SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BC19800D)

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 phase 2, multicenter, open label titration study to assess the efficacy, safety and tolerability of RO4389620 in doses up to 200 mg BID in patients with type 2 diabetes mellitus not optimally controlled with previous treatment with one oral antihyperglycemic agent.		
INVESTIGATORS / CENTERS AND COUNTRIES	20 centers in four countries worldwide: Latvia (3 centers, 19 patients), Estonia (3 centers, 6 patients), United States (10 centers, 40 patients), and Mexico (4 centers, 62 patients).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	July 25, 2006 to May 15, 2007	CLINICAL PHASE	II
OBJECTIVES	**Primary**: To determine the treatment response in patients with type 2 diabetes mellitus treated with RO4389620 administered at increasing doses up to 200 mg twice daily (BID) **Secondary**: 1) To assess efficacy of RO4389620 administered at increasing doses up to 200 mg BID; 2) To evaluate the safety and tolerability of RO4389620 administered at increasing doses up to 200 mg BID; 3) To evaluate in an exploratory manner possible trends in demographic and biologic parameters and safety and tolerability in patients requiring doses of RO4389620 up to 200 mg BID		
STUDY DESIGN	An open label, multi-center, titration study with RO4389620 titrated to target fasting plasma glucose (FPG) < 100 mg/dL (fasting blood glucose [FBG] < 90 mg/dL) using a bi-weekly titration algorithm. Up titration, down titration or cessation of titration, was based on the target glycemic goal, and safety and tolerability including occurrence of hypoglycemia or increased risk of repeated hypoglycemia. Patients were maintained on the maximum tolerated dose of RO4389620 until the end of the treatment period.		
NUMBER OF SUBJECTS	A total of 127 patients treated, with 113 patients achieving 200 mg BID, and 5, 4, 2, and 3 patients achieving 150 mg BID, 100 mg BID, 50 mg BID, and 25 mg BID, respectively.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients 18 to 75 years old with type 2 diabetes mellitus, not optimally controlled by a current therapy with one oral antihyperglycemic agent, treated according to manufacturer's instructions, for at least three months prior to screening.		
TRIAL DRUG / STROKE (BATCH) No.	RO4389620 soft gelatin capsules: 25 mg: [redacted] 50 mg: [redacted] 100 mg: [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	RO4389620 was administered orally, twice daily, before breakfast and before dinner, at increasing doses of 25 mg BID, 50 mg BID, 100 mg BID, 150 mg BID, 200 mg BID over a 20 week period.		

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REFERENCE DRUG / STROKE (BATCH) No.	Not applicable
DOSE / ROUTE / REGIMEN / DURATION	Not applicable
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint**: the percentage of patients at each dose who achieved FPG < 100 mg/dL and did not experience episodes of severe hypoglycemia for the duration of the study **Secondary endpoint**s: • change from baseline HbA1c and FPG • change from baseline lipid profiles of triglycerides, FFA, total cholesterol, HDL cholesterol and LDL/HDL ratio • change from baseline in overall diabetic state: C-peptide, glucagons and fructosamine
PHARMACOKINETICS/ PHARMACODYNAMICS:	Pre- and post-dose blood samples were collected for measurement of RO4389620 and its metabolites at defined time points.
SAFETY:	Adverse events, clinical laboratory tests, physical examinations, vital signs, electrocardiograms, and incidence of hypoglycemia Information on premature withdrawals, concurrent diseases, and medications taken, other than the study drug, was collected to assess safety.
STATISTICAL METHODS:	The response rate for the primary study variable was listed and summarized by highest achieved dose. The 95% confidence intervals were calculated on the responder rates using Pearson-Clopper methodology.

METHODOLOGY:

Screening: Patients who met all inclusion criteria at screening proceeded to the 14-day washout period. Patients were provided with, and trained in the use of, a diary and a home blood glucose self-monitoring device (BGSM) and were asked to check their glucose levels at least 3 times daily, 3 days a week, or more frequently if requested by local guidelines or deemed appropriate by the Investigator. This included the day immediately prior to the pre-baseline visit. A diet and exercise plan was discussed based on local guidelines and the recommendation of the Investigator.

Up Titration: On Day 1 all patients started treatment with RO4389620 at a dose of 25 mg taken twice daily. If, after 2 weeks of treatment with a current dose of RO4389620, a higher dose was required to achieve the glycemic control goal, or the maximal tolerated dose, up titration was performed in the following order: 50 mg BID, 100 mg BID, 150 mg BID, to a maximum dose of 200 mg BID. The up titration was performed only at scheduled clinic visits, which occurred at 2-week intervals. RO4389620 was up titrated to the next dose level if at the scheduled clinic visit on Weeks 2 to 10, patients demonstrated FPG ≥ 100 mg/dL (5.6 mmol/L) or FBG ≥ 90 mg/dL (5.0 mmol/L), AND absence of severe hypoglycemia due to study medication during the last two weeks of treatment, AND absence of repeated hypoglycemia, measured on three independent occasions, due to the study medication during the prior two weeks of treatment, AND no other safety and tolerability issues, including an increased risk of repeated hypoglycemia, determined by the Investigator.

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Down Titration: In the event of severe or repeated hypoglycemia, on at least three independent occasions, or if the Investigator determined that the administered dose of RO4389620 could not be tolerated, down titration was permitted in the reverse order to the up titration. Down titration could be performed at any time during the treatment period, if required, to the minimum dose of 25 mg BID. If, after two consecutive down titrations, a patient required a third down titration due to severe hypoglycemia, the drug was discontinued and the patient was withdrawn from the study.

Study Medication on Clinic Visit Days: Patients were instructed not to take any study medication at home on the mornings of their scheduled clinic visits. All study medication was brought to the clinic at each visit, entrusted to the investigational site staff, and taken per their instructions. On all study assessment days, study medication was dispensed to the patient from his/her own supplies after blood samples were drawn.

Assessments and Procedures at Follow-Up: Patients assessed their glucose levels 3 times daily, at least 3 days a week or more frequently if required by local guidelines and/or deemed appropriate by the Investigator. After the follow up visit, initiation of any anti-diabetic treatment was left to the discretion of the Investigator and, thereafter, patients were treated according to individual center practice.

Procedures in Case of Hypoglycemia: Patients were instructed to contact the Investigator if they recorded blood glucose level ≤ 50 mg/dL (2.8 mmol/L) or if they experienced symptoms of hypoglycemia including, but not limited to, trembling, hot flashes, dizziness, increased anxiety, lightheadedness, excessive hunger, palpitations, and blurred vision. Patients were instructed not to take the next scheduled dose of the study drug prior to consulting the Investigator. They were advised not to skip meals and to carry hard candies and sugar packets during the study conduct and were instructed never to drive a car or operate a machine when blood glucose was low.

Procedures in Case of Hyperglycemia: Patients were advised to contact the Investigator in case of protocol defined hyperglycemia. The Investigator was to be contacted if, on two confirmed occasions, the results of fasting plasma glucose measured before breakfast met the criteria, and/or if they experienced symptoms of hyperglycemia including excessive thirst, frequent urination, dehydration, nausea, vomiting, heavy breathing, confusion, and breath odor resembling the smell of fruits.

PK Study Procedures: A maximum of seven pre-dose blood samples were collected for measurement of RO4389620 and its metabolites, one taken at Week 2 (Visit 5), and additional samples taken at other visits only if patients received doses of RO4389620 ≥ 100 mg per day. A maximum of seven post-dose blood samples were collected for measurement of RO4389620 and its metabolites at 90 ± 15 minutes after the morning dose of study medication, immediately after post-dose ECG measurements. One post-dose sample was taken at Week 2 (Visit 5), and additional samples were taken at other visits only if patients achieved doses of RO4389620 ≥ 100 mg/day.

On the day before the visit that included pharmacokinetic (PK) assessments, the time of morning and evening study medication intake was recorded by the patient in the diary and subsequently in the electronic case report form (eCRF). Actual PK sampling times were documented in the eCRF. If PK samples were missed or taken in error, reasons for these discrepancies were provided in the eCRF.

Samples for biomarker discovery and validation were collected from consenting patients. An additional 4.9 mL blood sample collected in EDTA was obtained from patients for plasma isolation. These samples were used to measure adiponectin and to validate protein assays. All samples for biomarkers research were taken in a fasting state prior to drug intake.

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EFFICACY RESULTS:

This study was primarily evaluated as a safety study and only limited efficacy results are discussed in this report. The ITT population was used for all efficacy analyses. All planned analyses were performed.

SAFETY RESULTS:

The safety population consisted of 127 patients. All but 14 patients in this study achieved a dose of 200 mg BID. One of the four patients in the 100 mg BID group, and one of the five patients in the 150 mg BID group, completed 138 days of treatment.

Fifty-one of 113 patients in the 200 mg BID group completed more than 138 days of treatment. Each of the 62 patients withdrawn from this group completed at least 54 days of treatment.

At the end of the study a total of 74 of the 127 patients had been withdrawn from all dose groups. All three of the patients in the 25 mg BID group, and both of the patients in the 50 mg BID group had withdrawn prior to end of treatment after receiving 26 days treatment or less. One of the four patients in the 100 mg BID group, and one of the five patients in the 150 mg BID group, completed 138 days of treatment.

Adverse events reported by patients in all dose groups (n = 127) are summarized as follows:

Patients with	No. of Patients	% of Patients	No. of Events
Any AE	90	71	241
Severe AEs	11	9	13
Related AEs (Possible and Probable)	53	42	73
Serious AEs	4	3	6
Deaths	1	<1	1
Hypoglycemia	5	4	5
AEs Leading to Withdrawal	18	14	21

Of the 241 adverse events reported by 90 patients receiving RO4389620, 127 were considered mild, 100 were deemed moderate, and 13 were judged to be severe. The most common adverse events reported were metabolism and nutrition disorders (41 events), experienced by 40 patients (31%), the most common of which was hyperglycemia, reported by 32 patients (25%).

Infections and infestations were reported in 38 patients (30%) and gastrointestinal disorders were experienced by 24 patients (19%). One death, due to myocardial infarction, considered unrelated to the study drug, occurred during the study in a patient in the 200 mg BID group. Six serious adverse events were reported in four patients treated with RO4389620, one in the 25 mg BID group and three in the 200 mg BID group.

Thirty-one patients withdrew from the study due to hyperglycemia (insufficient therapeutic response). One patient in the 100 mg RO4389620 BID group withdrew due to unresolved moderate hyperglycemia considered probably related to the trial treatment. Four patients withdrew from the 150 mg BID group due to hyperglycemia.

The other 26 hyperglycemia-related withdrawals were in the RO4389620, 200 mg BID group. One case of severe unresolved hyperglycemia was considered related to the trial treatment. The other cases of hyperglycemia were either moderate (19 patients) or mild (7 patients). These cases were considered by the Investigator to be probably related (15 patients), possibly related (6 patients), remotely related (2 patients), or unrelated (3 patients). Eighteen of these hyperglycemic withdrawals were unresolved and eight were resolved. Withdrawals due to events other than hyperglycemia were seen in a total of 18 patients, 14 of

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which were in the investigations category.

Five patients reported hypoglycemic events during the trial. None required dose adjustment or discontinuation. One patient in the RO4389620, 150 mg BID group reported five adverse events. All were mild, all were considered probably related to treatment, and all resolved without sequellae. Four patients, each treated with 200 mg, BID, reported a total of 12 events. Three were considered moderate and nine were considered to be mild. One of the moderate events was considered to be probably related to the trial treatment. Two moderate and one mild event were considered to be remotely related to the treatment. The remaining eight mild events were considered unrelated to the trial treatment.

Marked laboratory abnormalities, reported in ≥ 3% of patients in the RO4389620, 200 mg BID group, were seen in the liver function, electrolytes, and urinalysis test results. The most frequent laboratory abnormalities were observed in the liver function evaluations with elevated ALT reported most frequently. Forty-six patients (41%) had at least one high ALT reading. In 34 of these patients (30%) the high value was observed either as a replicated or last reading.

The next most commonly observed laboratory abnormalities were in the AST (SGOT) liver function test and urinalysis glycosuria readings. Both were observed in 35 patients (31%) with the most common reading being either a replicated or last reading (22 patients [19%] and 28 patients [25%], respectively).

One patient in the RO4389620, 150 mg BID group had two ALT readings that were five times the upper limit of normal. Thirty patients in 12 centers, treated with RO4389620, 200 mg BID, reported between one and five events of ALT readings that were three times the upper limit of normal. Of these patients and events, 12 patients in six centers had between one and three ALT events that were also five times the upper limit of normal.

There were no reported adverse events related to vital signs. A mean weight loss was observed in all treatment groups, with group averages ranging between one and four kilograms. One patient experienced mild cardiac ischemia with abnormal pre- and post-dose ECG readings, which was reported as an adverse event. One patient died suddenly of a myocardial infarction considered unrelated to the study drug.

CONCLUSIONS:

The following conclusions can be drawn from this study:

- Doses of RO4389620, up to 200 mg BID, were not able to establish an improvement in the glycemic control of type 2 diabetes in patients switched from a previous oral blood glucose lowering drug; however RO4389620 appeared to maintain glycemic control at the same level as their previous medication.
- The relatively large number of patients withdrawn from the study due to liver function test abnormalities suggests that 200 mg doses of RO4389620 BID are not well tolerated by all patients.
- The number of patients withdrawn due to hyperglycemia might suggest that RO4389620 has not reached its maximum effect with a dose of 200 mg BID, as that dose did not sufficiently lower blood glucose in patients with type 2 diabetes who have been switched from their previous oral blood glucose lowering medication.