SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20963)

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 BC20963 - 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 inadequately controlled with metformin plus pioglitazone. Report No. [redacted]. June 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	83 centers in 8 countries (Brazil, Canada, Costa Rica, France, Germany, Guatemala, Mexico, USA)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	15 September 2008 to 09 November 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 patients with T2D inadequately controlled with metformin plus pioglitazone 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%).		

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NUMBER OF SUBJECTS	Planned: 330 patients (110 per treatment arm) Actual: 326 patients (102 placebo, 109 taspoglutide 10 mg, 115 taspoglutide 20 mg)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Diagnosed with T2D, and treated with pioglitazone ≥ 30 mg/day and metformin ≥ 1500 mg/day, at a stable dose for at least 12 weeks prior to screening. • Male and female patients, 18 to 75 years of age, at screening. • HbA1c ≥ 7.0% and ≤ 10.0 % at screening. • Body mass index (BMI) $\geqslant$ 25 kg/m^2 (> 23 kg/m^2 for Asians) and $\leqslant$ 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]

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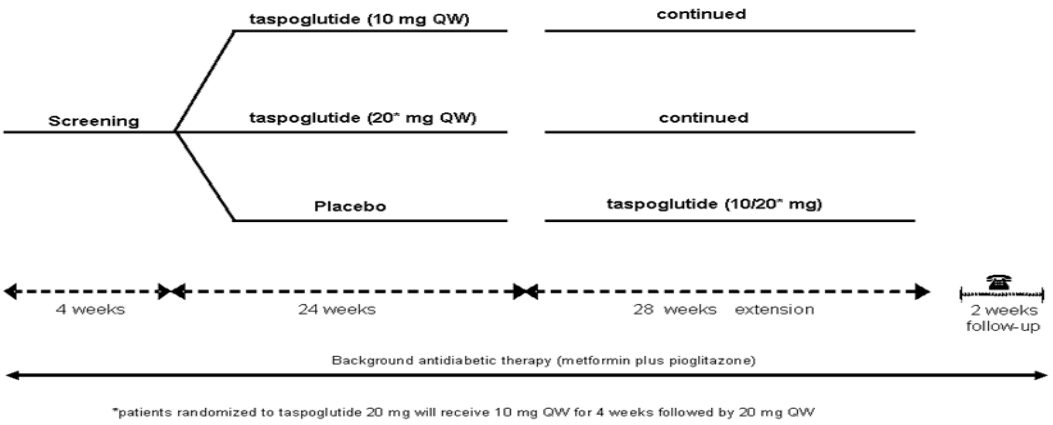
DOSE / ROUTE / REGIMEN / DURATION	QW subcutaneous injection in the abdomen before breakfast: • placebo to taspoglutide 10 mg QW • placebo to taspoglutide 20 mg QW Patients randomized to placebo received placebo during the 24-week core phase and switched to taspoglutide (10 or 20 mg) from Week 25 onwards.
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 fasting plasma glucose (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 phase: • 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.

METHODOLOGY:

The study consisted of a screening period, 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 in addition to their continued treatment with metformin and pioglitazone. 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 receiving background therapy with metformin and pioglitazone. Treatment with both doses of taspoglutide for 24 weeks also resulted in statistically significantly larger improvements in FPG concentrations and body weight compared to placebo (Table 1).

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

	Placebo N=94	Taspoglutide 10 mg N = 106	Taspoglutide 20 mg N=113
HbA1c (%)			
LS mean	-0.454	-1.346	-1.402
95% CI	(-0.649, -0.259)	(-1.527, -1.165)	(-1.577, -1.228)
Diff from placebo			
LS mean		-0.892	-0.940
p-value [a]		<0.0001	<0.0001
FPG (mmol/L)			
LS mean	-0.567	-1.872	-2.115
95% CI	(-1.022, -0.112)	(-2.297, -1.448)	(-2.524, -1.706)
Diff from placebo			
LS mean		-1.305	-1.548
p-value [a]		<0.0001	<0.0001
Body weight (kg)			
LS mean	0.586	-0.643	-1.036
95% CI	(-0.146, 1.318)	(-1.326, 0.040)	(-1.692, -0.379)
Diff from placebo			
LS mean		-1.229	-1.622
p-value [a]		0.0064	0.0003

a Unadjusted.

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

During the 24-week double-blind treatment period, the incidences of overall AEs (59% placebo vs. 75% and 84% taspoglutide 10 and 20 mg, respectively) and of AEs leading to withdrawal (1% vs. 9% and 9%, 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.

Four patients experienced an SAE; one (1%) in the placebo group and three (3%) in the taspoglutide 20 mg group. No individual SAE (preferred term) occurred in more than one patient per treatment group. All SAEs 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; in addition, there were no reports of pancreatitis or systemic allergic reactions in the taspoglutide treatment groups through Week 24. One patient each in the placebo and taspoglutide 20 mg groups had a thyroid neoplasm during the core phase. The thyroid neoplasm (nodule; mild in intensity) in the taspoglutide-treated patient was considered related to an underlying multimodal goiter. The thyroid neoplasm (papillary thyroid carcinoma confirmed by biopsy; severe in intensity) in the placebo-treated subject resulted in treatment discontinuation. Both of these AEs were assessed as unrelated to study drug.

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

ae24 Summary of Adverse Events, Deaths and Withdrawals
Protocol(s): BC20963
Analysis: SAFETY POPULATION Center: ALL CENTERS
Phase: Core

	PLACEBO N = 101 No. (%)	TASPOGLUTIDE 10 MG N = 108 No. (%)	TASPOGLUTIDE 20 MG N = 115 No. (%)
Total Pts with at Least one AE	60 (59.4)	81 (75.0)	97 (84.3)
Total Number of AEs	148	272	325
Deaths #	0 (0.0)	0 (0.0)	0 (0.0)
Study withdrawals due to an AE #	1 (1.0)	10 (9.3)	11 (9.6)
Patients with at least one			
AE leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	1 (1.0)	0 (0.0)	3 (2.6)
AE leading to withdrawal from treatment	1 (1.0)	10 (9.3)	10 (8.7)

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' does not include one patient who terminated due to an AE which began prior to the start of study medication. This patient is included in 'Study withdrawals due to an AE'. AEs which began on the first day of the Extension Phase are excluded.
AE24 22APR2010:22:53:51 (1 of 1)

SAFETY RESULTS UP TO WEEK 52 – CONTINUOUS TREATMENT PATIENTS

At the end of the 52-week treatment period, 94/108 (87%) patients in the taspoglutide 10 mg group and 104/115 (90%) 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.

There were no deaths, and no reports of pancreatitis during the extension phase.

Six (6%) subjects in the taspoglutide 10 mg group and six (5%) subjects in the taspoglutide 20 mg group experienced a SAE during the 52-week treatment period; most of the SAEs occurred during the 28-week extension phase. No individual SAE (preferred term) occurred in more than one patient per treatment group.

A total of 37 continuous treatment patients, 18 (17%) in the 10 mg group and 19 (17%) 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 phase 21 out of 37 patients). Approximately two-thirds of the AEs that led to premature withdrawal from treatment were gastrointestinal events.

Systemic allergic reactions occurred in a total of nine continuous treatment patients, three (3%) in the 10 mg group and six (5%) in the 20 mg group. All of these cases occurred in the 28-week extension phase, and included six cases of hypersensitivity (two led to discontinuation), one case of anaphylactic reaction (considered serious and led to discontinuation), one case of face oedema, and one case of pruritus.

Two additional cases of thyroid neoplasm (nodule) occurred during the extension phase in the taspoglutide groups. Both of these AEs were mild in intensity and non-serious, and neither led to premature withdrawal. Biopsy results for one patient were negative for malignant cells, and a repeat ultrasound for the other patient failed to confirm the presence of the nodule.

No clinically relevant effects of taspoglutide were observed on laboratory parameters, ECG

parameters, or vital signs up to week 52.

A total of 103/223 (48%) continuous treatment patients had at least one confirmed positive anti-tasopoglutide antibody result post-baseline; 50/108 (48%) patients who received taspoglutide 10 mg and 53/115 (48%) patients who received taspoglutide 20 mg.

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, 30/44 (68%) patients in the placebo switch taspoglutide 10 mg group and 35/44 (80%) patients in the placebo switch taspoglutide 20 mg group had reported one or more AE. As observed among taspoglutide-treated patients in the core phase, the most frequently reported AEs were gastrointestinal disorders such as nausea and vomiting. Three patients in each group experienced an SAE, and two (5%) patients in the 10 mg group and three (7%) patients in the 20 mg group experienced an AE that led to withdrawal.

No deaths, and no cases of systemic allergic reactions, or pancreatitis were reported in placebo switch patients after receiving taspoglutide. There were two patients with thyroid neoplasms (nodules), one of which was serious. Biopsies in both patients failed to identify malignant cells.

A total of 30/88 (34%) placebo switch patients had at least one confirmed positive anti-taspoglutide antibody result after receiving taspoglutide for up to 28 weeks, including 11/44 (25%) patients who received taspoglutide 10 mg and 19/44 (43%) 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), added to background therapy with metformin or pioglitazone, was shown to be superior to that of placebo plus metformin or pioglitazone in patients with T2D inadequately controlled with metformin and pioglitazone.

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