SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BM18248)

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 multicenter, phase, 2 randomized, double-blind, placebo-controlled dose-ranging study to determine the efficacy, safety, tolerability, and pharmacokinetics of RO4389620 in patients with type 2 diabetes mellitus (BM18248). Report No. [redacted] Final Date: October 05, 2007		
INVESTIGATORS / CENTERS AND COUNTRIES	41 centers in 7 countries worldwide: US (18 centers), Mexico (7 enters), Bulgaria (6 centers), Poland (4 centers), Hungary (3 centers), Croatia (2 centers), and Guatemala (1 center)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	30 November 2005 17 January 2007	CLINICAL PHASE	2
OBJECTIVES	**Primary objective:** To determine the BID dose(s) of RO4389620, which, when compared to placebo, are efficacious, safe and tolerable in improving glycemic control in patients with type 2 diabetes. **Secondary objectives**: To investigate the effects of RO4389620 on additional parameters of glycemic and lipid control. To investigate, by a population analysis approach, the pharmacokinetics and the exposure-response relationship of RO4389620 in the target population, including the influence of covariates. To explore the efficacy and safety of 100 mg QD regimen of RO4389620.		
STUDY DESIGN	A multicenter, randomized, double-blind, placebo-controlled, study in type 2 diabetic patients who were treatment-naïve and inadequately controlled despite diet/exercise or who were inadequately controlled on their current oral antihyperglycemic medication (monotherapy or combination of 2 medications). There are 4 periods: screening (up to 2 weeks), single-blind washout/placebo run-in (4 weeks), double-blind treatment (12 weeks), and safety follow-up (2 weeks) or open-label extension. Stratification was based on glycosylated hemoglobin ([HbA1c] where HbA1c < 8.5% or HbA1c ≥ 8.5 %) and pre-study treatment (naïve or pre-treated).		
NUMBER OF SUBJECTS	250 patients planned (50 patients in each of the 5 treatment arms). 267 patients were randomized to treatment (55 to placebo; 61 to 25 mg BID; 51 to 50 mg BID; 45 to 100 mg QD; and 55 to 100 mg BID).		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Type 2 diabetes, male or female patients either treatment-naïve inadequately controlled despite diet/exercise or inadequately controlled with oral antidiabetic agents (up to 2); age 30 to 75 years at the time of the screening examination; HbA1c ≤ 10.0 % at screening and HbA1c ≥ 7.0 % and ≤ 10.0 % at pre-randomization visit; fasting blood glucose (FPG) > 126 mg/dL (7.0 mmol/L) and ≤ 240 mg/dL (13.3 mmol/L) at pre-randomization visit; body mass index (BMI) ≤ 45 kg/m^2 at screening.
TRIAL DRUG / STROKE (BATCH) No.	25 mg RO4389620: [redacted] 50 mg RO4389620: [redacted] 100 mg RO4389620: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	During the single-blind washout/placebo run-in period (prior to the double-blind period), patients received placebo capsules given orally, 30 minutes before meals, twice daily approximately 12 hours apart for 4 weeks. Following the 4-week single-blind washout/placebo run-in period, RO4389620 (25 mg BID, 50 mg BID, 100 mg BID, or 100 mg QD) was administered orally twice daily, 30 minutes before breakfast and dinner, approximately 12 hours apart for 12 weeks. Patients in the 100 mg QD group were given placebo capsules in the evening.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Matching placebo capsules were administered orally twice daily, 30 minutes before breakfast and dinner, approximately 12 hours apart for 12 weeks.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary Endpoint:** HbA1c mean change from baseline at the end of treatment (week 12) compared to placebo. **Secondary Endpoints:** HbA1c response rate (defined as percentage of patients who achieved HbA1c < 7.0% or percentage of patients with HbA1c decrease ≥ 0.7% from baseline at end of treatment). FPG response rate (defined as percentage of patients with a decrease from baseline in FPG ≥ 30 mg/dL (1.66 mmol/L) at the end of treatment period). Mean change in FPG from baseline as compared to placebo. Absolute/relative change in glucose area under the curve (AUC), insulin, pro-insulin, c-peptide, lactate and free fatty acids (FFA) following an oral glucose tolerance test (OGTT) in a subset of patients (approximately 35% of patients) from baseline to the end of treatment. Mean change in fasting insulin, c-peptide, lactate, glucagon,

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	fructosamine, fibrinogen, plasminogen activator inhibitor 1 (PAI-1) from baseline to end of treatment as compared to placebo. Absolute/relative changes in lipid profile: triglycerides, FFA, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and LDL/HDL ratio from baseline as compared to placebo.
PHARMACOKINETICS/ PHARMACODYNAMICS:	Blood samples were collected for the measurement of pharmacokinetic (PK) parameters for RO4386920 and its metabolites (if possible), population PK, and explorative PK/pharmacodynamic (PD) analyses. A summary of OGTT summary values are presented in this report. Additional PK and PD/PK results are presented in a separate Bioanalytical Report.
SAFETY:	Adverse events (AEs), incidence of hypoglycemia, vital signs, body temperature, physical examination, clinical laboratory tests, body weight, waist to hip ratio, and electrocardiogram (ECG).
STATISTICAL METHODS	**Sample Size:** The planned sample size for this study was 250 patients (50 patients per treatment arm). For the primary analysis, a minimum of 45 patients per arm was required to detect, at the nominal significance level of = 0.025 (one-sided) with power of 0.80, a difference in HbA1c at least -0.9% (ie, RO4389620 minus placebo), assuming a common standard deviation of change from baseline of 1.5. In addition, 5 patients (10%) were added per group to account for dropouts. **Efficacy:** All parameters were analyzed descriptively. Summary tables with mean, standard deviation, median, minimum and maximum for continuous variables and frequency tables for rates are provided. The primary efficacy endpoint (the change from baseline in HbA1c at the end of treatment [week 12]) was evaluated using an analysis of covariance (ANCOVA), with treatment and region as fixed factors and baseline HbA1c as covariate in the model. Each RO4389620 BID dose regimen (25 mg BID, 50 mg BID, and 100 mg BID) was compared against placebo and the null hypothesis was used to test whether the mean difference exceeded 0%. The sequence of testing was as follows: 100 mg BID versus placebo, 50 mg BID versus placebo, and 25 mg BID versus placebo. The primary analysis was the pairwise comparison of all the RO4389620 BID doses against placebo. For all treatment arms, an ANCOVA was used to calculate the least squares mean (LSM) of the difference from baseline and 95% confidence intervals at each visit where the endpoint was assessed. The placebo-corrected difference from baseline and corresponding 95% confidence intervals were calculated at week 12. The same statistical analysis used for the primary endpoint was

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applied to the secondary efficacy endpoints. The response rates for HbA1c and related 95% confidence intervals for the pairwise comparisons to placebo were calculated by treatment group.
All statistical analysis were conducted in the full analysis set (intent-to-treat [ITT]), which included all randomized patients with at least 1 intake of active study medication, 1 baseline and 1 post randomization assessment of HbA1c. Missing observations were replaced by carrying forward the last observation. The analysis of the secondary study parameters and the pre defined subsets were considered exploratory.
Safety/Tolerability: All randomized patients who had at least 1 dose of study medication were included in the safety analysis. Adverse events (AEs) are listed per individual and summarized using the MedDRA dictionary. Hypoglycemic events are presented separately. Tolerability and safety results are presented by individual listings, summary tables and graphs, as appropriate. Clinical laboratory tests and vital signs are presented as individual listings and as mean changes from baseline (including frequency tables of marked abnormalities for clinical laboratory tests). No statistical testing was performed on the safety parameters.

METHODOLOGY:

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled, 5-arm, parallel group study of RO4389620 in patients with type 2 diabetes.
The study consisted of 4 periods: a screening period that was as short as possible and up to a maximum of 2 weeks (up to 14 days), a 4-week, single-blind washout/placebo run-in period (between 28 and 35 days, inclusive), a 12-week, double-blind treatment period (days 1 to 84), and a follow-up period (days 85 to 98).
Patients who met all of the screening inclusion/exclusion criteria were eligible for the 4-week, single-blind washout/placebo run-in period at visit 2. Those patients who were treated with an oral antidiabetic medication were instructed to discontinue their medication before starting the single-blind washout/placebo run-in. Eligible patients were provided with, and trained in the use of, a diary and a home glucose monitoring device (Accu-Chek®) and instructed to assess their blood glucose profile at least 3 days a week (before study medication intake and breakfast, before lunch, before dinner, and before going to sleep) or more frequently, if necessary, throughout the study. Patients were also trained in the detection of hypoglycemia and hyperglycemia. Study medication was not to be taken at home on the mornings before their scheduled clinic visits. Patients returned to the clinic for 2 control visits (V3 and V4), which were 2 weeks apart.
Following completion of the 4-week, single-blind washout/placebo run-in period, a pre-randomization visit (V4, ideally day -5 to -2 prior to randomization) was conducted to assess patient eligibility based on the final inclusion/exclusion criteria, which required patients to have an HbA1c $\geq$ 7.0 % and $\leq$ 10.0 % and an FPG >°126 mg/dL (7.0°mmol/L) and $\leq$ 240°mg/dL (13.3°mmol/L).
On day 1, eligible patients were randomized to receive one of the following treatments: 25 mg BID, 50 mg BID, 100 mg BID, or 100 mg QD of RO4389620 or matching placebo for 12 weeks. Capsules were given orally, 30 minutes before breakfast and dinner (approximately 12 hours apart), twice daily for 12 weeks.

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Patients in the 100 mg QD group were given placebo capsules in the evening.
Safety and efficacy assessments were performed at weeks 2, 4, 6, 8, and 12. PK sampling was performed on all patients at baseline and at weeks 4, 8, and 12. Additional PK sampling was performed on a subset of patients at baseline 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 at weeks 4 and 12. All blood samples were taken with patients in a fasting state before study medication intake. In approximately 35% of patients, an OGTT was performed at randomization (day 1) and at week 12.
Patients who experienced severe hypoglycemia (requiring third party assistance) or who had repeated (at least 3 independent occasions) blood glucose values ≤ 50 mg/dL (2.8°mmol/L) or plasma glucose values ≤ 54 mg/dL (3.0 mmol/L) with RO4389620 as the most likely cause were instructed to discontinue study medication and to withdrawal from the study.
If a patient's FPG was > 240 mg/dL (13.3 mmol/L), a retest was required within 1 week. If the retest confirmed the > 240 mg/dL measurement, study medication was discontinued and the patient was withdrawn from the study. Retests were not required at the screening, pre-randomization, week 12, or follow-up visits.
Patients with ALT > 3x upper limit of normal (ULN) required a retest within 1 week. If the ALT was further increased, study medication was stopped at the investigator's discretion. ALT levels were monitored at weekly intervals, until the value normalized to pre-treatment levels. If study medication was stopped due to the ALT levels, it could be re-started upon this normalization to pre-treatment levels. If ALT increased to > 3x ULN after rechallenge, study medication was discontinued and the patient was withdrawn from the study.
After completion of the 12-week treatment period, or after premature withdrawal, patients were required to return for a safety follow-up visit within 2 weeks (5 to 14 days) of the last study medication intake. A long-term, open-label extension study (NC19794), which was administered under a separate protocol, was offered to eligible patients who completed the study at the week 12 visit. Patients participating in the long-term extension study were not scheduled for a safety follow-up visit under the BM18248 protocol; instead, these subjects had their initial open-label assessment at this time. Those patients who did not participate in the extension study were treated with the standard of care at the investigator's discretion.

EFFICACY RESULTS:

The ITT population consisted of 263 of the 267 randomized patients; 4 patients were excluded from the ITT population due to missing valid post baseline HbA1c assessments. The PP population consisted of 201 patients: exclusions were due to failure to complete study treatment (58 patients) or major protocol violations (8 patients).
When the RO4389620 BID doses were compared with placebo using ANCOVA for HbA1c change from baseline, all 3 doses had a statistically significant effect with the LSM difference from placebo (100 mg BID was -0.732%, $p < 0.01$; 50 mg BID was -0.510%, $p < 0.01$; 25 mg BID was -0.511%, $p < 0.01$) in the ITT population. Mean baseline HbA1c values were 7.84% for the placebo group, 7.85% for the 25 mg BID group, 7.78% for the 50 mg BID group, 7.88% for the 100 mg QD group, and 7.92% for the 100 mg BID group. Similar reductions were observed when ANCOVA was performed for the placebo and BID RO4389620 dose groups in the ITT population and PP populations.
In the subgroup analyses of the primary parameter, there was a statistically significant effect of dose by baseline HbA1c values and diabetic status on HbA1c at week 12, indicating that patients on higher study medication doses, with baseline HbA1c ≥ 8.5, and who were treatment-naive experienced the greatest

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reduction in HbA1c values at the end of treatment, but no effect of region was observed. No higher order interactions with treatments were observed, indicating that the simple effects were not confounded by dose. No clear differences within the gender, ethnicity, age, and BMI subgroups were observed.
Categorical assessments of HbA1c and FPG were consistent with the primary efficacy findings. The proportion of patients with HbA1c below 6.5% at the end of treatment was greater in 100 mg BID group (15%) than in the 100 mg QD (4%), 50 mg BID (8%), 25 mg BID (3%), and the placebo groups (2%). Patients were classified as responders based on HbA1c change if their post baseline HbA1c was < 7.0% at the end of treatment and/or if they experienced a decrease from baseline in HbA1c ≥ 0.7%. At the end of treatment, 33% of patients in the 100 mg BID group were considered responders based on HbA1c values. Responder rates were 26% for the 50 mg BID group, 21% for the 25 mg BID group, and 7% for the placebo group. The HbA1c response rate based on the 4 criteria (patients with HbA1c < 7.0%, HbA1c reduction ≥ 0.7%, either or both) appeared to increase in a dose-dependent manner for each of the 4 criteria.
Compared with placebo, there were no statistically significant absolute changes in FPG observed for any of the BID doses groups in the ITT or PP population. The number of FPG responders, defined as an FPG change from baseline of ≥ 30 mg/dL (1.66 mmol/L), were 25%, 23%, and 37% in the 25 mg BID group, the 50 mg BID group, and the 100 mg BID group, respectively, compared with placebo at 11% for the ITT population.
Results of the additional secondary parameters, which included fasting insulin, c-peptide, lactate, glucagon, fructosamine, fibrinogen, PAI-1, adiponectin, lipid parameters which included triglycerides, FFA, total cholesterol, HDL cholesterol, LDL cholesterol, LDL/HDL ratio (calculated), and results of the exploratory secondary analyses between BID and QD regimens of same daily dose are not discussed in this report.

SAFETY RESULTS:

A total of 267 patients received at least 1 dose of study medication (RO4389620 BID or QD dosing, or placebo), and are included in the safety evaluations presented in this section. Between 76% to 85% of patients in the RO4389620 dose groups (BID and QD) and 73% of the patients in the placebo group received study medication for 71 to 99 days. The distribution of patients taking study medication for different durations was similar across all treatment groups.
Overall, the number of AEs was similar across the treatment groups, with the exception of the 100 mg BID group. A total of 31% of patients in the placebo group reported at least 1 AE compared with 30% in the 25 mg BID group, 29% in the 50 mg BID group, 31% in the 100 mg QD group, followed by 45% in the 100 mg BID group. Across all 5 treatment groups, diarrhea and hypoglycemia or hyperglycemia were reported by at least 2 patients, with the exception of the 50 mg BID dose group. Although the proportion of AEs and certain types of AEs occurred more frequently in the 100 mg BID dose group, no clear dose relationship was established.
Most AEs were considered mild in intensity (22% for 25 mg BID and placebo; 14% for 50 mg BID; 12% for 100 mg QD; 30% for 100 mg BID). AEs of severe intensity were experienced by 6 patients: 2 in the 100 mg QD group and 4 in the 100 mg BID group. No AEs of severe intensity were reported in the 25 mg BID, 50 mg BID, or placebo groups.
There were no deaths during the study.
There was 1 SAE in this study. Patient [redacted] in the 100 mg QD group experienced an event that was documented as ‘drug-induced hepatitis’ and was judged related to study medication by the investigator. Upon review, Roche determined that the event (coded to hepatitis) was medically significant and upgraded it from an AE to an SAE. The case was further reported to health authorities as a suspected unexpected

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serious adverse reaction (SUSAR).
AEs that led to premature withdrawal were reported in 5 patients: 2 in the 100 mg QD group (including patient [redacted] with the SAE/SUSAR of hepatitis), 2 in the 100 mg BID group, and 1 in the 25 mg BID group.
Hypoglycemia was reported as an AE in 8 patients across the active treatments (2 patients [3%] in the 25 mg BID, 1 patient [2%] in the 50 mg BID group, 2 patients [4%] in 100 mg QD group, and 3 patients [5%] in the 100 mg BID group). No patients in the placebo group reported hypoglycemia.
Only 1 patient [redacted] had an FPG < 50 mg/dL during the study.
Most hypoglycemic AEs (both symptomatic and asymptomatic, see below) were mild in intensity; 1 patient [redacted] in the 100 mg QD group reported symptomatic hypoglycemia of severe intensity with an FPG of 37 mg/dL on day 85 and 1 patient [redacted] in the 100 mg BID group reported symptomatic hypoglycemia of moderate intensity with an FPG of 61 mg/dL on day 52. Patient [redacted] was administered fruit juice, and the symptoms of hypoglycemia improved. The investigator determined that the event may have been due to a combination of medication (oral glucosa and study medication) and a reactive hypoglycemia. Patient [redacted] did not receive treatment for hypoglycemia. Both events resolved without sequelae the same day as onset.
The majority of AEs were considered unrelated to study treatment. In the RO4389620 dose groups, the majority of possibly or probably related events were observed in the 100 mg QD and 100 mg BID groups. The majority of the related AEs were associated with blood glucose levels, either hypoglycemia or hypergylcemia.
ALT elevations occurred in 11 patients (9 patients > 3x ULN and 2 patients >5 x ULN) These elevations began after 4 weeks of treatment in the majority of patients and returned to baseline or were returning to baseline levels with 2 to 4 weeks, regardless of whether study drug was continued, interrupted, or discontinued. The etiology of the elevated liver function test is not currently understood.
Other than the marked changes in the liver function tests, there were no clinically relevant findings in the laboratory tests (including hematology and chemistry).
There were no clinically relevant changes or trends observed in the mean or median change from baseline in diastolic blood pressure, systolic blood pressure, body temperature, or pulse rate for any of the RO4389620 dose groups or the placebo group.
The mean maximum post baseline QTcB intervals in the placebo group was 426.2, and in the RO4389620 dose groups ranged from 430.1 ms in the 25 mg BID group to 433.0 ms in the 100 mg BID group.
Although mean values remained within normal limits (≤ 450 ms), minimal increases in the mean maximum value were seen with increasing doses of RO4389620. One patient (2%) in the 100 mg BID group had a QTcB value > 500 ms. Thirteen patients had maximum QTcB changes from baseline > 60 ms: 3 patients (6%) in the placebo group, 2 patients (3%) in the 25 mg BID group, 3 patients (6%) in the 50 mg BID group, and 5 patients (9%) in the 100 mg BID group. No patients in the 100 mg QD group experienced a QTcB change from baseline > 60 ms.
No safety signals were observed for glucose levels, body weight, WHR, or physical examinations.

CONCLUSIONS:

The primary endpoint (change from baseline in HbA1c at week 12) was achieved. RO4389620 was effective in lowering HbA1c in patients with type 2 diabetes. The change from baseline in HbA1c values was statistically significant across all 3 RO4389620 treatment groups (25 mg BID, 50 mg BID, and 100 mg BID; $p < 0.01$) when compared with placebo.
Overall, RO4389620 was well tolerated and hypoglycemia did not seem to be a safety concern.

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The slight numerical imbalance of patients experiencing QTcB intervals > 500 ms and QTcB changes from baseline > 60 ms who were taking RO4389620 compared with placebo is not currently understood and warrants further investigation in a thorough QT study.
No clinically relevant safety signals were noted, with the exception of the elevated liver function tests, which were unexpected and appeared to be dose-related. The etiology of the elevated liver function test is not currently understood.