SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL NC19794)

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, open label, extension study to evaluate the long-term safety and tolerability of RO4389620 in type 2 diabetic patients from studies BM18248 or BM18249 /Report No [redacted] / May, 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	51 investigators in 10 countries (Australia, Bulgaria, Canada, Croatia, Germany, Guatemala, Hungary, Mexico, Poland, United States)		
PUBLICATION (REFERENCE)	Not applicable		
PERIOD OF TRIAL	28-Feb-06 to 03-Jul-07	CLINICAL PHASE	2
OBJECTIVES	**Primary:** To evaluate the long-term safety and tolerability profile of RO4389620 at a dose ranging from 25 mg BID to 100 mg BID, administered alone or in combination with metformin, during 52-week treatment in patients with type 2 diabetes mellitus by monitoring adverse events, hypoglycemic events, physical examination, and selected laboratory variables. **Secondary:** The effect of RO4389620 on long-term glycemic control when administered as either a monotherapy regimen or in combination with metformin will be analyzed descriptively at the end of the study.		
STUDY DESIGN	This was a multicenter, open-label, extension study of RO4389620 administered orally using a dose titration approach for 52 weeks in type 2 diabetic patients who completed the phase 2 studies, BM18248 or BM18249, or who discontinued their participation in either study because of hypoglycemia. RO4389620 was administered alone or in combination with metformin. The study consisted of a 6-week dose titration phase, a 46-week maintenance phase, and a 2-week follow-up phase. The study was prematurely terminated because the development of RO4389620 was stopped.		
NUMBER OF SUBJECTS	370 patients planned		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with type 2 diabetes (defined using WHO criteria) who completed the phase 2 studies, BM18248 or BM18249 or who discontinued their participation in either study because of hypoglycemia		
TRIAL DRUG / STROKE (BATCH) No.	RO4389620 / [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	25 mg, 50 mg, or 100 mg / orally / twice daily / 52 weeks		

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REFERENCE DRUG / STROKE (BATCH) No.	Not applicable
CRITERIA FOR EVALUATION	
EFFICACY:	Diabetic control was assessed by examining the following: 1. Mean changes from parent study baseline in HbA1c and fasting plasma glucose 2. Categorical assessment of HbA1c response rate 3. Mean changes from parent study baseline in lipids
SAFETY:	Safety assessments included adverse events, the incidence of hypoglycemia, vital signs, body weight, anthropometic measurements (body mass index, waist to hip ratio), clinical laboratory tests, and electrocardiograms (ECGs). Hypoglycemia was defined as follows: • Severe – plasma/blood glucose value of ≤ 40 mg/dL (2.2 mmol/L). • Symptomatic – plasma glucose value of ≤ 60 mg/dL (3.3 mmol/L) or blood glucose value of ≤ 58 mg/dL (3.2 mmol/L) with palpitation, tremor, hunger, sweating increased anxiety, dizziness, difficulty thinking, and/or frank confusion. • Asymptomatic – plasma glucose of ≤ 60 mg/dL (3.3 mmol/L) or blood glucose of of ≤ 58 mg/dL (3.2 mmol/L) without any symptoms.
STATISTICAL METHODS	All patients who received study drug and had one valid post-baseline assessment of fasting plasma glucose were included in the efficacy analysis. All patients who received study drug were included in the safety analysis. Results for efficacy and safety parameters are presented descriptively.

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METHODOLOGY:

The screening period was ≤ 7 days with the end-of-treatment or premature withdrawal visit in the parent study serving as the screening visit. During the screening period, patients from study BM18248 were instructed not to take any diabetic medication, while patients from study BM18249 were continued on metformin.

During the dose-titration phase, RO4389620 was started at a dose of 25 mg twice daily (bid) and titrated stepwise every 2 weeks (50 mg bid, 100 mg bid) until either the target glycemic goal (mean fasting plasma glucose of ≥ 70 mg/dL and < 100 mg/dL or fasting blood glucose of ≥ 67 mg/dL and < 95 mg/dL), the maximum tolerated dose, or the highest dose of 100 mg bid was reached. Patients were titrated to a higher RO4389620 dose if:

- Mean fasting plasma glucose was ≥ 100 mg/dL [5.6 mmol/L] based on plasma calibrated glucose meter readings; or mean fasting blood glucose was ≥ 95 mg/dL [5.3 mmol/L] based on whole blood calibrated glucose meter readings during the week immediately prior to the clinic visit; and
- There was an absence of hypoglycemic events directly caused by the study drug.

Once the target glycemic goal, maximum tolerated dose, or highest dose of 100 mg was reached, the patient was maintained at that dose throughout the maintenance phase of the study. The dose of RO4389620 was allowed to be adjusted during the maintenance phase if clinically indicated. Patients returned to the investigational center at biweekly intervals during the maintenance phase. Patients were withdrawn from the study if, at any visit, ALT was > 3x the upper limit of normal (ULN). Patients in the 25 mg group who experienced severe hypoglycemia (requiring third party assistance with a documented plasma/blood glucose of ≤ 40 mg/dL [2.2 mmol/L]) with RO4389620 as the most likely cause were also withdrawn from the study as were patients with repeated plasma glucose of ≤ 60 mg/dL (3.3 mmol/L) or whole blood glucose of ≤ 58 mg/dL (3.2 mmol/L). All patients had a follow-up visit 7 to 14 days after the last dose of study medication.

STUDY POPULATION:

Disposition of patients / Analysis populations: A total of 259 patients entered the study (page 12). One patient was excluded from the safety and efficacy analyses because the patient did not receive any study medication (page 13). An additional 3 patients were excluded from the efficacy analysis because they did not have any post-baseline fasting plasma glucose results. Overall, 216 patients (84%) were prematurely withdrawn from the study (page 14). The majority of withdrawals were because the study was terminated prematurely (117 patients; 45%) or because of insufficient therapy (54 patients; 21%) (page 15).

Demographics and Baseline Disease Characteristics: Overall, 54% of the patients were male and 46% were female (page 34). Most patients were White (81%). Mean duration of diabetes was 6.4 years (page 36). Mean baseline HbA1c was 7.5% and mean fasting plasma glucose was 9.26 mmol/L (166.8 mg/dL) (page 36).

Previous and Concurrent Diseases: Twelve patients (5%) reported at least one previous disease other than type 2 diabetes (page 37). The most common previous diseases were osteoarthritis (2 patients; <1%)

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and anemia (2 patients; <1%). Twenty-three patients (9%) reported at least one active concurrent disease (page 39). Hypertension (3 patients; 1%) was the most frequent concurrent disease. Active diabetic complications and/or cardiovascular risk factors were reported by 6 patients (2%) (page 43). The most frequent risk factors were hypertension (4 patients; 2%) and lipid disorder (4 patients; 2%).

Previous and Concomitant Medications: Ten patients (4%) received a previous treatment that wasn't an anti-diabetic (page 44). All of the previous treatments were received by 1 patient each. Overall, 81% of patients (210 patients) received a concomitant treatment (page 46). The most commonly used concomitant treatments were were angiotensin-converting enzymes (73 patients; 28%), statins (59 patients; 23%), salicyclates (57 patients; 22%), and β-adrenoreceptor blocking agents (53 patients; 21%). Four patients (2%) received anti-diabetic medications other than RO4389620 or metformin during the study; these patients were protocol violators (page 70). Eleven patients (4%) received anti-diabetic medications after the active treatment period (page 71). The most frequently used anti-diabetic medication after the active treatment period was glibenclamide (4 patients; 2%).

EFFICACY RESULTS:

HbA1c, fasting plasma glucose, and lipids were maintained at baseline levels throughout the study (page 72 , page 73 , page 74 , page 75 , and page 77). The percentage of patients with HbA1c below 6.5% at the end of treatment was 10% (14 patients) and the percentage of patients with HbA1c of ≥ 6.5% and < 7% was 16% (25 patients) (page 82). It must be noted that the interpretation of efficacy data is difficult due to the premature termination of the study.

SAFETY RESULTS:

Extent of Exposure to Trial Treatment: Overall, 258 patients received at least one dose of RO4389620 with 22% of patients (56 patients) received RO4389620 for at least 338 days (page 83).

Adverse Events: Overall, 51% of patients (132 patients) reported at least one adverse event during the study (page 84). The most common adverse event was nasopharyngitis (23 patients; 9%). Most adverse events were mild or moderate in intensity. Eight patients had at least one severe adverse event. Severe adverse events reported included intervetebral disc protrusion, increased transaminases, cholelithiasis, dizziness, asthenia, abdominal pain, urinary calculus, diarrhea, headache, and myocardial infarction. Myocardial infarction was the only severe adverse event reported by more than 1 patient (2 patients) (page 94).

Deaths, Serious Adverse Events, and Adverse Events leading to Withdrawal: There were no deaths during the study. Twelve patients (5%) had at least one serious adverse event (page 122). Myocardial infarction (2 patients) was the only serious adverse event reported by more than 1 patient. All serious adverse events were judged by the investigator as unrelated to study medication (page 124). Six patients (2.3%) experienced adverse events that led to premature withdrawal (page 126). The most common AE resulting in premature withdrawal was elevated liver enzymes (4 patients; 2%). Narratives for patients with serious adverse events or adverse events that led to withdrawal are provided on page 128 .

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Hypoglycemia: Hypoglycemia was reported in 11 patients (4%) (page 133). Eight patients (3%) had symptomatic hypoglycemic events (page 134) and 3 patients (1%) had asymptomatic hypoglycemic events (page 135).

Laboratory Safety Tests: ALT elevations occurred in 12 patients (4.6%) (12 patients > 3x ULN with 3 patients > 5X ULN) (page 136 and page 140). In all cases, ALT was returning to baseline levels regardless of whether study drug was discontinued or continued (protocol violation in 1 patient). Other than the marked changes in liver function tests, there were no clinically relevant findings in laboratory tests (page 141 , page 143 , page 149).

Vital Signs, Body Weight, Anthropometric Measurements, and ECGs: There were no clinically relevant changes in vital signs, body weight, or anthropometric measurements (page 155 , page 159 , and page 160). Eleven patients (5%) had maximum QTcB changes from baseline > 60 msec (page 163). Four patients (2%) had maximum post baseline QTcB intervals > 500 msec (page 164).

CONCLUSIONS:

Clinically relevant safety signals seen with long-term administration of RO4389620, either alone or in combination with metformin, included elevated liver function tests and QTcB changes from baseline.