SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BM18249)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A multi-center, double-blind, randomized, placebo-controlled, dose-ranging phase II study to investigate efficacy, safety, tolerability and pharmacokinetics of RO4389620 in patients with type 2 diabetes mellitus treated with a stable dose of metformin. Report No. [redacted]. May 2007.		
INVESTIGATORS / CENTERS AND COUNTRIES	38 centers in six countries worldwide: USA (11 centers) Germany (10 centers), Great Britain (6 centers), Spain (4 centers) Canada (4 centers), Australia (3 centers).		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL	December 5, 2005, to November 09, 2006.	CLINICAL PHASE	II
OBJECTIVES	**Primary:** to determine the BID dose(s) of RO4389620 administered in combination with metformin, which were efficacious, safe and tolerable compared with metformin alone (placebo) in patients with type 2 diabetes. **Secondary:** 1. to compare the effects of RO4389620 and placebo (when both were taken in combination with metformin) on additional parameters of glycemic and lipid control; 2. to evaluate the potential pharmacokinetic (PK) and/or pharmacodynamic (PD) interaction between metformin and RO4389620 and its major metabolites in patients on day 1 and after 4, 8 and 12 weeks; 3. to investigate, by a population analysis approach, the PK and the exposure-response relationship of RO4389620 in the target population, including the influence of covariates; and 4. to explore whether a QD regimen could be equivalent to a BID regimen in terms of efficacy and safety.		
STUDY DESIGN	A multi-center, double-blind, randomized, placebo-controlled, dose-ranging study in type 2 diabetic patients treated with a stable metformin dose. Three phases (screening, 12-week treatment and follow-up). Stratification based on severity of disease (HbA1c $< 8.5\%$ or $\geq 8.5\%$).		
NUMBER OF SUBJECTS	210 patients planned (35 patients in each of six treatment arms). 217 patients randomized to treatment (41 to placebo; 34 to 25 mg BID; 38 to 50 mg QD; 32 to 50 mg BID; 39 to 100 mg QD and 33 to 100 mg BID).		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Type 2 diabetes; treated with a stable metformin dose (minimum daily dose ≥ 1.5 g); BMI ≤ 45 kg/m^2, age 30-75 years and: - HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ at screening; - Fasting plasma glucose (FPG) > 126 mg/dL (7.0 mmol/L) and ≤ 240 mg/dL (13.3 mmol/L) at screening.		
TRIAL DRUG / STROKE (BATCH) No.	25 mg RO4389620 capsules: [redacted] + stable dose of metformin (minimal daily dose equal to or greater than 1.5 g; maximum not		

	higher than recommended in the label). 50 mg RO4389620 capsules: [redacted] + stable dose of metformin (minimal daily dose equal to or greater than 1.5 g; maximum not higher than recommended in the label). 100 mg RO4389620 capsules: [redacted] + stable dose of metformin (minimal daily dose equal to or greater than 1.5 g; maximum not higher than recommended in the label).
DOSE / ROUTE / REGIMEN / DURATION	RO4389620 (25 mg BID, 50 mg BID, 100 mg BID, 50 mg QD, 100 mg QD) administered orally twice daily, 30 minutes before breakfast and dinner, for 12 weeks. In all groups, one tablet in the morning and one tablet in the evening were taken in order to keep the blinding (evening doses of 50 mg QD and 100 mg QD arms were placebo).
REFERENCE DRUG / STROKE (BATCH) No.	Placebo: [redacted] + stable dose of metformin (minimal daily dose equal to or greater than 1.5 g; maximum not higher than recommended in the label).
DOSE / ROUTE / REGIMEN / DURATION	Placebo administered orally twice daily, 30 minutes before breakfast and dinner, for 12 weeks.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint:** HbA_{1c} absolute change from baseline compared with placebo at the end of the treatment period. **Secondary endpoints:** - A categorical definition of response rate based on the primary parameter: HbA1c change from baseline. Patients were classified as responders if their post baseline HbA1c was <7.0% at the end of treatment and/or if they experienced a decrease from baseline in HbA1c $\geq$ 0.7%. - A categorical definition of response rate for FPG (defined as percentage of patients with a decrease from baseline in FPG $\geq$ 30 mg/dL [1.66 mmol/L]). FPG was measured at each visit. - Absolute change from baseline to end of treatment in FPG, fasting insulin, pro-insulin, C-peptide, lactate, glucagon, fructosamine, fibrinogen, PAI-1 and adiponectin. - Absolute and percent change from baseline to end of treatment in triglycerides, free fatty acids (FFA), total cholesterol, HDL cholesterol, LDL cholesterol and LDL/HDL ratio (calculated). Total cholesterol, LDL and HDL cholesterol and triglycerides were measured at screening, baseline, weeks 2, 4, 6, 8 and 12/premature withdrawal. Fasting insulin, pro-insulin, glucagon, C-peptide, lactate, FFA and fructosamine were measured at baseline, weeks 4, 8 and 12/premature withdrawal. Fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and adinopectin were measured at baseline and week 12/premature withdrawal.
PHARMACOKINETICS/ PHARMACODYNAMICS:	Plasma concentrations of metformin, RO4389620 and RO4517354 (metabolite M4), population PK, explorative PK/PD and metformin drug-drug interaction analyses are presented and described in separate bioanalytical reports
SAFETY:	Adverse events (AE), incidence of hypoglycemia, vital signs, clinical laboratory tests, physical examination, body weight, waist/hip ratio, electrocardiogram (ECG).

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STATISTICAL METHODS	**Efficacy:** *Primary efficacy endpoint (HbA_{1c} absolute change from baseline compared with placebo at week 12):* an analysis of covariance (ANCOVA) with treatment and region as fixed factors and baseline HbA1c as covariate was performed. Each RO4389620 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: 100 mg BID versus placebo, 50 mg BID versus placebo and 25 mg BID versus placebo. An ANCOVA was used to calculate the least squares mean of the difference from baseline and 95% confidence intervals at each visit where the endpoint was assessed. The placebo-corrected difference from baseline at week 12 was also calculated. *Secondary efficacy endpoints:* as for the primary efficacy endpoint with baseline of the variable of interest as the covariate. **Safety:** All data are presented by individual patient listings and summary tables as appropriate. No statistical testing was performed.

METHODOLOGY:

The screening period was up to a maximum of two weeks. Eligible patients were randomly assigned to receive 25 mg BID, 50 mg BID, 100 mg BID, 50 mg QD or 100 mg QD RO4389620 or placebo administered orally twice daily, 30 minutes before breakfast and dinner, for 12 weeks. Patients were to remain on their stable dose and regimen of metformin throughout the study. Eligible patients were provided with, and trained in the use of, a diary and a home glucose monitoring device (Accu-Chek®), including test strips, for close blood glucose monitoring. Patients were also trained in detection of hypoglycemia and hyperglycemia. Patients brought their glucometers and diaries to each clinic visit. A diet and exercise plan based on local guidelines and the recommendation of the investigator was discussed with each patient.

Patients returned for efficacy and safety assessments every two weeks until week 8, at week 12 and at week 13 or 14 (one to two weeks after the last dose of study medication). PK sampling was performed on all patients at randomization and at weeks 4, 8 and 12. Additional PK sampling was performed on a subset of patients at randomization, and at weeks 4 and 12. PD sampling on various parameters was performed at every visit. Serum samples for biomarker discovery and validation were collected from consenting patients at baseline and weeks 4 and 12. All blood samples were taken with patients in a fasting state before study medication intake.

At the investigator's discretion and after consultation with the Sponsor Medical Monitor, study medication could be titrated down for patients who experienced at least two independent blood glucose values $\leq$ 65 mg/dL (3.6 mmol/L) or plasma glucose values $\leq$ 70 mg/dL (3.9 mmol/L) with RO4389620 as the most likely cause.

Patient's who experienced severe hypoglycemia (requiring third party assistance) with RO4389620 as the most likely cause discontinued study medication and were withdrawn from the study.

Patients with repeated (at least three independent occasions) blood glucose levels $\leq$ 50 mg/dL (2.8 mmol/L) or plasma glucose levels $\leq$ 54 mg/dL (3.0 mmol/L) with or without symptoms and with RO4389620 as the most likely cause, discontinued study medication and were withdrawn from the study.

If a patient's FPG was > 240 mg/dL (13.3 mmol/L) a retest was required within one week. If the retest confirmed the >240 mg/dL measurement, study medication was discontinued and the patient was withdrawn from the study. Retest was not required at screening, week 12 or follow-up.

Patients with ALT > 3x the ULN required retesting within one week. If the ALT was further increased, study medication was stopped at the investigator's discretion. ALT continued to be monitored at weekly intervals until it normalized to pretreatment levels, at which time study medication could be restarted (in all countries except Canada, where patients were withdrawn if ALT remained at 3x the ULN at the retest). If

ALT increased to > 3x the ULN after rechallenge, study medication was discontinued and the patient was withdrawn from the study.

Investigators followed the contraindications of metformin treatment; thus, metformin would be discontinued and the patient withdrawn from the study in the event of renal insufficiency or impairment, any condition that could worsen renal function, acute or chronic diseases leading to hypoxia, or lactic acidosis.

EFFICACY RESULTS:

The intent-to treat (ITT) population consisted of 215 of the 217 randomized patients on a stable dose of metformin; two patients were excluded due to missing post baseline HbA1c assessments. In the ITT population, compared with placebo, reduction in HbA1c was statistically significant in only the 100 mg BID RO4389620 group with a least squares mean difference from placebo of -0.392% ($p<0.0049$). Compared with placebo, there were no meaningful reductions in HbA1c in the 25 mg BID RO4389620 group (-0.068%; $p = 0.6192$), or the 50 mg BID RO4389620 group (-0.104%; $p = 0.4625$). Similar results were obtained for the per protocol (PP) population analyses of the primary parameter. The PP population consisted of 178 patients: exclusions were due to failure to complete study treatment (28 patients), major protocol violations (10 patients), or lack of evaluable HbA1c at week 12 (1 patient).

In subgroup analyses of the primary parameter, there was a statistically significant effect of dose and starting HbA1c value on HbA1c at week 12 (patients on higher study medication doses and with HbA1c values > 8.5 at baseline fared better) but no effect of region. There were no significant region by study medication dose interactions, indicating that the doses behaved the same way across regions, and no significant baseline HbA1c value by study medication dose interactions, which satisfies the assumption of analysis covariance methodology. No clear differences within the sex, age, ethnicity or BMI subgroups could be observed.

Secondary endpoint analyses supported the primary efficacy findings. The proportion of patients with HbA1c below 6.5% at the end of treatment was markedly greater in the 100 mg BID RO4389620 group (30%) than in the 50 mg BID (19%), 25 mg BID (9%) and placebo (7%) groups. Of patients in the 100 mg BID RO4389620 group, 52% had a week 12 HbA1c value <7% and 67% had a statistically significant reduction in HbA1c from baseline of $\geq 0.7\%$. Respective corresponding placebo values were 29% and 32%, 25 mg BID RO4389620 values were 35% and 38%, and 50 mg BID RO4389620 values were 52% and 39%.

Compared to placebo, there were no statistically significant absolute changes from baseline in FPG observed in any of the RO4389620 BID doses. At end of treatment, the number of responders, defined as an FPG change from baseline of $\geq$ 30 mg/dL (1.6653 mmol/L), was increased in a dose-dependent manner. The response rate was 15%, 26% and 53%, respectively, in the 25 mg, 50 mg and 100 mg BID RO4389620 groups, compared with 20% in the placebo group. The difference to placebo was significant in only the 100 mg BID RO4389620 group. Forty-one percent (41%) of patients in the 100 mg BID RO4389620 group had a FPG value < 140 mg/dL at week 12, compared with 30% of patients in the placebo group.

No statistically significant effects of RO4389620 were observed in the lipid profile parameters.

A statistically significant reduction in fructosamine levels was seen in the 100 mg BID RO4389620 group compared with placebo ($p < 0.0230$). No statistically significant effects of RO4389620 were seen in any other parameters of glycemic/metabolic control.

Similar results were seen in the planned exploratory analyses of the QD RO4389620 dose groups.

SAFETY RESULTS:

The safety population consisted of all 217 patients. Overall, the number of AEs were similar across all groups, with 56% of patients in the placebo group experiencing at least one AE compared with 47% to 64% of patients in the RO4389620 dose groups. The most commonly reported AE was hypoglycemia, followed by nasopharyngitis, hyperglycemia, dizziness and headache. The majority of AEs were of mild intensity and considered by the investigator to be unrelated to study treatment. In the RO4389620 dose groups, there was no clear dose relationship for relatedness, although the majority of events considered to be related by the investigator were in the 100 mg QD and 100 mg BID groups.

Nine patients, including three in the placebo group and six in four of the RO4389620 groups (25 mg BID,

50 mg QD, 50 mg BID and 100 mg BID), experienced a severe AE.

Serious AEs were experienced by seven patients, including two in the placebo group (respiratory failure; hernia repair), two in the 25 mg BID group (gastroenteritis; carotid artery stenosis) and one each in the 50 mg QD (ear infection), 50 mg BID (angina pectoris) and 100 mg BID (breast cancer) RO4389620 groups. All serious AEs were considered by the investigator to be unrelated to study treatment.

Seven patients experienced AEs that led to premature withdrawal, including two in the placebo group (respiratory failure; upper respiratory tract infection), one each in the 25 mg BID (transaminases increased) and 100 mg QD (cough) RO4389620 groups, and 3 in the 100 mg BID RO4389620 group (alanine aminotransferase increase; hepatic enzyme increased; liver function test abnormal). Additionally, six patients withdrew due to hyperglycemia (insufficient therapeutic response) reported as AEs.

There were no deaths during the study.

Hypoglycemia was reported by 23 patients, including one patient in the placebo group and 22 patients in all five RO4389620 groups ((25 mg BID, 50 mg QD, 50 mg BID, 100 mg QD and 100 mg BID). All but three patients had events of mild intensity, none had events of severe intensity. The majority of these patient's events were considered by the investigator to be possibly or probably related to study treatment, one was considered remotely related and two patients had events that were considered unrelated. All of these events resolved, most without treatment and some after treatment with carbohydrates.

Of the 23 patients who experienced hypoglycemia during the study, twelve patients experienced symptomatic hypoglycemia (eg, tremors, dizziness, hot flashes), including one patient in the placebo group and 11 patients in four of the RO4389620 groups (25 mg BID, 50 mg BID, 100 mg QD and 100 mg BID).

Two patients' RO4389620 doses were titrated down according to the protocol specifications.

One patient in the 25 mg BID RO4389620 group and three patients in the 100 mg QD RO 4389620 group experienced hypoglycemia on at least three occasions during the course of the study and were not withdrawn (they were excluded from the PP population as major protocol violators).

Nine patients had ALT values > 3x the ULN: one patient each in the 25 mg BID, 50 mg QD and 100 mg QD RO4389620 groups and six patients in the 100 mg BID RO4389620 group. None of these patients had associated symptoms or concurrent bilirubin elevations. Five of these nine patients had single ALT elevations > 3x the ULN. Three of the nine patients, all in the 100 mg BID RO4389620 group, had ALT elevations > 5x the ULN. The elevations began between weeks 4 and 8 in seven patients and at week 2 in two patients. In all nine patients, liver function test values returned to or were returning to baseline levels within 2 to 4 weeks regardless of whether study drug was continued, interrupted or discontinued. Four of the nine patients' ALT elevations were reported as AEs, three of these patients withdrew due to the ALT elevations and one patient withdrew due to hyperglycemia.

Marked AST elevations were observed in seven patients, predominantly in the 100 mg BID RO4389620 group with 6 patients, along with 1 patient in the 50 mg QD RO4389620 group. All elevations returned or were returning to baseline levels.

Marked GGT elevations were observed in seven patients distributed across treatment groups. With the exception of 2 patients whose elevated baseline levels continued to elevate throughout the study, all GGT levels returned or were returning to baseline levels at week 12.

Other marked laboratories abnormalities were detected during the study; however, most were not considered to be clinically significant. Two patients had microscopic hematuria with associated AEs that were considered by the investigator to be unrelated to study medication.

There were no clinically relevant effects seen on vital signs or anthropometric measurements (body weight or waist:hip ratio) in any of the treatment groups, including placebo.

ECGs were recorded at several time points during the study. The mean maximum post baseline change in QTc in the RO4389620 treatment groups did not show a dose-dependent increase (-0.5 to +18.0), although all groups other than the 25 mg BID group were higher than placebo (+1.9). Seven patients had maximum QTcB changes from baseline > 60 ms: one patient in the placebo group, two patients in the 50 mg QD RO4389620 group, three patients in the 100 mg QD RO4389620 group and one patient in the 100 mg BID RO4389620 group. Five patients in the RO4389620 dose groups had maximum post baseline QTcB intervals > 500 ms: two patients in the 50 mg QD group, two patients in the 100 mg group and one patient in the 100 mg BID group.

CONCLUSIONS:

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- In type 2 diabetic patients on a stable dose of metformin, the addition of 100 mg BID RO4389620 for 12 weeks resulted in a statistically significant improvement in HbA1c (the primary parameter).
- The overall efficacy of RO4389620 compared with placebo (metformin monotherapy) at the end of treatment was likely underestimated due to a surprisingly large HbA1c decrease in the placebo group.
- Overall, RO4389620 was well tolerated and hypoglycemia did not seem to be of concern.
- Liver function test elevations were unexpected and seem to be dose-related. Further investigation is necessary to understand the mechanism of action for this finding.