SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BC20688)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Clinical Study Report – Protocol BC20688: A multicenter, double-blind, randomized, placebo-controlled, dose-ranging phase 2 study to investigate pharmacodynamics, safety, tolerability and pharmacokinetics of RO5073031 in patients with type 2 diabetes mellitus treated with a stable dose of metformin Report No. [redacted] / November 2008.		
INVESTIGATORS / CENTERS AND COUNTRIES	48 centers in Romania, Mexico, Germany, Bulgaria, USA, Latvia, Lithuania, Guatamala, Australia and Hong Kong.		
PUBLICATION (REFERENCE)	Balena R, Ratner R, Berria R, Asnaghi V, Grant R, Snaith J, Boldrin M, Nauck M. American Diabetes Association 68th Annual Scientific Sessions, San Francisco, California, USA, June 2008. Abstract No. 108-OR.		
PERIOD OF TRIAL	13 February 2007 - 14 September 2007	CLINICAL PHASE	2
OBJECTIVES	**Primary objective:** • to determine the efficacy, with respect to glycemic control, of multiple doses and regimens of RO5073031 which, when added to metformin, are safe and tolerable compared with placebo in patients with type 2 diabetes. **Secondary objectives:** • to compare the effects of RO5073031 with placebo, when both are added to metformin, on body weight and additional parameters of glycemic and lipid control; • to investigate, by a population analysis approach, the pharmacokinetics and the exposure-response relationship of RO5073031 in the target population, including the influence of covariates.		
STUDY DESIGN	Randomized, double-blind, parallel group, placebo-controlled, multicenter study. Stratification based on HbA1c (HbA1c < 8.0% or HbA1c ≥ 8.0 %) and participation in the mixed liquid meal test (MLMT).		
NUMBER OF PATIENTS	306 patients randomized.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with type 2 diabetes mellitus treated with an individual maximum tolerated daily dose of metformin (≥ 1.5 g maximum and not higher than in the label) for 3 months. At screening: HbA1c ≥ 7.0% and ≤ 9.5%; BMI > 25 kg/m^2 and ≤ 45 kg/m^2; stable weight ± 10% for at least 3 months.		
TRIAL DRUG / STROKE (BATCH) No.	RO5073031 10% sustained release formulation / batches [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	5 mg, 10 mg or 20 mg once weekly (QW), 10 mg or 20 mg once every two weeks (Q2W) administered in the morning before breakfast for 8 weeks by subcutaneous (sc) injection. To keep the study double-blinded, patients randomized to Q2W		

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	regimen had alternate weekly injections of RO5073031 or placebo.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo: saline solution 0.9% for sc injection / batch [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Placebo (200 µL) matching RO5073031 was administered in the morning before breakfast for 8 weeks by weekly sc injections in the abdomen. Throughout the study, patients continued to receive their existing metformin treatment.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint:** • absolute change from baseline in HbA1c **Secondary endpoints:** • Response rates for HbA1c (last value < 6.5%, and/or a decrease from baseline of ≥ 0.7%) and using frequency distributions • Absolute change from baseline in fasting plasma glucose (FPG) • Response rates for FPG • Absolute change from baseline in body weight • Absolute change from baseline in fructosamine • Absolute and relative changes from baseline in lipid profiles: triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and ratio of LDL cholesterol to HDL cholesterol, FFA • Absolute change from baseline in fasting insulin, proinsulin, pro-insulin/insulin ratio (derived), C-peptide and glucagon • Absolute and relative change in HOMA B, hsCRP and leptin • Relative change of AUC from baseline in post-prandial glucose, insulin, proinsulin, C-peptide and glucagon following a MLMT (in a subset of patients) **Exploratory endpoints:** • Change from baseline in HOMA-S, quantitative insulin sensitivity (QUICKI), adiponectin, and inflammatory and cardiovascular biomarkers.
SAFETY:	Adverse events, local tolerance, clinical laboratory parameters, electrocardiograms, vital signs and antibodies (anti-RO5073031, anti-GLP-1).
STATISTICAL METHODS	Using the intent to treat population (ITT) and the last observation carried forward (LOCF) for drop-outs, an analysis of variance (ANOVA) was used to assess the difference in the absolute change in HbA1c between the treatment groups. Treatment and region were fixed factors with baseline as covariate. The difference in the least squares means allowed estimation of the difference in the absolute change of HbA1c from baseline between any two treatment groups. The same model was also used for absolute

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	change from baseline of secondary parameters (with baseline of parameter as covariate). Categorical assessments were provided for HbA1c and FPG. Other parameters including safety were summarized descriptively.

METHODOLOGY:

After the 3-week screening period, eligible patients were randomized to one of the 6 double-blind treatment regimens. During the 8-week treatment period, patients visited the study center every week for their sc injection. Patients on the Q2W regimen received alternate weekly injections of RO5073031 or placebo in order to maintain the blinding. Two follow-up visits were scheduled to take place one week and three weeks after the end of the treatment period. Routine blood samples were collected at each visit for efficacy and safety assessments, special tests, antibody assessment and sparse pharmacokinetic sampling as specified in the protocol. A MLMT was performed in a subset of patients.

EFFICACY RESULTS:

Treatment with RO5073031 for 8 weeks resulted in statistically significant reductions ($p < 0.0001$) in HbA1c levels in all groups receiving the active drug, with a change from baseline of approximately -0.9% to -1.2% (compared with -0.2% for the placebo group). This change from baseline was also apparent when normalized versus placebo, with all treatment arms showing a decrease in HbA1c i.e. -0.78% at 5 mg QW dose and -1.0% at both 10 and 20 mg QW. The 10 and 20 mg doses were less efficacious when given once every two weeks compared with weekly administration. The reductions were apparent after one week of treatment and a plateau had not been reached at the end of 8 weeks of treatment. A clear dose-response was not observed and there was no apparent difference between 10 and 20 mg QW with regard to HbA1c.

Group mean response rates for HbA1c, when defined as a decrease from baseline of $\geq 0.7\%$, ranged from 67% to 85% in RO5073031 groups, with the highest rate being achieved in patients at 10 mg QW, compared with a response rate of 29% among placebo control patients. When patients with a last value of HbA1c below 6.5% was used as a criterion, 42% were considered responders at the highest dose (20 mg QW), compared with 6% in the placebo group.

A reduction of FPG occurred in all RO5073031 groups when compared with the placebo group. The greatest reductions were observed in the 10 mg QW and 20 mg QW dose groups ($p < 0.0001$). The number of responders, based on FPG decrease from baseline of ≥ 1.66 mmol/L, was greater among RO5073031 groups compared with the placebo group (group mean response rates of 40% to 66% in treated groups compared with 25% in the control).

Body weight loss occurred in all groups but was greater among RO5073031 groups compared with the placebo group; the loss decreased progressively and dose-dependently, with statistically significant reductions from baseline of 2.1 kg, 2.8 kg and 1.9 kg, (LS means) in the groups receiving 10 mg QW, 20 mg QW and 20 mg Q2W, respectively.

Fructosamine showed significant reductions ($p< 0.0001$) in all groups receiving active drug compared with the placebo controls. No clear trends for RO5073031 on other parameters of glycemic control were apparent except for a decrease in proinsulin concentrations, particularly for those groups receiving the once weekly treatment.

No dose-related trends were apparent among lipid parameters investigated after fasting, although the changes from baseline in lipid levels for RO5073031-treated groups were generally below that of the placebo group. The main finding of note was a decrease in total cholesterol levels in all RO5073031-treated

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groups ($p < 0.001$) when compared with the placebo controls after 8 weeks of treatment.

In the MLMT, improvements in postprandial glucose AUC were greater in the RO5073031 groups (-9.2% to -27.5%) than in the placebo group (-7.2%), particularly for groups receiving the once weekly administration. Minor improvements in insulin and C-peptide were also observed for the once weekly regimens.

SAFETY RESULTS:

Overall, RO5073031 was well tolerated in this study. A total of 43% of patients in the placebo control and 46% to 68% of patients across the six RO5073031 groups reported one or more adverse events. Six patients, including two in the placebo group, experienced a serious adverse events (all events were considered unrelated to study medication) and eight patients in the RO5073031-treated groups experienced an adverse events that led to premature withdrawal from treatment. The overall incidence of hypoglycemic events was low and none of the cases were severe in intensity. There were no deaths during the study.

	Placebo (N=49) No. (%)	**RO5073031 5 mg QW (N=50) No. (%)**	**RO5073031 10 mg QW (N=49) No. (%)**	**RO5073031 20 mg QW (N=50) No. (%)**	**RO5073031 10 mg Q2W (N=50) No. (%)**	**RO5073031 20 mg Q2W (N=49) No. (%)**
Total No. AEs	34	45	66	107	100	99
No. patients with:						
Any AE	21 (43)	23 (46)	25 (51)	34 (68)	29 (58)	31 (63)
Serious AE	2 (4)	0	0	3 (6)	0	1 (2)
Severe AE	2 (4)	0	2 (4)	5 (10)	5 (10)	1 (2)
Hypoglycemia	0	1 (2)	1 (2)	1 (2)	3 (6)	0
Death	0	0	0	0	0	0
AE leading to withdrawal	0	1 (2)	2 (4)	3 (6)	1 (2)	1 (2)

Gastrointestinal adverse events of nausea, diarrhea and vomiting were the individual events most often observed, followed by headache, decreased appetite, dyspepsia, and abdominal distension.

The most frequent individual adverse event was dose-dependent, transient mild-to-moderate nausea, which occurred at an incidence of 6% in the placebo group, 22%, 24% and 52% in the 5, 10 and 20 mg QW arms, and 32% and 41% in the 10 and 20 mg Q2W arms, respectively. Nausea tended to occur more frequently after the first drug administration, and have a lower incidence with subsequent administrations of RO5073031. Vomiting showed an increased incidence in RO5073031-treated groups receiving 20 mg, either weekly or every two weeks and in the group receiving 10 mg Q2W. The incidence of vomiting was 4% in the placebo group compared with 4%, 4% and 22% in the 5, 10 and 20 QW arms, and 12% and 24% in the 10 and 20 mg Q2W arms, respectively.

Approximately half of the patients from each RO5073031 group experienced a local reaction (44% to 68% across the groups) compared with 4% of the placebo group; the highest incidence was observed at 20 mg QW (68%). No severe injection site reactions (grade 3) were reported and no patient withdrew because of an injection site reaction.

There were no clinically relevant effects on laboratory parameters or vital signs and no electrocardiogram abnormalities were observed. Analysis of the maximum post-baseline QTcF interval and the maximum changes from baseline in the recorded ECGs did not give any indication that RO5073031 had a likelihood of prolonging the QTcF interval.

A higher incidence of positive antibody results was observed for RO5073031 groups receiving 10 or 20 mg weekly or every two weeks, compared with the placebo control (14% to 29% compared with 6% in the

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placebo and 5 mg QW groups). However, only 5 patients (1 in the 10 mg QW, 2 in the 20 mg QW and 2 in the 10 mg Q2W groups) were shown to have positive anti-GLP-1 antibodies on the same day as confirmed (≥ 230 ng-eq/mL) anti-RO5073031 antibodies. Review of the data showed no identifiable clinical correlates, with respect to efficacy and adverse reactions, in patients where antibodies were detected.

CONCLUSIONS:

In patients with type 2 diabetes, the addition of RO5073031 (weekly or once every two weeks) to a stable dose of metformin for 8 weeks resulted in significant improvements in glycemic control and body weight loss at all doses tested, while maintaining an acceptable safety profile. These findings indicate that RO5073031 is a promising long-acting, human GLP-1 analogue for the treatment of patients with type 2 diabetes.