SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20750)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Abbreviated Clinical Study Report – Protocol BC20750 - A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of taspoglutide (RO5073031) compared to placebo in patients with type 2 diabetes mellitus (T2D) inadequately controlled with diet and exercise. Report No. [redacted]. April 2011. *This clinical study report has been prepared in an abbreviated format due to termination of the clinical development program for taspoglutide.*		
INVESTIGATORS / CENTERS AND COUNTRIES	53 centers in 10 countries (Australia, Guatemala, Israel, Mexico, Peru, Russia, Romania, Slovakia, Taiwan, USA)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	24 July 2008 to 20 April 2010	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** • to determine the efficacy of taspoglutide based on glycemic control (as assessed by HbA1c) compared with placebo in drug-naïve patients with T2D after 24 weeks of treatment. **Secondary Objectives:** • to assess the effects of taspoglutide versus placebo on additional parameters of diabetes control, body weight and cardiovascular risk factors. • to assess the safety and tolerability of taspoglutide versus placebo. • to describe the pharmacokinetics (PK) of taspoglutide and to estimate between-patient variability using a population PK approach. To explore and quantify the potential influence of covariates that contribute significantly to the between-patient differences in PK parameters of taspoglutide. *Data are not reported.*		
STUDY DESIGN	Multicenter, randomized, double-blind, parallel group, placebo-controlled phase 3 study. Stratification based on HbA1c (HbA1c < 8.0% or ⩾ 8.0%).		
NUMBER OF SUBJECTS	Planned: 330 patients (110 per treatment arm) Actual: 373 patients (125 placebo, 118 taspoglutide 10 mg, 131 taspoglutide 20 mg)		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Drug naive patients with T2D inadequately controlled by diet and exercise alone. • Male and female patients, 18 to 80 years of age, at screening. • Negative test for anti-glutamic acid decarboxylase (GAD) antibodies. • C-peptide (fasting) ≥ 1.0 ng/mL (333 pmol/L). • HbA1c ≥ 6.5% and ≤ 10.0 % at screening. • Body mass index (BMI) ⩾ 25 kg/m^2 (> 23 kg/m^2 for Asians) and ⩽ 45 kg/m^2 at screening. • Stable weight ± 5% for at least 12 weeks prior to screening.
TRIAL DRUG / STROKE (BATCH) No.	Taspoglutide - provided in single-dose pre-filled syringes containing a 10% sustained release formulation: • taspoglutide 10 mg (100 µL) - Ro 507-3031/F04-04 – batch numbers [redacted] • taspoglutide 20 mg (200 µL) - Ro 507-3031/F04-01 – batch numbers [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Once weekly (QW) subcutaneous injection of taspoglutide in the abdomen before breakfast: • taspoglutide 10 mg QW. • taspoglutide 20 mg QW. Dosed at 10 mg QW for the first 4 weeks then up-titrated to 20 mg QW from week 5 onwards. Patients randomized to taspoglutide received QW injections throughout the 52-week treatment period. Patients randomized to placebo switched to taspoglutide (10 or 20 mg) from week 25 onwards.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo - provided in single-dose pre-filled syringes, identical in appearance to the taspoglutide syringes, containing zinc chloride solution: • placebo to taspoglutide 10 mg (100 µL): Ro 507-3031/F06-04 – batch number [redacted] • placebo to taspoglutide 20 mg (200 µL): Ro 507-3031/F06-01 – batch number [redacted]
DOSE / ROUTE / REGIMEN / DURATION	QW subcutaneous injection in the abdomen before breakfast: • placebo to taspoglutide 10 mg QW • placebo to taspoglutide 20 mg QW Patients randomized to placebo received placebo during the 24-week core phase and switched to taspoglutide (10 or 20 mg) from week 25 onwards.

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CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint:** • the absolute change from baseline in HbA1c after 24 weeks of treatment. **Secondary and exploratory endpoints**: • the absolute change from baseline in FPG at week 24; • the absolute change from baseline in body weight at week 24. No other efficacy endpoints listed in the protocol are reported.
PHARMACODYNAMICS:	Data not reported
PHARMACOKINETICS:	Data not reported
SAFETY:	Safety during the 24-week double-blind core period: • adverse events (AEs), laboratory tests, vital signs, and 12-lead electrocardiogram (ECG). Continuous treatment patients – cumulative safety from day 1 to week 52: • AEs, laboratory tests, vital signs, 12-lead ECG, anti-taspoglutide antibodies. Placebo/taspoglutide switch patients – safety during the 28-week extension: • AEs, laboratory tests (limited), anti-taspoglutide antibodies.
STATISTICAL METHODS	**Efficacy** Analysis of covariance (ANCOVA) was used to assess possible differences in the absolute change in HbA1c (%), FPG and body weight at week 24 between the different treatment groups. All analyses are based on the Intent to Treat (ITT) population with the Last Observation Carried Forward (LOCF) principle applied for missing post-baseline assessments. **Safety Analyses** Presented in individual patient listings and summary tables as appropriate.

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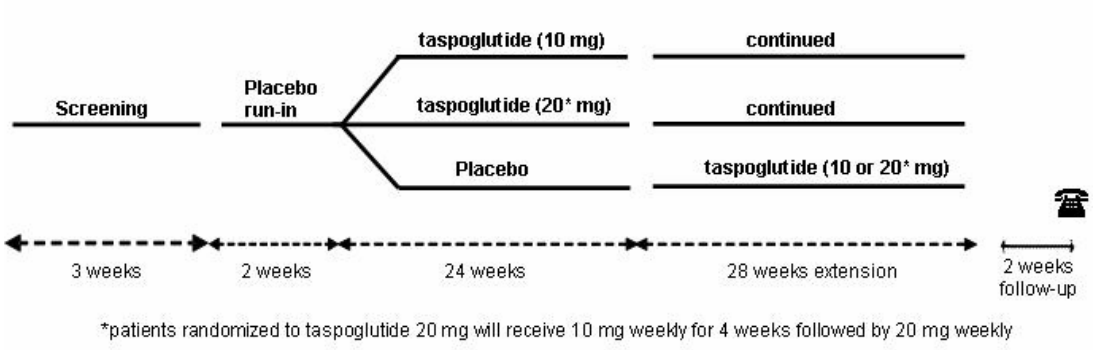
METHODOLOGY:

The study consisted of a screening period, a 2-week placebo run-in (during which all patients received placebo QW injections), a 24-week double-blind treatment period (core phase), a 28-week open-label extension (extension phase), and a follow-up phone call (Figure 1). On day 1 of the core phase, patients were allocated in a 1:1:1 ratio to receive either taspoglutide 10 mg, taspoglutide 20 mg, or placebo for 24 weeks. At the end of week 24, patients on taspoglutide continued taking the same dose for a further 28 weeks ('continuous treatment patients') while patients in the placebo group were switched to taspoglutide ('placebo switch patients'). Half the placebo patients received taspoglutide 10 mg and half received taspoglutide 20 mg.

Figure 1 Overview of Study Design and Dosing Regimen



EFFICACY RESULTS

After 24 weeks of treatment, the efficacy of taspoglutide 10 mg and 20 mg (as assessed by the absolute change from baseline in HbA1c) was shown to be superior to that of placebo in patients with T2D inadequately controlled by diet and exercise alone. Treatment with taspoglutide for 24 weeks also resulted in statistically significant improvements compared to placebo in FPG concentrations (both doses) and body weight (20 mg dose only) (Table 1).

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Table 1 ANCOVA of Absolute Change from Baseline at Week 24 (LOCF, ITT Population)

	Placebo N=115	Taspoglutide 10 mg N = 112	Taspoglutide 20 mg N=127
HbA1c (%)			
LS mean	-0.088	-1.009	-1.181
95% CI	(-0.217, 0.041)	(-1.141, -0.878)	(-1.307, -1.056)
Diff from placebo			
LS mean		-0.921	-1.093
p-value [a]		<0.0001	<0.0001
FPG (mmol/L)			
LS mean	-0.081	-1.553	-1.902
95% CI	(-0.416, 0.254)	(-1.893, -1.214)	(-2.226, -1.577)
Diff from placebo			
LS mean		-1.472	-1.820
p-value [a]		<0.0001	<0.0001
Body weight (kg)			
LS mean	-1.232	-1.454	-2.246
95% CI	(-1.842, -0.623)	(-2.073, -0.836)	(-2.839, -1.653)
Diff from placebo			
LS mean		-0.222	-1.014
p-value [a]		0.6071	0.0161

a Unadjusted.

SAFETY RESULTS IN THE CORE PERIOD (UP TO WEEK 24):

During the 24-week double-blind core treatment period, the incidences of overall AEs (45% placebo vs. 69% and 75% taspoglutide 10 and 20 mg, respectively) and of AEs leading to withdrawal (3% vs. 11% and 13%, respectively) were higher in the taspoglutide groups than in the placebo group (Table 2). The higher incidences in the taspoglutide groups were mainly due to a higher occurrence of gastrointestinal AEs such as nausea and vomiting and of injection site reactions.

Ten patients experienced an SAE; 2/123 (2%) in the placebo group, 5/116 (4%) in the taspoglutide 10 mg group, and 3/129 (2%) in the taspoglutide 20 mg group. No individual SAE (preferred term) occurred in more than one patient per treatment group. All SAEs except two were reported by the investigator as unrelated to treatment.

No clinically relevant effects of taspoglutide were observed on laboratory parameters, ECG parameters, or vital signs measured at week 24. There were no deaths, and no reports of pancreatitis or thyroid tumours. Four hypersensitivity reactions (two per dose) were reported in taspoglutide-treated patients, two of which were reported as SAEs.

Table 2 Summary of Adverse Events, Deaths, and Withdrawals (Week 24, Safety Population)

ae24 Summary of Adverse Events, Deaths and Withdrawals
Protocol(s): BC20750
Analysis: SAFETY POPULATION Center: ALL CENTERS
Phase: Core

	PLACEBO N = 123 No. (%)	TASPOGLUTIDE 10 MG N = 116 No. (%)	TASPOGLUTIDE 20 MG N = 129 No. (%)
Total Pts with at Least one AE	55 (44.7)	80 (69.0)	97 (75.2)
Total Number of AEs	124	257	291
Deaths #	0 (0.0)	0 (0.0)	0 (0.0)
Study withdrawals due to an AE #	2 (1.6)	10 (8.6)	16 (12.4)
Patients with at least one			
AE leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	2 (1.6)	5 (4.3)	3 (2.3)
AE leading to withdrawal from treatment	4 (3.3)	13 (11.2)	17 (13.2)

Investigator text for Adverse Events encoded using MedDRA version 12.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Deaths derived from Death page, Withdrawals derived from Study Completion page.
'AE leading to withdrawal from treatment' also includes patients who completed the Core Phase but then shortly thereafter discontinued treatment due to an adverse event which was ongoing at the time of Core Phase completion and patients who terminate early due to Insufficient Therapeutic Response.
AEs which began on the first day of the Extension Phase are excluded.
AE24 10FEB2010:23:47:43 (1 of 1)

SAFETY RESULTS UP TO WEEK 52 – CONTINUOUS TREATMENT PATIENTS

At the end of the 52-week treatment period, 93/116 (80%) patients in the taspoglutide 10 mg group and 98/129 (76%) patients in the taspoglutide 20 mg group had reported one or more AE. As observed at week 24, the most frequently reported AEs were gastrointestinal disorders such as nausea and vomiting.

A total of 44 continuous treatment patients, 19 (16%) in the 10 mg group and 25 (19%) in the 20 mg group, experienced an AE that led to premature withdrawal from treatment. The majority of these patients were withdrawn during the 24-week core period (30 out of 44 patients). Over half of the AEs that led to premature withdrawal from treatment were gastrointestinal events.

A total of 44 continuous treatment patients, 19 (16%) in the 10 mg group and 25 (19%) in the 20 mg group, experienced an AE that led to premature withdrawal from treatment during the 52 week treatment period. More patients were withdrawn during the 24-week core period (30 out of 44 patients) than during the 28-week extension (14 out of 44 patients). Approximately two thirds of all AEs leading to withdrawal up to week 52 (28/44, 64%) were gastrointestinal events.

Systemic allergic reactions occurred in a total of 7 continuous treatment patients, 2 (2%) in the 10 mg group and 5 (4%) in the 20 mg group. Both cases in the 10 mg group and two cases in the 20 mg group occurred in the core 24-week period. The three new cases in the extension period included two cases of hypersensitivity (one of which was reported as an SAE) and one case of urticaria. Per protocol, both hypersensitivity AEs led to premature withdrawal from treatment.

No clinically relevant effects of taspoglutide were observed on laboratory parameters, ECG parameters, or vital signs up to week 52. There were no deaths, and no reports of pancreatitis or thyroid tumours.

A total of 105/224 (47%) continuous treatment patients had at least one confirmed positive anti-tasopoglutide antibody result post-baseline; 44/106 (42%) patients who received taspoglutide 10 mg and 61/118 (52%) patients who received taspoglutide 20 mg.

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SAFETY RESULTS IN THE EXTENSION (WEEKS 24 TO 52) – PLACEBO SWITCH PATIENTS:

After receiving open-label taspoglutide for up to 28 weeks during the extension phase of the study, 28/53 (53%) patients in the placebo switch taspoglutide 10 mg group and 36/57 (63%) patients in the placebo switch taspoglutide 20 mg group had reported one or more AE. As observed among taspoglutide-treated patients in the core period, the most frequently reported AEs were gastrointestinal disorders such as nausea and vomiting. One patient in each group experienced an SAE, and 2 (4%) patients in the 10 mg group and 5 (9%) patients in the 20 mg group experienced an AE that led to withdrawal.

No deaths, and no cases of pancreatitis, thyroid tumours or hypersensitivity reactions were reported in placebo switch patients after receiving taspoglutide.

A total of 42/106 (40%) placebo switch patients had at least one confirmed positive anti-taspoglutide antibody result after receiving taspoglutide for up to 28 weeks; 17/52 (33%) patients who received taspoglutide 10 mg and 25/54 (46%) patients who received taspoglutide 20 mg.

CONCLUSIONS:

After 24 weeks of treatment, the efficacy of taspoglutide 10 mg and 20 mg (as assessed by the absolute change from baseline in HbA1c) was shown to be superior to that of placebo in patients with T2D inadequately controlled by diet and exercise alone.

The safety and tolerability profile of taspoglutide in this study was characterized by higher incidences of overall AEs and of AEs leading to withdrawal in taspoglutide-treated patients compared with placebo-treated patients, primarily due to higher incidences of gastrointestinal-related AEs (mainly vomiting and nausea) and injection site reactions. No clinically relevant adverse effects of taspoglutide were identified on laboratory safety parameters, vital signs or ECGs.