# SYNOPSIS OF RESEARCH REPORT [redacted]
# (PROTOCOL BM17864)

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| COMPANY:<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE SUBSTANCE(S): | (FOR NATIONAL AUTHORITY USE ONLY) |

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| TITLE OF THE STUDY / REPORT No. / DATE OF REPORT | A randomized, double-blind, parallel group, placebo-controlled (with open-label active comparator arm), dose-ranging study to determine the efficacy, safety, tolerability and pharmacokinetics of aleglitazar (dual PPAR $\alpha/\gamma$ agonist) therapy when administered to patients with type 2 diabetes mellitus.<br>[redacted] November 2008 | | |
| INVESTIGATORS / CENTERS AND COUNTRIES | Multicenter study involving 47 centers in 7 countries:<br>USA (14 centers), Mexico (11 centers), Russia (7 centers), Italy (6 centers), Romania (5 centers), Serbia (4 centers) and Hong Kong (2 centers) | | |
| PUBLICATION (REFERENCE) | N/A | | |
| PERIOD OF TRIAL | 9 October 2006 – 27 December 2007 | CLINICAL PHASE | II |
| OBJECTIVES | Primary objective: to determine the dose(s) of aleglitazar which are efficacious in improving glycemic control, safe, and tolerable in patients with T2D when administered orally, once daily for 16 weeks compared with placebo<br>Secondary objectives: to explore by a population analysis approach the pharmacokinetics (PK) and exposure-response relationship of aleglitazar in the target patient population;<br>to use active comparator (pioglitazone) data to support the dose selection of aleglitazar for comparative phase 3 studies with model-based simulation, if feasible. | | |
| STUDY DESIGN | Multicenter, randomized, double-blind, parallel group, placebo-controlled study with open-label active comparator arm, comprising six treatment groups: placebo, 4 dose levels of aleglitazar (0.05, 0.15, 0.3 and 0.6 mg) and 45 mg pioglitazone. Patients were stratified according to their disease severity (baseline A1C $< 8.5\%$ or $\geq 8.5\%$) | | |
| NUMBER OF SUBJECTS | Planned: 300 (50 per treatment group)<br>Actual: 332 (55-57 per treatment group) | | |
| DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION | Adult patients with T2D for at least 1 month, either drug-naive or pre-treated with monotherapy or combination therapy (max. 2 OADs, excluding insulin and TZDs), with A1C of 7.0%-10.0% and FPG $\leq$ 240 mg/dL. | | |
| TRIAL DRUG / STROKE (BATCH) No. | 0.05 mg RO0728804/F04: [redacted]<br>0.1 mg RO0728804/F05: [redacted]<br>0.2 mg RO0728804/F06: [redacted]<br>0.3 mg RO0728804/F02: [redacted] | | |

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| DOSE / ROUTE / REGIMEN / DURATION | 0.05, 0.15, 0.3 or 0.6 mg administered orally every morning for 16 weeks during the double-blind treatment period. |
| REFERENCE DRUG / STROKE (BATCH) No. | Placebo RO0728804/[redacted]<br>45 mg pioglitazone (Actos®): [redacted] |
| DOSE / ROUTE / REGIMEN / DURATION | Placebo run-in period: 2 placebo tablets each morning for 4 weeks. Double-blind treatment period: placebo or 45 mg pioglitazone administered orally every morning for 16 weeks. |
| CRITERIA FOR EVALUATION | |
| EFFICACY: | <u>Primary parameter</u>:<br>• A1c absolute change from baseline at the end of the treatment period (week 16)<br><u>Secondary parameters</u>:<br>• absolute change in FPG from baseline at the end of treatment period<br>• response rate in terms of absolute A1C reduction at the end of the treatment period<br>• response rate in terms of actual A1C value at the end of the treatment period<br>• absolute and relative change in the lipid profile [triglycerides, total cholesterol, HDL- and LDL-cholesterol, Apo-A1, Apo-B, total cholesterol/HDL-cholesterol ratio and lipoprotein (HDL, LDL, IDL and VLDL) subclass distribution] from baseline at the end of treatment period<br>• absolute change in insulin resistance from baseline to end of treatment period (HOMA-IR)<br>• absolute change in β-cell-function from baseline to end of treatment period (HOMA-B)<br>• absolute change in cardiovascular markers (hsCRP and adiponectin) from baseline to end of treatment period |
| PHARMACOKINETICS: | Primary PK parameters CL/F and $V_{ss}$/F and secondary parameters AUC, $C_{max}$ and $C_{min}$ estimated using population pharmacokinetic methods. |
| SAFETY: | Adverse events (including edema and hypoglycemia), clinical laboratory tests, ECG, echocardiography, vital signs, physical examination, body weight, waist to hip ratio and hair health questionnaire |

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STATISTICAL METHODS

For the primary efficacy parameter (absolute change of A1C from baseline at week 16), an analysis of covariance (ANCOVA) with treatment and region as fixed factors and A1C at baseline as covariate was performed. Each aleglitazar dose regimen was compared against placebo, and the null-hypothesis was used to test whether the mean differences exceeded 0%. The nominal one-sided significance level alpha = 0.025 was applied for each of the pairwise comparisons. Hypotheses were tested with the following hierarchical decision procedure: 0.6 mg vs. placebo, 0.3 mg vs. placebo, 0.15 mg vs. placebo, and finally 0.05 mg vs. placebo.

An ANCOVA was used to calculate least squares means of the difference from baseline and 95% confidence intervals at each timepoint. The placebo-corrected difference from baseline at Week 16 was also calculated. Similar analyses were applied to the secondary efficacy endpoints in an exploratory manner. Responder analyses are presented by rates within each treatment arm. Any comparison with pioglitazone is purely descriptive.

All safety data are presented by individual patient listings and summary tables as appropriate. For safety parameters of special interest, statistical analyses were performed using a one-way analysis of variance (ANOVA) with treatment group as the independent variable, for observed values only.

METHODOLOGY:

The study consisted of four phases: screening (max 2 weeks), a 4-week washout/placebo run-in period, a 16-week treatment, and follow-up (4 weeks after last dose). For eligible patients, a diet and exercise plan was implemented based on recommendations from the investigator. OADs and weight lowering drugs were discontinued at the start of the wash-out/placebo run-in period and patients took 2 placebo capsules every morning for 4 weeks. A pre-randomization visit was conducted between five and two days before the end of this period (day -5 to day -2) to determine eligibility based in final inclusion/exclusion criteria.

Eligible patients were randomly assigned one of six treatment groups: placebo, 0.05, 0.15, 0.3 or 0.6 mg aleglitazar, or 45 mg pioglitazone once daily for 16 weeks. Baseline measurements for efficacy and safety parameters were taken either at the pre-randomization visit (days -2 to -5) or on day 1 prior to first dose. Patients returned to the site at weeks 2, 4, 8, 12 and 16 for the evaluation of efficacy, safety and PK parameters. A final follow-up visit was conducted 4 weeks after the last study medication intake.

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EFFICACY RESULTS:

Treatment with aleglitazar for 16 weeks resulted in statistically significant, dose-dependent reductions from baseline in A1C of between 0.002% and 0.994%, compared with an increase of 0.354% in patients taking placebo. The decrease in A1C for the dose of 0.15 mg aleglitazar (-0.494%) was numerically similar to that seen following treatment with 45 mg pioglitazone (-0.353%). The reduction in A1C started to become apparent between 2 and 4 weeks of treatment and had not yet reached a plateau at the end of the 16 week treatment period. Similar results were seen for FPG but a plateau appeared to be reached after 8-12 weeks.

Dose-dependent increases in A1C response rates were observed based on both a decrease of ≥ 0.6% from baseline and an absolute A1C value of < 7% at end of treatment. Aleglitazar treatment also had a beneficial effect on other indicators of glycemic control and insulin sensitivity such as HOMA-IR, insulin, FFAs and C-peptide, with statistically significant differences from placebo observed for the higher doses.

A favorable shift in the lipid profile was confirmed following 16 weeks of treatment with aleglitazar. Decreases in triglycerides, LDL-cholesterol and total cholesterol were observed along with increases in HDL-cholesterol. Statistically significant differences from placebo were seen for all doses tested. These changes were accompanied with increases in HDL and LDL particle size.

Aleglitazar also appeared to have positive effects on cardiovascular markers, demonstrated by dose-dependent increases in adiponectin, and decreases in fibrinogen and PAI-1.

PHARMACOKINETIC RESULTS:

The serum concentration-time course for aleglitazar in T2D patients was accurately described by a two disposition compartments model with first order absorption and linear elimination pathway from the central compartment. Body surface area was found to have a statistical impact on the volume of distribution of the central compartment (V2/F) and on the inter-compartmental clearance (Q/F). No other covariates were found to significantly influence the final primary and secondary PK parameters and no dose adjustment was needed. The linear clearance led to a dose-proportional increase in AUC, $C_{min}$ and $C_{max.}$

SAFETY RESULTS:

Aleglitazar was generally well tolerated in this study. Adverse events occurred in between 38% and 47% of patients receiving aleglitazar, compared with 45% of patients on placebo and 53% of patients taking pioglitazone. The majority of adverse events were of mild intensity and unrelated to treatment. Adverse events that appeared to occur more frequently in patients treated with aleglitazar than placebo included edema, increased blood creatine phosphokinase (CPK), decreased hemoglobin and decreased WBC count, with most of these events recorded predominantly in patients receiving the highest dose (0.6 mg) of aleglitazar. Serious adverse events were recorded by three patients treated with aleglitazar and one patient receiving pioglitazone, all of which were considered to be unrelated to study treatment. Nine patients treated with aleglitazar were withdrawn prematurely from the study due to an adverse event, five of whom were taking the top dose of 0.6 mg, compared with three placebo patients and two patients taking pioglitazone. A total of 16 aleglitazar patients recorded peripheral edema, mostly at the higher doses of 0.3 and 0.6 mg; the incidence on 0.05 and 0.15 mg was similar to placebo and numerically less than for pioglitazone. Two patients treated with 0.6 mg aleglitazar were withdrawn as a result of peripheral edema. Eight patients were sent to the Clinical Endpoints Committee for adjudication of CHF; two were confirmed as CHF (one patient on 0.3 mg and one on 0.6 mg aleglitazar).

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| **Total No. of Patients** | **Placebo (N=55)** | **0.05 mg Aleglitazar (N=55)** | **0.15 mg Aleglitazar (N=55)** | **0.3 mg Aleglitazar (N=55)** | **0.6 mg Aleglitazar (N=55)** | **45 mg Pioglitazone (N=57)** |
|---|---|---|---|---|---|---|
| Any AE | 25 (45%) | 21 (38%) | 24 (44%) | 23 (42%) | 26 (47%) | 30 (53%) |
| Serious AEs | - | - | 1 | 1 | 1 | 1 |
| AE leading to withdrawal | 3 | 1 | 2 | 1 | 5 | 2 |
| Peripheral edema (incl. edema) AEs | 3 | 1 | 2 | 7 | 6 | 4 |
| ↓Hb / Anemia AEs | 1 | 1 | - | 1 | 6 | - |
| CEC Adjudication of CHF / +ve CHF | 1/- | -/- | 2/- | 1/1 | 3/1 | 1/- |
| Marked ↑ in CPK | 5 | - | 4 | 4 | 11 | 4 |

Dose dependent decreases in hemoglobin were observed following aleglitazar treatment, with levels reaching a plateau after 8 weeks. Anemia or decreases in hemoglobin were recorded as adverse events by eight aleglitazar patients, six of whom received 0.6 mg, compared to one placebo patient. All these events were of mild intensity and none led to the withdrawn of the patient from the study. Dose-dependent effects on renal function were observed following aleglitazar treatment, notably increases in serum creatinine and cystatin C, along with decreases in estimated GFR. These effects reached a plateau after 4 weeks with no increase thereafter. One patient treated with 0.15 mg aleglitazar was withdrawn from the study due to abnormal renal function test results (increases in serum creatinine and cystatin C). One placebo patient was withdrawn according to the protocol stopping rule for increased serum creatinine. Dose-dependent increases in mean blood CPK levels were observed in patients treated with aleglitazar. Marked increases in CPK were recorded by 19 aleglitazar-treated patients (4 each on 0.15 and 0.3 mg, and 11 on 0.6 mg aleglitazar), compared with 5 patients in the placebo group and 4 in the pioglitazone group. Two patients recorded increases of $> 5 \times$ ULN, one treated with 0.3 mg and one with 0.6 mg aleglitazar; both recorded single transient increases which returned to baseline while remaining on study medication. Slight decreases from baseline in systolic (-1.7 to -3.8 mmHg) and diastolic (-3.1 to -7.4 mmHg) blood pressures were observed following treatment with aleglitazar, comparable to changes seen with pioglitazone treatment. Dose-dependent increases in body weight over time were seen following treatment with aleglitazar and pioglitazone.

CONCLUSIONS:

Treatment with aleglitazar for 16 weeks led to dose-dependent reductions in A1C. Compared to placebo, statistically significant ($p < 0.05$) reductions were observed for all doses of aleglitazar. Improvements in other parameters of glycemic control including FPG and insulin resistance were also noted. Beneficial effects on the lipid profile were observed, with statistically significant differences to placebo at all doses for triglycerides, HDL-cholesterol and LDL-cholesterol. Aleglitazar was well tolerated in the study. Drug-related increases in edema, bodyweight, serum creatinine and CPK were noted predominantly at doses of $\geq 0.3$ mg, and are known effects of PPAR$\alpha$ or PPAR$\gamma$ activation. There were no unexpected safety signals. A dose of 0.15 mg appears to be the most appropriate therapeutic dose for further development, with glycemic effects similar to 45 mg pioglitazone, favorable lipids effects and an acceptable safety profile.