SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20728)

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 BC20728: A multicenter, double-blind, randomized, placebo-controlled, titration study to investigate the safety, the tolerability and the pharmacodynamic profiles of different doses 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	27 centers in the USA, France, Mexico, Germany, Peru and Australia.		
PUBLICATION (REFERENCE)	Ratner R, Nauck M, Asnaghi V, Berria R, Cressier F, Boldrin M, Balena R. American Diabetes Association 68th Annual Scientific Sessions, San Francisco, California, USA, June 2008. Abstract No. 10-OR.		
PERIOD OF TRIAL	10 April 2007 – 24 October 2007	CLINICAL PHASE	2
OBJECTIVES	**Primary objective:** The objective of the study was to evaluate the tolerability and the safety of a broad spectrum of doses of RO5073031 (up to 30 mg and 40 mg weekly), when administered following injection of 20 mg weekly for 4 weeks to diabetic patients treated with a stable dose of metformin monotherapy. The primary endpoint was the proportion of patients withdrawn because of gastrointestinal (GI) adverse events. **Secondary objectives:** • to investigate the glycemic response in the different treatment groups, evaluating 24–hour blood glucose concentrations (based on 7-point sampling profile) and additional parameters of glycemic control; • to investigate the effects of different doses of RO5073031 on body weight; • 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, placebo-controlled, multicenter study. Stratification based on HbA1c (HbA1c < 8.0% or HbA1c ≥ 8.0%).		
NUMBER OF SUBJECTS	133 patients randomized.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients aged 18 – 75 years with type 2 diabetes mellitus treated with stable metformin monotherapy (at any dose but not higher than recommended in the label) for 3 months. At screening: HbA1c ≥ 7.0% and ≤ 9.5%; BMI > 25 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]		

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DOSE / ROUTE / REGIMEN / DURATION	20 mg once weekly (QW) for 4 weeks, followed by 20 mg, 30 mg or 40 mg weekly for 4 weeks. RO5073031 was administered in the morning before breakfast by subcutaneous (sc) injection into the abdomen.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo: saline solution 0.9% for sc injection / batch [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Placebo (200 μL) was administered in the morning before breakfast for 8 weeks by weekly sc injections into the abdomen. Throughout the study, patients continued to receive their existing metformin treatment.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint:** • The primary endpoint of the study was the proportion of patients withdrawn because of GI adverse events by treatment group **Secondary endpoints**: • Absolute mean changes in HbA1c • Response rates for HbA1c • Mean changes in 24-hour blood glucose AUC (based on 7-point sampling profile) • Mean changes in fasting plasma glucose • Mean changes in fructosamine • Mean change in body weight • Absolute/relative change in β cell function, expressed by the HOMA • Mean change in fasting insulin, proinsulin, C-peptide and glucagon • Absolute and relative changes from baseline in lipid profiles: triglycerides, FFA, total cholesterol, HDL cholesterol, LDL cholesterol, and ratio of LDL cholesterol to HDL cholesterol • Absolute and relative change in hsCRP, leptin and adiponectin • Anthropometric measurements
SAFETY:	Adverse events, local tolerance, clinical laboratory parameters, electrocardiograms, vital signs and antibodies (anti-RO5073031).
STATISTICAL METHODS	Using the intent to treat population (ITT) and the last observation carried forward (LOCF) for drop-outs, parameters were reported at each post-baseline treatment visit to the end of week 8 using general linear models with change from baseline as response, treatment as fixed effect term and baseline as covariate. For differences from placebo, 95% confidence intervals were also provided.

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The results of these analyses were also displayed graphically. Least square means for the absolute change from baseline including 95% confidence intervals were plotted for each of the four treatment groups. Categorical assessments were provided for HbA1c. Other parameters including safety were summarized descriptively.

METHODOLOGY:

After the 2-week screening period, eligible patients were randomized to one of the four double-blind treatment regimens. During the 8-week treatment period, patients visited the study center every week for their sc injection. 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 7-point blood glucose profile was collected by patients once weekly before each visit.

EFFICACY RESULTS:

Three patients were withdrawn from RO5073031 because of a GI adverse event (either dyspepsia [20/30 mg], vomiting [20/30 mg] or upper abdominal pain [20/40 mg]). The very low incidence and the timing of the withdrawals showed no indication that titration to a higher dose (30 or 40 mg) after four weeks at 20 mg resulted in an increase in the proportion of patients withdrawn for GI adverse events.

Treatment with RO5073031 over 8 weeks resulted in significant reductions in HbA1c levels in all groups receiving active drug when compared with the placebo control group. Although the study was not designed to be statistically powered to assess the effect on HbA1c, statistical significance ($p<0.0001$) was achieved in all groups receiving active drug when compared with the placebo control.

Group mean response rates, using a definition of a last value of HbA1c below 7.0%, were 72% (n=21), 53% (n=18) and 70% (n=21) at 20 mg, 20/30 mg and 20/40 mg, respectively compared with 19% (n=6) in the placebo group. Using a stricter threshold (HbA1c below 6.5%), the response rates were 41% (n=12), 21% (n=7) and 37% (n=11) at 20 mg, 20/30 mg and 20/40 mg, respectively, with no responders 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 20 mg and 20/40 mg dose groups and although the study was not designed to be powered to assess the effect on FPG, a statistical significance of $p<0.0001$ was observed in these two groups. A reduction in fructosamine values was also observed in all groups receiving active drug, with a placebo-corrected decline ranging from 25 to 34 μmol/L after 8 weeks of treatment. The 7-point glucose profiles obtained with the home glucometer demonstrated decreases of 23%, 15% and 28% in group median pre-breakfast values at 20 mg, 20/30 mg and 20/40 mg, respectively after 8 weeks of treatment with RO5073031 compared with baseline values.

Body weight loss was greater among all groups receiving RO5073031 when compared with the placebo group, albeit only marginally at 20 mg, and decreased progressively, with changes from baseline ranging from 2 to 3 kg after 8 weeks of treatment.

No clear dose-related trends were apparent among lipid parameters investigated (after fasting) with the exception of a slight decrease in triglyceride concentrations in all groups after 8 weeks of treatment, which was more pronounced in the groups receiving RO5073031 compared with the placebo group. In addition, although not dose dependent, decreases in total cholesterol and LDL cholesterol of up to 9% were observed after 8 weeks of treatment in groups receiving RO5073031 compared with a decrease of 1% in the placebo

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group.

After 8 weeks of treatment with RO5073031, minor improvements were observed in other parameters of glycemic control, demonstrated by slight increases in insulin, C-peptide and beta cell function (HOMA-B) and decreases in glucagon and C-reactive protein (as a marker of cardiovascular risk).

SAFETY RESULTS:

Overall, RO5073031 was well tolerated in this study. A total of 38% of patients in the placebo control and 63% to 73% of patients across the three RO5073031 groups reported one or more adverse events. The single serious adverse event among RO5073031-treated patients was considered unrelated to study medication and six patients in the RO5073031-treated groups experienced an adverse events that led to premature withdrawal from treatment (events of dyspepsia, vomiting, upper abdominal pain, ventricular systoles, contusion and hypoglycemia). 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=32) No. (%)	**RO5073031 20 mg (N=32) No. (%)**	**RO5073031 20/30 mg (N=33) No. (%)**	**RO5073031 20/40 mg (N=32) No. (%)**
Total No. AEs	29	55	85	59
No. patients with:				
Any AE	12 (38)	21 (66)	24 (73)	20 (63)
Serious AE	1 (3)	0	0	1 (3)
Severe AE	1 (3)	2 (6)	3 (9)	3 (9)
Hypoglycemia	1 (3)	1 (3)	3 (9)	2 (6)
Death	0	0	0	0
AE leading to withdrawal	1 (3)	0	2 (6)	4 (13)

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

The most frequent individual adverse event was transient mild-to-moderate nausea, which occurred at an incidence of 13% in the placebo group, compared with 38%, 52% and 34% in the 20, 20/30 and 20/40 mg groups, respectively. Nausea tended to occur more frequently after the first drug administration, and have a lower incidence with subsequent administrations of RO5073031. Vomiting was only observed in RO5073031-treated groups: in four patients (13%) in each of the 20, and 20/40 mg groups, and in nine patients (27%) receiving 20/30 mg. The vomiting was assessed as severe by the investigator in two patients (one receiving 20 mg and one receiving 20/40 mg). The number of patients with GI adverse events did not increase following dose titration to 30 mg or 40 mg RO5073031 in the two groups previously receiving 20 mg for 4 weeks. At 20/40 mg, the overall incidence was 38% before titration versus 36% after titration; at 20/30 mg this was 48% before versus 41% after. Among placebo patients and patients receiving 20 mg throughout the study, a lower incidence of GI events was observed during weeks 5 to 8 (placebo 10%, 20 mg 30%) compared with weeks 1 to 4 (placebo 19%, 20 mg 53%). A total of seven patients experienced signs and symptoms of hypoglycemia during the study. Only two of these events were accompanied by glucose levels confirming a hypoglycemic event (at or below 2.8 mmol/L or 50 mg/dL). There were no events of severe hypoglycemia.

Over half of the patients from each RO5073031 group experienced a local reaction to some degree (52% to 69% across the groups) compared with 13% of the placebo group. The highest incidence of local reaction was observed at 20 mg (69%). No severe injection site reactions (grade 3) were reported and no patient withdrew because of an injection site reaction.

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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.

The incidence of patients presenting with antibodies was low (two, three and one patients at 20, 20/30 and 20/40 mg, respectively) and after review of the data there were no identifiable clinical correlates with respect to efficacy and adverse reactions in these patients.

CONCLUSIONS:

In patients with type 2 diabetes, the addition of RO5073031, given once-weekly for 8 weeks to a stable dose of metformin, was safe, well tolerated and efficacious at doses titrated up to 40 mg. Up-titration of the RO5073031 dose was not associated with a worsening of the gastrointestinal adverse event profile or with any obvious additional benefit to glycemic control after 4 weeks of treatment at the higher dose. These findings indicate that RO5073031 is a promising long-acting, human GLP-1 analogue for the treatment of patients with type 2 diabetes.