SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC21625)

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 BC21625 - A multicenter, randomized, open label, active-comparator controlled study to assess the efficacy, safety and tolerability of taspoglutide (RO5073031) compared to exenatide in patients with type 2 diabetes mellitus (T2D) inadequately controlled with metformin, thiazolidinedione or a combination of both. 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	1189 patients from 189 centers in 23 countries (Argentina, Australia, Brazil, Canada, Denmark, Finland, France, Germany, Guatemala, Israel, Italy, Korea, Mexico, Spain, Peru, New Zealand, Russia, South Africa, Sweden, Thailand, Ukraine, United Kingdom, USA).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	25 July 2008 to 22 December 2010	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** • to assess the efficacy of taspoglutide based on glycemic control (as assessed by glycosylated hemoglobin A1c [HbA1c]) after 24 weeks of treatment in patients with T2D inadequately controlled with metformin, thiazolidinedione, or a combination of metformin and thiazolidinedione compared with exenatide twice daily (b.i.d.). **Secondary Objectives:** • to assess the effects of taspoglutide versus exenatide on additional parameters of diabetes control, body weight and cardiovascular risk factors. • to assess the safety and tolerability of taspoglutide versus exenatide b.i.d. • 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.*		

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STUDY DESIGN	Multicenter, randomized, open-label, parallel group, active-comparator, phase 3 study. Stratification based on HbA1c (HbA1c < 8.0% or ⩾ 8.0%) and background therapy (metformin alone, thiazolidinedione alone, metformin and thiazolidinedione combined).
NUMBER OF SUBJECTS	Planned: 990 patients (330 per treatment arm) Actual: 1189 patients (399 taspoglutide 10 mg, 398 taspoglutide 20 mg, 392 exenatide)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Diagnosed with T2D, and treated with pioglitazone ≥ 30 mg/day, rosiglitazone ≥ 4 mg/day metformin ≥ 1500 mg/day (or the maximum dose specified in the label), 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) ⩾ 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.
REFERENCE DRUG / STROKE (BATCH) No.	Exenatide - multidose prefilled pens for subcutaneous injection into the abdomen, thigh, or upper arm.
DOSE / ROUTE / REGIMEN / DURATION	Dosed at an initial dose of 5 mcg b.i.d. for the first 4 weeks followed by 10 mcg b.i.d. for the remainder of the study.

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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 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 entire study period (24-week core phase, 28-week extension phase, and 104-week long-term [LT] extension phase): • adverse events (AEs), laboratory tests, vital signs, and 12-lead electrocardiogram (ECG), 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. An assessment of noninferiority of each taspoglutide group to the exenatide group was made using the noninferiority limits of 0.4%, 0.5 mmol/L, and 3 kg for the treatment difference in the mean change from baseline in HbA1c, FPG, and body weight, respectively. 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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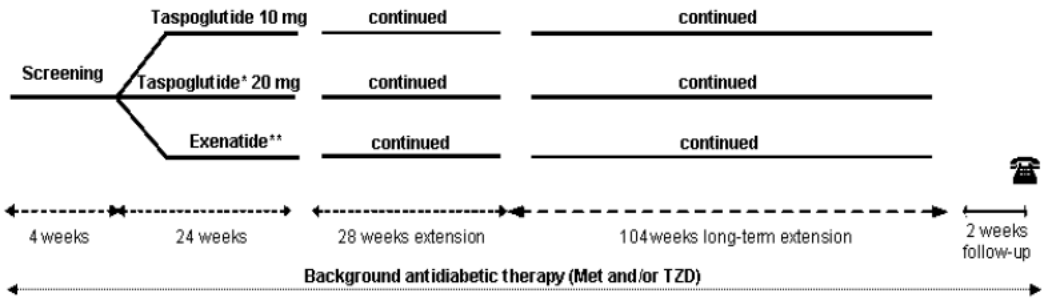
METHODOLOGY:

This was a multicenter, randomized, parallel group, open-label, active-controlled, phase 3 study with a 24-week core phase, a 28-week extension phase, an optional 104-week LT 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 exenatide 10 mcg b.i.d. in addition to their continued treatment with metformin alone, thiazolidinedione alone, or metformin and thiazolidinedione combined. Patients remained on the same study medication that they had been randomized to throughout the study. Participation in the 104-week LT extension phase was voluntary, and patients were required to sign a separate informed consent if they elected to continue treatment in this phase.

Figure 1 Overview of Study Design and Dosing Regimen



*Taspoglutide 10 mg weekly for 4 weeks followed by 20 mg weekly
**Exenatide 5 mcg twice daily for 4 weeks followed by 10 mcg twice daily

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) in patients with T2D receiving background therapy with metformin and/or a thiazolidinedione was noninferior to that for patients treated with exenatide, using the pre-established limit of 0.4%. Furthermore, under closed test procedures, superiority was achieved for each of the taspoglutide doses relative to exenatide. Results for the mean improvements in FPG at week 24 were similar as those described for HbA1c. With respect to the mean change from baseline in body weight at week 24, noninferiority of both doses of taspoglutide to exenatide was shown based on a pre-established noninferiority limit of 3 kg; however, the mean changes in body weight at week 24 was significantly less in the taspoglutide 10 mg group compared with exenatide (Table 1).

The efficacy responses at week 24 were sustainable up to one year of treatment.

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

	Taspoglutide 10 mg N = 384	Taspoglutide 20 mg N=392	Exenatide 10 mcg N=373
HbA1c (%)			
LS mean	-1.241	-1.312	-0.981
95% CI	(-1.408, -1.075)	(-1.478, -1.146)	(-1.144, -0.818)
Diff from exenatide			
LS mean	-0.260	-0.331	
p-value [a]	<0.0001	<0.0001	
FPG (mmol/L)			
LS mean	-2.179	-2.483	-1.809
95% CI	(-2.568, -1.790)	(-2.870, -2.095)	(-2.189, -1.428)
Diff from exenatide			
LS mean	-0.370	-0.674	
p-value [a]	0.0061	<0.0001	
Body weight (kg)			
LS mean	-1.604	-2.325	-2.270
95% CI	(-2.332, -0.876)	(-3.050, -1.600)	(-2.983, -1.558)
Diff from exenatide			
LS mean	0.666	-0.054	
p-value [a]	0.0167	0.8283	

a Adjusted.

SAFETY RESULTS FOR ENTIRE STUDY (CORE + EXTENSION + LT EXTENSION PHASES)

During the entire study treatment period (core, extension, and LT extension phases), the overall incidence of AEs was similar for the taspoglutide 10 mg (92%), taspoglutide 20 mg (94%), and exenatide (89%) groups (Table 2). While gastrointestinal disorders were the most frequently reported AEs in all three treatment groups, they were reported at a higher rate in the taspoglutide groups (68% and 72% in 10 and 20 mg groups, respectively) than in the exenatide group (57%). This treatment difference was most apparent for the gastrointestinal AEs of nausea, vomiting, and constipation.

Table 2 Summary of Adverse Events, Deaths, and Withdrawals During Entire Study (LT Extension Safety Population)

f_ae24 Summary of Adverse Events, Deaths and Study Withdrawals
Protocol(s): BC21625 Analysis: SAFETY POPULATION Center: ALL CENTERS Phase: LTE

	TASPOGLUTIDE 10 MG N = 394 No. (%)	TASPOGLUTIDE 20 MG N = 394 No. (%)	EXENATIDE N = 385 No. (%)
Total Pts with at Least one AE	363 (92.1)	370 (93.9)	343 (89.1)
Total Number of AEs	1791	2009	1430
Deaths #	2 (0.5)	1 (0.3)	1 (0.3)
Study withdrawals due to an AE #	101 (25.6)	133 (33.8)	59 (15.3)
Patients with at least one			
AE leading to Death	2 (0.5)	1 (0.3)	1 (0.3)
Serious AE	50 (12.7)	33 (8.4)	38 (9.9)
AE leading to withdrawal from treatment	103 (26.1)	135 (34.3)	60 (15.6)

Investigator text for Adverse Events encoded using MedDRA version 13.1.
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.
AE24 09MAY2011:07:35:20

Across the entire study, SAEs was reported for 8% and 10% of patients in the taspoglutide 20 mg and exenatide groups, respectively, compared with 13% of patients treated with taspoglutide 10 mg. Serious adverse events did not show a consistent pattern for system organ class or type of AE. The most common SAEs in all treatment groups were 'Cardiac Disorders' (11/62 SAEs in taspoglutide 10 mg group, 8/38 SAEs in taspoglutide 20 mg group, 10/41 SAEs in exenatide group). In each treatment group, most of the SAEs were assessed as not related to study drug. For four patients, the SAE resulted in death (two in the taspoglutide 10 mg group [completed suicide, hemorrhage stroke], one each in the taspoglutide 20 mg [myocardial infarction] and exenatide [bleeding varicose vein] groups). Each of these deaths were considered by the investigator to be not related to study drug.

More patients in the taspoglutide 10 mg and 20 mg groups had an AE(s) that led to withdrawal (26% and 34%, respectively) compared with exenatide group (16%). The higher incidence of AEs leading to withdrawal in the taspoglutide groups was primarily due to more patients in these groups withdrawing due to gastrointestinal disorders (including nausea and vomiting), immune system disorders (including hypersensitivity, anaphylactoid or anaphylactic reactions), and injection-site reaction AEs.

Systemic allergic reactions were more common in the taspoglutide 10 mg (6%) and 20 mg (6%) groups than in the exenatide group (1%). For nine patients treated with taspoglutide, the systemic allergic reaction was serious. Thirty-one of the 48 patients in the taspoglutide groups with a systemic allergic reaction were withdrawn as a result of this AE. All of these AEs resolved without sequelae.

Injection-site reactions were reported for 35% and 42% of patients treated with taspoglutide 10 mg or 20 mg, respectively (6% in exenatide group). Most of these AEs were mild or moderate in intensity, and only one was serious (injection site abscess). Among the 304 patients in the taspoglutide groups reporting an injection site reaction AE, treatment discontinued as a result of the event for 15.

Pancreatitis was reported as an AE in one patient (taspoglutide 20 mg) across the entire study period, and this event was serious and resulted in discontinuation of treatment.

Pre-specified thyroid neoplasm-related AEs occurred at a similar rate in the taspoglutide 10 mg (2%), 20 mg (2%), and exenatide (2%) groups. The majority of these AEs consisted of the

reported laboratory abnormality, increased blood calcitonin. Three thyroid neoplasms were reported (one in each treatment group); all of them were benign.

No clinically relevant effects of taspoglutide were observed on laboratory parameters, ECG parameters, or vital signs measured throughout the study.

At least one confirmed positive anti-taspoglutide antibody result (below limit of quantitation, above limit or quantitation, or real) was reported post-baseline for 49% of patients in the taspoglutide groups (43% in 10 mg group; 55% in 20 mg group).

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 noninferior and statistically superior to that of exenatide 100 mcg b.i.d. in patients with T2D inadequately controlled with metformin, thiazolidinedione, or a combination of metformin and thiazolidinedione. Both noninferiority and superiority of both doses of taspoglutide versus exenatide were maintained at Week 52.

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