% lowering of LDL-cholesterol at Week 12 versus Baseline, was analyzed with a logistic regression with LDL-cholesterol at Baseline as a covariate and treatment as a factor in the model. If the model assumptions were not fulfilled non-parametric tests were to be applied. For Lp(a) and triglycerides, dose responses were assessed as for the primary variable.

The secondary safety and tolerability variables [TSH, free T3, total T3, free T4, total T4, TBG, S-CTX, bone specific ALP, S-P1NP, body weight and heart rate and QTcF (corrected

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		

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.

Blood concentrations of Eprotirome and KB42899 at each sample point were summarized and mean concentration versus time profiles were presented graphically by treatment group. C_{max}, t_{max} and T_{lag} were listed and also summarized using descriptive statistics and compared between doses. For subjects with extensive blood sampling for PK evaluation, C_{m+ax}, t_{max} and T_{lag}, AUC, CL/F, and $t_{½}$ were listed and summarized using descriptive statistics and compared treatment groups. C_{max} and AUC (for Eprotirome and KB42899) were log-transformed and explored by means of a power model for dose proportionality. In addition, assessment of Atorvastatin concentrations at Baseline, Week 4 and Week 12 were made in the subset of subjects with extensive blood sampling for PK evaluation.

SUMMARY AND CONCLUSION(S):

EFFICACY RESULTS:

The change in LDL-cholesterol from Baseline to Week 12, 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 21.6%, 27.6% and 32.1% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 6.5%). Mean LDL-cholesterol levels decreased by 0.82, 1.01 and 1.23 mmol/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.29 mmol/L in the Placebo group.

The proportion of responders (subjects with a 15% decrease in LDL-cholesterol from Baseline to Week 12) was 76.6%, 84.8% and 88.6% in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with 34.0% in the Placebo group.

Statistically significant differences in the Eprotirome treatment groups relative to Placebo for the change from Baseline to Week 12 were also observed for the secondary efficacy variables total cholesterol, HDL-cholesterol, triglycerides, apo A-1, apo B, apo B/ apo A-1 ratio, and Lp(a).

Total cholesterol decreased by 16.7%, 20.9% and 25.7% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 4.5%). Mean total cholesterol levels decreased by 0.93, 1.17 and 1.48 mmol/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.31 mmol/L in the Placebo group.

HDL-cholesterol decreased by 4.3%, 5.1% and 3.4% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 3.0%). Mean HDL-cholesterol levels decreased by 0.07, 0.08 and 0.06 mmol/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with an increase by 0.02 mmol/L in the Placebo

group.

Triglyceride levels decreased by 15.7%, 15.7% and 32.6% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was an increase by 4.7%). Mean triglyceride levels decreased by 0.32, 0.39 and 0.69 mmol/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.03 mmol/L in the Placebo group. In the subset of subjects with Baseline triglyceride levels > 1.70 mmol/L, there was a decrease in triglyceride levels by 1.38 mmol/L (50.7%) compared with 0.58 mmol/L (25.2%) in the Placebo group.

Apo A-1 decreased by 7.9%, 9.7% and 9.7% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 2.3%). Mean apo A-1 levels decreased by 0.15, 0.17 and 0.17 g/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.05 g/L in the Placebo group.

Apo B decreased by 20.3%, 24.5% and 30.1% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 5.6%). Mean apo B levels decreased by 0.24, 0.28 and 0.36 g/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.08 g/L in the Placebo group.

The apo B/ apo A-1 ratio decreased by 12.8%, 16.2% and 22.2% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 3.2%). Mean apo B/ apo A-1 ratios decreased by 0.10, 0.11 and 0.16 in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 0.02 in the Placebo group.

Lp(a) decreased by 27.7%, 28.1% and 41.5% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 7.6%). Mean Lp(a) levels decreased by 151, 162 and 232 mg/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 53 mg/L in the Placebo group. In the subset of subjects with Baseline Lp(a) levels > 100 mg/L, Lp(a) levels decreased by 31.5%, 34.2% and 46.1% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 8.0%). In this subgroup, mean Lp(a) levels decreased by 181, 192 and 267 mg/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 59 mg/L in the Placebo group. In the subset of subjects with Baseline Lp(a) levels > 200 mg/L, Lp(a) levels decreased by 28.9%, 33.8% and 42.9% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 6.4%). In this subgroup, mean Lp(a) levels decreased by 225, 212 and 347 mg/L in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a decrease by 69 mg/L in the Placebo group. In the subset of subjects with Baseline Lp(a) levels > 300 mg/L, Lp(a) levels decreased by 27.0%, 29.7% and 41.5% in the Eprotirome 25, 50 and 100 mcg group, respectively (the change in the Placebo group was a decrease by 4.9%). In this subgroup, mean Lp(a) levels decreased by 251, 233 and 432 mg/L in the Eprotirome 25, 50 and 100

mcg group, respectively, compared with a decrease by 83 mg/L in the Placebo group.

There were no statistically significant changes in free fatty acid 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, 362 AEs were reported by 118 subjects. AEs reported in more than two subjects in a treatment group were nasopharyngitis in the Placebo group; upper abdominal pain, nasopharyngitis, headache, and pruritus in the Eprotirome 25 mcg group; fatigue, nasopharyngitis, back pain, headache and cough in the Eprotirome 50 mcg group; and nasopharyngitis and pruritus in the Eprotirome 100 mcg group. Out of the 362 AEs, 85 were ADRs to Eprotirome, i.e., judged by the investigator to be possibly or probably related to Eprotirome, and 37 were ADRs to statin treatment. ADRs to Eprotirome reported in more than two subjects in a treatment group were fatigue in the Placebo group, pruritus in the Eprotirome 25 mcg group, and palpitations in the Eprotirome 50 mcg group. There were no ADRs to statin reported in more than two subjects per treatment group.

The majority of the AEs were mild or moderate. Eight subjects experienced severe AEs [one in the Placebo group (pneumonia), three in the Eprotirome 25 mcg group (erysipelas, ankle fracture, and musculoskeletal chest pain), two in the Eprotirome 50 mcg group (abdominal pain, and dizziness), and two in the Eprotirome 100 mcg group (fibula fracture, and loss of consciousness).

In all, there were eight SAEs reported, one in the Placebo group (salmonella food poisoning), three in the Eprotirome 25 mcg group (erysipelas and ankle fracture as listed above, and duodenal ulcer), one in the Eprotirome 50 mcg group (dizziness, as listed above), and three in the Eprotirome 100 mcg group (fibula fracture and loss of consciousness as listed above, and worsening of arthrosis). None of the SAEs were judged as related to the study medications (Eprotirome and/or statin) by the investigator.

Twenty one subjects withdrew from the study: nine subjects withdrew due to safety reasons/ AEs [two in the Placebo group (abnormal thyroid function tests; and neck pain), two in the Eprotirome 25 mcg group (stomach pain, nausea, pruritus and urticaria in one subject; and change in skin touch sensitivity in another subject), four in the Eprotirome 50 mcg group (palpitation; a combination of headache, tiredness, dizziness and nausea; increased liver function tests; and abdominal pain) and one in the Eprotirome 100 mcg group (worsening of preexisting rosacea)]; four subjects withdrew their consent to participate in the study (two in the Placebo and Eprotirome 100 mcg group each); three subjects were withdrawn due to incorrect enrolment (one in the Placebo group and two in the Eprotirome 50 mcg group); one subject (Eprotirome 50 mcg group) was withdrawn due to protocol violation; and four

subjects were withdrawn due to other reasons (one in the Placebo group, two in the Eprotirome 25 mcg group and one in the Eprotirome 100 mcg group).

Transient and apparently dose dependent increases in ALT, AST and GGT were observed. A total of 7 subjects had transient increases in ALT >3xULN during the study (6 women, 2 in each Eprotirome group, and 1 man in the Eprotirome 50 mcg group). Two of these were consecutive following re-test within one week) (one woman in the Eprotirome 25 mcg group had ALT >3-fold at week 4 and week 5 and the highest value was 5.04xULN. This subject continued treatment and completed the study. The other subject was a woman in the Eprotirome 50 mcg group who had ALT >3xULN during four consecutive weeks and consequently was withdrawn from the study according to algorithm predefined by the DSMB. The highest measured value was 5.34xULN in that subject). In none of the subjects with increase in ALT were concomitant increases in bilirubin seen.

There were no statistically significant changes in TSH, fT3 or T3, whereas moderate reductions in total and free T4, and in TBG ($p<0.001$) were observed in a dose dependent fashion. The changes were reversible and returned to Baseline levels at the follow up visit. Mean values remained within the normal range for all thyroid variables. No single value below the respective LLN was seen in any patient at any time point for TSH and T3. A single value below LLN was seen in fT3 in three subjects in the Placebo group (Week 4, Week 1 and Week 12), in two subjects in the Eprotirome 25 mcg group (Baseline and Week 16), in two subjects in the Eprotirome 50 mcg group (Baseline and Week 12) and in four subjects in the Eprotirome 100 mcg group (two at Baseline, one in Week 1, and one in Week 12).

No apparent trends were observed for the other laboratory evaluations except for SHBG for both male and female subjects, and for FSH, LH and total testosterone for male subjects. In males, apparently dose dependent increases were observed for SHBG and total testosterone ($p<0.001$ for each Eprotirome group relative to Placebo). There were no changes in calculated free testosterone. In females, the increase in SHBG was also dose dependent ($p<0.001$ for each Eprotirome group relative to Placebo).

There were no apparent changes in vital signs during the study. ECG's with central manual reading were performed at each study visit (two before, five during and one after the dosing period). Abnormal ECG's were observed before but not during treatment (two in the Eprotirome 25 mcg group at Baseline and one in the Eprotirome 50 mcg group at Week -4 and Baseline. 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 3.3 beats/min at week 12 in the Placebo group, 2.4 beats/min at Week 4 in the Eprotirome 25 mcg group, 2.7 beats/min at Week 1 in the Eprotirome 50 mcg group, and 2.1 beats/min at Week 6 in the Eprotirome 100 mcg group. There were no QTcF values above 480 ms or change in QTcF from Baseline greater than 60 ms in any subject.

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: To be determined	**Volume:**	
Name of Active Ingredient: Eprotirome	**Page:**	

CONCLUSIONS:

For the primary endpoint, change in LDL-cholesterol from Baseline to Week 12, there were statistically significant ($p<0.0001$) differences between each Eprotirome group (25, 50 and 100 mcg) and the Placebo group. Thus, treatment with Eprotirome as add on to statin treatment was efficacious in reducing LDL-cholesterol levels over a 12-week treatment period.

The reduction in LDL-cholesterol levels at Week 12 relative to Baseline was 21.5%, 27.6%, and 32.1% in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with a reduction by 6.5% in the Placebo group. The proportion of responders, i.e., the percentage of subjects reaching a 15% lowering of LDL-cholesterol from Baseline to Week 12 was 76.6%, 84.8% and 88.6% in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with 34.0% in the Placebo group.

Treatment with Eprotirome as add on to statin treatment also resulted in marked lowering of total cholesterol, triglycerides, apo B, apo B/ apo A-1 ratio, and Lp(a) at 25, 50 and 100 mcg/day. Minor but statistically significant decreases relative to Placebo were also noted for HDL-cholesterol and apo A-1. There were no changes in free fatty acids.

Lp(a) and triglycerides in subjects with Baseline levels above current accepted treatment recommendations (Lp(a) >300 mg/L or 30 mg/dl, and triglycerides >1.7 mmol/L or 150 mg/dl) were reduced in the Eprotirome 25, 50 and 100 mcg groups by 27.0%, 29.7%, and 41.5% for Lp(a), respectively, compared with 4.9% in the Placebo group, and 27.9%, 33.0%, and 50.7% for triglycerides, compared with 25.2% in the Placebo group. The reductions in apo B were 20.3%, 24.5%, and 30.1% in the Eprotirome 25, 50 and 100 mcg group, respectively, compared with 5.9% in the Placebo group.

The systemic exposure of Eprotirome appeared to be roughly proportional to dose, although full evaluation of pharmacokinetic parameters was only possible in a small number of subjects. The absorption of Eprotirome typically started after a lag time of approximately one hour. The presence of KB42899, a nitrated reaction product of Eprotirome, was assessed in all samples assayed for Eprotirome. No measurable amounts of KB 42899 were detected in any of the subjects at any time point

Safety evaluations were adverse event reporting, 12-lead ECG and echocardiography, vital signs, and monitoring of hematology and clinical chemistry laboratory panels including thyroid function tests, liver function tests, and muscle and bone biochemistry measures. An Independent Safety Monitoring Board (DSMB) with clinical experts in endocrinology, cardiology, hepatology, and pharmacology was engaged for safety surveillance.

Add on to statin treatment with multiple doses of Eprotirome at 25, 50 and 100 mcg/day in subjects receiving stable treatment with low- to medium dose Atorvastatin or Simvastatin during 12 weeks were well tolerated and the majority of AEs were mild or moderate in intensity. There were no apparent changes in vital signs. There were no statistically

significant or clinically meaningful changes in heart rate or QTcF.

Slight and apparently dose related increases in ALT, AST and GGT were observed. All increases in liver enzymes were mild and reversible, mostly within a few weeks. There were 2 incidences of consecutive ALT > 3 fold ULN (within 1 week of re analysis), but there were no indications of overt hepatotoxicity in these subjects, as judged by fast reversibility and the absence of a typical hepatotoxicity pattern within the set of liver biomarkers (ALT, AST, ALP, GGT, and bilirubin).

There were no statistically significant changes in TSH, total or free T3, whereas moderate reductions in total and free T4, and in TBG were observed during add on to statin treatment with Eprotirome. Thus, Eprotirome at the administered doses does not disturb thyroid function, as judged by virtually unchanged TSH and free fraction of the active hormone T3, despite reductions in total and free T4.

No apparent trends were observed for the other laboratory evaluations except for SHBG for both male and female subjects, and for FSH, LH and total testosterone for male subjects. There were no changes in calculated free testosterone in males and there was no change in estradiol in females.

In conclusion, pronounced and clinically relevant reductions 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 low- and mid dose statin treatment in subjects with dyslipidemia at doses where extra-hepatic thyroid homeostasis was preserved. The addition of Eprotirome at daily doses ranging from 25 to 100 mcg to ongoing statin therapy reduced the serum concentration of LDL cholesterol (-15% to -26%), apo B (-14% to -24%), triglycerides (-20% to -37%) and Lp(a) (-20% to -33%), when adjusted for Placebo.