SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BC20779)

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 BC20779: Multicenter, double-blind, randomized, placebo-controlled, dose ranging phase 2 study to investigate efficacy, safety, tolerability and pharmacokinetics of the DPP-IV inhibitor RO4876904 in patients with type 2 diabetes. Report No. [redacted] December 2008.		
INVESTIGATORS / CENTERS AND COUNTRIES	48 centers in 9 countries (Australia, Brazil, Guatemala, Hong Kong,, Mexico, Russia, Spain, UK and the USA).		
PERIOD OF TRIAL	19 July 2007 to 28 April 2008	CLINICAL PHASE	II
OBJECTIVES	**Primary objective**: To determine absolute change in HbA1c from the baseline to end of treatment. **Secondary objectives**: • To determine additional efficacy parameters, safety and tolerability following RO4876904 compared to placebo. • To investigate, by a population analysis approach, the pharmacokinetics and the exposure response relationship of RO4876904 in the target population including the influence of covariates. These data will be reported separately.		
STUDY DESIGN	Multicenter, double blind, randomized, placebo-controlled, dose ranging study. Stratification based on severity of disease (HbA1c <8.0% or ≥ 8.0%) and prestudy treatment (drug naïve or pre-treated).		
NUMBER OF SUBJECTS	289 patients: (57 patients in the placebo arm, 57-59 patients in each of the four RO4876904 arms)		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Type 2 diabetes (drug naïve or pre-treated with maximum tolerated dose of metformin), BMI 25-45 kg/m^2, age 18 to 75 years and: • HbA1c 7.0%-10.0% at screening • FPG ≤ 13.3 mmol/L (>240 mg/dL) at screening and randomization		
TRIAL DRUG / STROKE (BATCH) No.	RO4876904 capsules • 12.5 mg (RO4876904/F04, batch no. [redacted]) • 25 mg (RO4876904/F02, batch no. [redacted] • 50 mg (RO4876904/F05, batch no. [redacted] • 100 mg (RO4876904/F03, batch no. [redacted]		

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20779)

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

DOSE / ROUTE / REGIMEN / DURATION	One capsule (12.5, 25, 50 or 100 mg RO4876904) administered orally immediately preceding breakfast for 12 weeks.
REFERENCE DRUG / STROKE (BATCH) No.	Matching placebo capsules to RO4876904 (F01, batch no. [redacted].
DOSE / ROUTE / REGIMEN / DURATION	One placebo capsule administered orally immediately preceding breakfast for 16 weeks (4 weeks single-blind placebo run-in period; 12 weeks double-blind treatment period).
CRITERIA FOR EVALUATION	
EFFICACY:	Primary efficacy endpoint: • absolute change in HbA1c from baseline to end of treatment. Secondary efficacy endpoints: • HbA1c response rate • absolute and relative change in body weight, fasting plasma glucose (FPG), insulin sensitivity (HOMA-S), β-cell-function (HOMA-B), proinsulin/insulin ratio and lipid profile (triglycerides, total cholesterol, HDL, non-HDL, LDL, LDL/HDL ratio) from baseline to end of treatment.

PHARMACODYNAMICS:	Absolute and/or relative change from baseline to end of treatment in:
	• **Special Pharmacodynamic Laboratory Test Parameters** (insulin, proinsulin intact, glucagon, C-peptide, FFA, IL-6, fructosamine, fibrinogen, hsCRP, leptin, adiponectin)
	• **Mixed Liquid Meal Test (MLMT) parameters**
	  o Glycemic and lipid parameters (glucose, insulin, glucagon, c-peptide, GLP1 active, triglycerides)
	  o DPP4 enzymatic activity
	  o Weight parameters (obestatin, ghrelin, NPY, PYY, PP, CCK)
	  o Insulin sensitivity index (ISI) and insulin secretion rate
	• **Visual analogue rating scale (VARS) variables** measured in the fasting state (ITT population) and in the postprandial state after intake of a mixed liquid meal (MLMT population).

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20779)

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

PHARMACOKINETICS:	AUC_{last}, C_{max}, and T_{max} of RO4876904 at Week 12 (extensive pharmacokinetic [PK] sampling population only)
SAFETY:	Adverse events, clinical laboratory tests, electrocardiograms (ECG), vital signs, waist circumference, waist hip ratio.
STATISTICAL METHODS	**Efficacy and Pharmacodynamics** *Primary endpoint (change from baseline in HbA1c to the end of treatment):* an analysis of covariance (ANCOVA) with treatment, region, and pre-study treatment as fixed factors and HbA1c at baseline as covariate was performed. Each RO4876904 regimen was compared against placebo, with the null hypothesis used to test whether the mean differences exceeded 0%. The nominal one-sided significance level alpha = 0.025 was applied for each of the pairwise comparisons. Hypotheses were tested with the following hierarchical decision procedure: 100 mg vs. placebo, 50 mg vs. placebo, 25 mg vs. placebo, and finally 12.5 mg vs. placebo. For testing the placebo-corrected effects of the different treatments, the related linear contrast was applied in the ANCOVA resulting in the placebo-corrected least square (LS) mean estimates and the two-sided 95% confidence intervals (CI). *Secondary endpoints (efficacy, pharmacodynamic)*: Absolute and/or relative change from baseline to the end of treatment data are summarized descriptively as appropriate. Differences from placebo are tested on the two-sided 5% level in an exploratory manner only. **Pharmacokinetics and Safety** All data are summarized descriptively as appropriate. No statistical testing was performed.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20779)

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

METHODOLOGY:

The study consisted of four period: a screening period, a 4-week single-blind placebo run-in period, a 12-week double-blind treatment period, and a follow-up visit conducted within 5 to 14 days of the last study medication intake.

During the treatment period, patients received a once daily dose of placebo or active drug (12.5, 25, 50 or 100 mg RO4876904) in the morning immediately preceding breakfast. The efficacy, safety, pharmacokinetics and pharmacodynamics of RO4876904 were assessed at Weeks 2, 4, 8 and 12. Mixed liquid meal tests (MLMT) were performed in a subgroup of patients on Day 1 and at the Week 12 visit in order to assess the effect of RO4876904 on insulin sensitivity and on several glycemic, weight and lipid parameters after food. Extensive pharmacokinetic sampling was also conducted in a subgroup of patients at Week 12.

EFFICACY RESULTS:

Treatment with RO4876904 for 12 weeks improved HbA1c concentrations and response rates in a clear dose dependent manner. Statistically significant reductions in placebo-corrected HbA1c were observed at all RO4876904 doses tested, with a maximum reduction compared to placebo of -0.712% ($p<0.0001$) (LS mean estimate) at the 100 mg dose. Statistically significant improvements in FPG were also observed at Week 12 for RO4876904 doses $\geq$ 25 mg (Table 1).

Table 1 **Absolute Change from Baseline at End of Treatment: Difference from Placebo (LS Mean [95% CI]) (LOCF, ITT Population)**

	RO4876904 12.5 mg N=57	RO4876904 25 mg N=57	RO4876904 50 mg N=58	RO4876904 100 mg N=59
HbA1c (%)	-0.369* [-0.621, -0.117]	-0.591* [-0.843, -0.340]	-0.589* [-0.840, -0.338]	-0.712* [-0.962, -0.462]
FPG (mmol/L)	-0.250 [-0.814, 0.314]	-0.606* [-1.170, -0.043]	-0.899* [-1.459, -0.338]	-0.615* [-1.173, -0.058]

* Unadjusted $p < 0.05$.

No clear effect of RO4876904 treatment was observed at the end of treatment on fasting β-cell function (HOMA-B or the proinsulin/insulin ratio), insulin sensitivity (HOMA-S), or cholesterol parameters. A trend for lower triglyceride concentrations was observed among RO4876904-treated patients, but there was no dose response and the difference from placebo was not statistically significant at any dose.

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20779)

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

PHARMACODYNAMIC RESULTS:

MLMT Parameters (MLMT Population)

RO4876904 inhibited DPP4 activity in a dose-dependent manner, with ≥ 80% inhibition maintained over 24 hours at the 50 and 100 mg doses. In association with the decreases in DPP4 activity, large dose related increases in active GLP1 were observed for all measured fasting and postprandial parameters (mean relative change at 100 mg dose: fasting 2.37-fold, $AUE_{0-4\ h}$ 4.5-fold; $E_{max\ (0-4\ h)}$ 7.8-fold).

Small improvements in postprandial glucose (glucose 2-h post-load, $mean_{0-4\ h}$ and $AUE_{0-4\ h}$) and triglyceride ($mean_{0-6\ h}$, $AUE_{0-6\ h}$) parameters were observed at Week 12 in all RO4876904 treatment groups, with significant differences from placebo at the higher doses. Trends for improvement in the insulin secretion rate and insulin sensitivity were also observed. No clear effects of RO4876904 treatment were observed on insulin, glucagon, C-peptide, or the hunger and satiety biomarkers (obestatin, ghrelin, NPY, PYY, PP or CCK).

Special Pharmacodynamic Test Parameters (Fasting) (ITT Population)

Compared to baseline, a dose-dependent decrease in mean fasting fructosamine concentrations was observed at the end of treatment among RO4876904 treated patients. The difference from placebo was statistically significant at doses ≥ 25 mg. No clear trends or RO4876904 dose response were seen at the end of treatment on the other special PD test parameters.

VARS

No clear effects of RO4876904 were seen at the end of treatment on hunger or satiety VARS variables in either the fasting (ITT population) or postprandial (MLMT population) state.

PHARMACOKINETIC RESULTS:

Peak plasma concentrations typically occurred 1.6 to 2.5 hours after drug dosing, although there was considerable variability between individuals. Dose proportionality was not formally tested, but steady state RO4876904 exposure at the Week 12 visit appeared to show greater than dose proportional increases across the dose range (Table 2).

Table 2 Summary of RO4876904 Pharmacokinetic Parameters at Week 12 Visit (Extensive PK Sampling Population)

Parameter	RO4876904 12.5 mg N=22	RO4876904 25 mg N=24	RO4876904 50 mg N=24	RO4876904 100 mg N=21
AUC_{last} (ng·h/mL)	53.2 (94.8)	116.3 (77.0)	243.6 (178.8)	586.4 (336.4)
C_{max} (ng/mL)	13.7 (43.0)	33.2 (26.2)	64.5 (81.9)	181.2 (115.3)
T_{max} (h)	2.51 (0.00–6.03)	2.06 (0.17–6.08)	1.6 (0.17–5.08)	2.02 (0.00–6.03)

SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20779)

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

SAFETY RESULTS:

RO4876904 was well tolerated in this study. The proportion of patients who experienced one or more AE was similar in all groups (42% [placebo] vs. 33%-43% [RO4876904 groups]), and there was no discernable dose response to RO4876904. (Table 3). The vast majority of events were of mild intensity and were considered by the investigator to be unrelated to trial treatment. There were two SAEs; one in the placebo group (hypercalcemia) and one in the 12.5 mg RO4876904 group (pancreatitis). Both were reported to be unrelated to trial treatment. There was only one premature withdrawal due to an AE (dizziness in the 12.5 mg RO4876904 group). There were no deaths.

Table 3 Overview of Adverse Events (Day 1 until Follow-up) (Safety Population)

	Placebo N=57	**RO4876904 12.5 mg N=57**	**RO4876904 25 mg N=58**	**RO4876904 50 mg N=58**	**RO4876904 100 mg N=59**
All body systems					
Total patients with ≥ 1 AE	24 (42%)	24 (42%)	19 (33%)	25 (43%)	21 (36%)
Total no. AEs	45	47	35	39	28
Serious AE	1 (2%)	1 (2%)	-	-	-
Withdrawal due to AE	-	1 (2%)	-	-	-
Death	-	-	-	-	-
Related AE					
Remote	3 (5%)	1 (2%)	4 (7%)	3 (5%)	2 (3%)
Possible	3 (5%)	1 (2%)	3 (5%)	2 (3%)	4 (7%)
Probable	1 (2%)	-	-	-	1 (2%)

No clinically relevant effects of RO4876904 were identified on laboratory safety parameters, ECG parameters or vital signs and anthropometric assessments.

SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BC20779)

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

CONCLUSIONS:

Based on the data obtained from this dose-ranging Phase 2 study in patients with T2D, a 100 mg dose of RO4876904 is considered to be an efficacious and safe dose for use in future Phase 3 studies and ultimately on the market.

- Treatment with RO4876904 (12.5-100 mg qd) for 12 weeks improved HbA1c concentrations in a dose-dependent manner with a maximum reduction of -0.712% ($p<0.0001$) (placebo-corrected LS mean estimate) at the highest dose tested (100 mg). Corresponding dose-dependent improvements in FPG and postprandial glucose parameters were also observed.
- RO4876904 inhibited DPP4 activity in a dose-dependent manner, with ≥ 80% inhibition (the level required for maximum efficacy) maintained over 24 hours at the 50 and 100 mg doses. This led to large dose-related increases in all fasting (2.37-fold) and postprandial (up to 4.5-fold for $AUE_{(0-4h)}$, 7.8-fold for $E_{max(0-4h)}$) GLP1 parameters measured during a MLMT and confirmed the mode of action of RO4876904.
- RO4876904 was tolerated as well as placebo at all doses tested, with no dose response or dose-limiting AEs identified among RO4876904-treated patients and no clinically relevant effects on laboratory, ECG or vital signs.