2 SYNOPSIS

Name of Sponsor/Company: Rheoscience A/S Glerupvej 2 DK-2610 Rødovre	Individual Study Table Referring to part of the Dossier	*For National Authority Use only:*
Name of the Finished Product: Pending	Volume:	
Name of the Active Ingredient: Balaglitazone	Page	
Title of the Study: Efficacy and safety of treatment with balaglitazone in type 2 diabetes patients on stable insulin therapy		
Investigators: International Coordinating Investigator: Hans Perrild, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV		
Study Centre:		
Publication: None		
Study Period: Date of First Enrolment: 10 July 2007 Last Subject Last Visit: 06 July 2009	Development Phase: Phase 3	

Objectives:

Primary objectives: To compare, in type 2 diabetes patients on stable insulin therapy, the efficacy of balaglitazone 10 mg and 20 mg against placebo on absolute change in HbA1c from baseline to end of trial.

Secondary objectives: To assess and compare the effect of balaglitazone against pioglitazone 45 mg or placebo on various pharmacodynamic measurements in patients with type 2 diabetes on stable insulin therapy from baseline to end of trial. The secondary outcome measures include change in:

1. Fasting serum glucose, 4- and 7-point blood glucose profiles
2. Percentage/proportion of patients achieving a HbA1c <7% or <6.5%
3. Blood lipid profile (TG, TC, LDL-C, HDL-C, LDL/HDL)
4. Body weight gain
5. Waist and hip circumferences
6. Plasma volume and serum NT-proBNP
7. Frequency of lower leg edema by clinical assessment or by water displacement
8. Change in body composition, as measured by DXA, as a measure of change in fat tissue mass and lean tissue mass, i.e. fluid retention
9. Daily dose of insulin

In addition, the safety of balaglitazone 10mg and 20mg will also be studied by the determination of changes in ECG, serum concentration of balaglitazone, hematology and biochemistry and adverse event recording over a 6 month treatment, and will be compared with pioglitazone (Actos®) 45 mg. The incidence of hypoglycemic episodes will be monitored and recorded from baseline to week 26 endpoints.

Methodology:

The study was a double-blind, parallel-group, multi-centre, randomized, placebo and comparator-controlled clinical trial in patients with type 2 diabetes on stable insulin therapy. The study was performed in 31 centers in Denmark (19 centers), Sweden (6 centers) and Finland (6 centers). The diagram below shows the study design in overview.

The study period included a Screening Visit and a treatment period lasting for six months. The subjects were monitored during the treatment period with regular examinations and samplings according to the Flow chart outlined in Table 6–1. A Follow-up telephone call was performed 4 weeks (±7 days) after the Final Visit (Visit 8). Assessments: The following assessments were taken at specified times throughout the study: HbA1c; body weight; frequency of edema; daily dose of insulin; safety parameters; waist and hip circumferences; fasting serum glucose (FPG) and 7-point blood glucose profiles; percentage of patients achieving an HbA1c <7.0% or <6.5%; incidence of hypoglycemic episodes; lipid profile (TC, LDL-C, HDL-C, TG, LDL/HDL); body composition measured by DXA as a measure of changes in fat tissue mass and lean tissue mass, i.e. fluid retention; change in lower leg edema by water displacement; change in plasma volume and NT-proBNP
Number of Trial Participants: 409 (randomized/starting trial medication), 271 in Denmark, 39 in Sweden and 99 in Finland. ITT-population: 402; Completers: 311; PP-population: 308
Diagnosis and Main Criteria for Inclusion: Inclusion criteria: Type 2 diabetes mellitus, being diagnosed according to the 1999 WHO criteria for at least 3 months Age ≥ 18 years BMI ≥ 25.0 kg/m2 HbA1c ≥ 7.0 % Treatment with insulin on stable dose of at least 30 U/day (± 4 U/day), for at least 75 days (Insulin adjustments during a previous and resolved short term acute disease are permitted). Exclusion criteria: Prior or current use of PPARγ agonist Hospitalization for a major CV event in the last 3 months, scheduled major CV intervention Diagnosed or receiving medication for heart failure, NYHA I to IV Uncontrolled treated/untreated systolic > 180 mmHg and/or diastolic blood pressure > 95 mmHg Serum creatinine > 130 μmol/L ALT, AST, total bilirubin or alkaline phosphatase ≥ 2.5 times the upper limit of normal Hemoglobin significantly (in the Investigators opinion, but not more than 1 mmol/L) below the lower limit of normal or hemoglobinopathy interfering with valid HbA1c assay Hematuria, defined as any, even trace of, hematuria on a urinary dipstick at the screening or randomization Visit. Contraindication/intolerance to study medication Pre-existing medical condition judged to preclude safe participation in the study Abuse of alcohol or drugs, or presence of any condition that in the Investigators opinion may lead to poor adherence to study protocol Recent use (< 3 months) of an investigational drug Pregnancy, breast feeding or planning pregnancy or not using adequate contraceptive methods (adequate contraceptive measures are an intrauterine device or oral contraceptives). Mental incapacity, unwillingness, or language barrier precluding adequate understanding or cooperation Use of any drug which in the Investigator's opinion could interfere with the glucose level (e.g. systemic corticosteroids). Any cancer history or currently diagnosed/treated cancer Diagnosis of clinically significant disease/disorder which in the Investigator's opinion could interfere with the results of the trial Known Diabetic macular edema Planned surgery

Test Product, Dose and Mode of Administration, Batch Numbers:
Product: Balaglitazone capsules
Dose: 10 or 20 mg; once daily
Administration: Oral
Batch Numbers:
Balaglitazone 10 mg: Batches CTC07-007, CTB08-002, CTF08-007
Balaglitazone 20 mg: Batches CTC07-008, CTB08-003, CTG08-008
Placebo: CTC07-006, CTB08-001, CTF08-006

Duration of Treatment: 6 months

Reference therapy, dose and mode of administration, batch numbers:
Product: Pioglitazone capsules
Dose: 45 mg; once daily
Administration: Oral
Batch Numbers:
Pioglitazone 45 mg: CTC07-009, CTB08-004, CTG08-009

Criteria for evaluation: Efficacy
Primary endpoint: HbA1c
Secondary endpoints: fasting serum glucose, insulin and lipids; 4- and 7-point blood glucose profiles; daily dose of insulin; hypoglycemic episodes; body weight; lower leg edema (ankle); NT-proBNP and plasma volume; body composition; waist and hip circumference.

Criteria for evaluation: Safety
ECG; serum concentrations of balaglitazone; hematology; biochemistry; urinalysis, vital signs, physical examination, adverse event (AE) recording; incidence of hypoglycemic episodes.

Statistical Methods:
Throughout the analyses a significance level of 5% was used, unless otherwise specified. Consequently 95% confidence intervals were employed. In all analyses the null hypothesis were that the two treatment groups under consideration were equal as opposed to the alternative that they differed.

The change from baseline in HbA1c (%) at the end of the treatment period (Visit 8) was analyzed using an analysis of covariance (ANCOVA) with treatment group and country as fixed effects (factors) and baseline HbA1c value as a covariate. The effect on glycemic control (assessed by change in HbA1c) was compared for the two doses of Balaglitazone (10 mg and 20 mg) versus Placebo. A two sided 95% confidence interval for the difference between treatment groups (Balaglitazone 10 and 20 mg – Placebo) was calculated. The comparison involving Balaglitazone 10 mg was only performed if Balaglitazone 20 mg could be concluded to be superior to Placebo. The primary endpoint was also summarized by displaying the summary statistics number of subjects, mean, SD, median, 5% percentile, 95% percentile, minimum and maximum for each treatment group

In general for secondary endpoints the change from baseline for the variable in question was analyzed using an analysis of covariance (ANCOVA) with treatment group and country as fixed effects (factors) and the baseline value for the variable in question as a covariate. For the pair wise comparisons of treatment groups p-values and confidence intervals were calculated using Tukey-Kramer's method in order to protect the overall type-I error. The change from baseline for the variable in question was summarized by displaying summary statistics number of subjects, mean, SD, median, 5% percentile, 95% percentile, minimum and maximum for each treatment group.

Efficacy results:

Primary endpoint

- Both the Bala 10 mg and the Bala 20 mg group were superior to placebo with respect of absolute change in HbA1c from baseline to end of trial.

Secondary endpoints

- HbA1c; The absolute decrease from baseline to end of trial in HbA1c was 0.99% and 1.11% in the Bala 10 mg and Bala 20 mg group compared to placebo, respectively, and this change was not different from the comparator, i.e. Pio 45 mg.
- HbA1c; At end of trial, 14 subjects in the Bala 10 mg, 16 in Bala 20 mg, 21 in Pio 45 mg and 2 in the placebo group had reached HbA1c levels $\leq$7.0%.
- Glucose & insulin; Bala 10 mg and Bala 20 mg was not statistically significant different from the Pio 45 mg group with respect of change from baseline to end of trial compared to placebo for fasting plasma glucose, mean post -prandial blood glucose, mean post-prandial blood glucose increment, and fasting serum insulin
    - Fasting glucose; Compared to placebo, the decrease in fasting glucose from baseline to end of trial was 1.42 mmol/L in Bala 10 mg, 1.80 mmol/L in Bala 20 mg, and 1.35 in Pio 45 mg (all $p<0.05$).
    - Fasting serum insulin; Compared to placebo, the reduction in fasting serum insulin was 0.25 pmol/L in Bala 10 mg ($p<0.05$), 0.23 pmol/L in Bala 20 mg ($p<0.05$), and 0.18 pmol/L in Pio 45 mg (NS).
    - At end of trial, all treatment arms were associated with an increased odds ratio for having reduced insulin dose, however the odds ratio for the Bala 10 mg group was smaller ($p<0.05$) than the odds ratio for the Pio 45 mg group. In the PP analysis, the difference between treatment groups all remained non-significant.
- Weight; All treatment arms experienced a weight gain, however, the Bala 10 mg group had a 1.43 kg less gain in weight ($p<0.05$) compared to the Pio 45 mg group at end of trial.
- Edema; At end of trial, all treatment arms had an increase in lower leg edema (as measured by displacement of water) compared to baseline, however, for the Bala 10 mg group this was not statistically significantly different from placebo.
- Fat & lean tissue mass; At end of the trial all treatment arms had increases in trunk and peripheral fat tissue mass compared to placebo ($p<0.05$), which for the Bala 10 mg group was significantly smaller in the peripheral compartment compared to the Pio 45 mg group. The corresponding changes in lean tissue mass were not different from placebo.
- BMD; At end of trial, no significant changes in total body BMD was identified in neither of the treatment arms compared to baseline or placebo. Although insignificant, a trend towards less skeletal effect in the Bala groups compared to the Pio 45 mg group was observed.
- NT-proBNP; All treatment groups had an increase in NT-proBNP from baseline to end of trial ($p<0.05$), whereas placebo did not. At end of trial, however, the three treatment arms remained within normal range.
- Lipids; No significant changes until end of trial was observed in LDL Cholesterol, whereas all treatment arms had significant increases in HDL Cholesterol.

Safety Results

- In the safety analysis subset, 409 subjects were included and a total of 818 adverse events (AE's) were reported of which 702 was designated treatment emergent AE (TEAE). The distribution of TEAE's was even across all treatment arms and placebo, i.e. Bala 10 mg; 180 TEAE's, Bala 20 mg; 162 TEAE's, Pio 45 mg; 178 TEAE's, and placebo; 182 TEAE's.
- A total of 38 TEAE's were classified as serious and they were also evenly distributed with Bala 10 mg; 6 serious TEAE's, Bala 20 mg; 12 serious TEAE's, Pio 45 mg; 12 serious TEAE's, and placebo; 8 serious TEAE's. Most frequent organ class was cardiac disorders (a total of 9 serious TEAE's) with Bala 10 mg; 0

serious TEAE's, Bala 20 mg; 3 serious TEAE's, Pio 45 mg; 4 serious TEAE's, and placebo; 2 serious TEAE's.

- A total of 160 TEAE's were considered to be related to the IMP, with Bala 10 mg; 53 TEAE's, Bala 20 mg; 41 TEAE's, Pio 45 mg; 43 TEAE's, and placebo; 23 TEAE's. Only two of these were designated cardiac disorders and neither of these was in the Bala groups.
- A total of 28 TEAE's were classified as of special interest (AEOSI) with Bala 10 mg; 2 AEOSI, Bala 20 mg; 7 AEOSI, Pio 45 mg; 11 AEOSI, and placebo; 8 AEOSI. The most frequent class of AEOSI was Ischemic Heart Disease with Bala 10 mg; 1 AEOSI, Bala 20 mg; 3 AEOSI, Pio 45 mg; 6 AEOSI, and placebo; 6 AEOSI. Second most frequent was Heart Failure with Bala 10 mg; 0 AEOSI, Bala 20 mg; 2 AEOSI, Pio 45 mg; 3 AEOSI, and placebo; 2 AEOSI.
- One suspected unexpected serious adverse reaction (SUSAR) diagnosed as deep vein thrombosis (DVT) was reported in the Bala 10 mg group. The subject recovered without sequelae.
- A total of 1536 hypoglycemic episodes were reported with Bala 10 mg; 0.72 episodes per subject month, Bala 20 mg; 1.01 episodes per subject month, Pio 45 mg; 0.83 episodes per subject month, and placebo; 0.45 episodes per subject month.
- A total of 15 hematology assessments were designated abnormal and clinical significant. At the end of trial 5 such assessments were reported with Bala 10 mg; 3, Bala 20 mg; 0, Pio 45 mg; 2, and placebo; 0.
- The most frequent change in biochemistry assessment from normal at baseline to high at end of trial was urea with Bala 10 mg; 29 subjects, Bala 20 mg; 28 subjects, Pio 45 mg; 20 subjects, and placebo; 20 subjects.
- A total of 73 urinalysis determinations were classified as abnormal and clinical significant with Bala 10 mg; 20 assessments, Bala 20 mg; 16 assessments, Pio 45 mg; 18 assessments, and placebo; 19 assessments.
- A total of 18 physical examinations changed from normal to abnormal and clinical significant. The most frequent worsening was relating to the cardiovascular system with Bala 10 mg; 3 subjects, Bala 20 mg; 3 subjects, Pio 45 mg; 1 subject, and placebo; none.
- Two subjects, one in each Bala group, had a change in ECG classified from normal at baseline to abnormal and clinically significant at end of study.
- Non-significant decreases were observed in all three treatment arms and placebo from baseline to end of trial in diastolic and systolic blood pressure.

Conclusion:

We conclude that treatment with daily doses of balaglitazone 10 and 20 mg in type II diabetes patients on stable insulin therapy leads to improvement in glycemic control matching that observed with pioglitazone 45 mg. Furthermore, balaglitazone 10 mg treatment has a favorable safety profile compared to pioglitazone 45 mg leading to fewer side effects, such as lower weight gain, less peripheral edema and fat tissue mass, as well as a trend towards less bone loss, fewer serious adverse events, and less serious cardiac events.

Thus, balaglitazone 10 mg is a promising treatment option for type 2 diabetes.

Date of Report:

Final version, 21 December 2009