SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC21893)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Abbreviated Clinical Study Report – Protocol BC21893. A multicenter, randomized, double blind (double dummy), active comparator controlled study to compare the efficacy, safety and tolerability of taspoglutide versus pioglitazone in type 2 diabetes patients inadequately controlled with sulfonylurea (SU) monotherapy or metformin plus SU combination therapy. Research Report Number [redacted]. July 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	760 patients from 130 centers in 17 countries (Australia, Brazil, Canada, Costa Rica, France, Germany, Mexico, New Zealand, Peru, Poland, Russia, Slovakia, Spain, Thailand, Ukraine, United Kingdom, USA).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	30-April-2009 to 30-November-2010	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** • to evaluate the efficacy of taspoglutide on glycemic control (as assessed by glycosylated hemoglobin A1c [HbA1c]) compared to pioglitazone after 24 weeks of treatment in patients with T2D mellitus inadequately controlled with sulfonylurea (SU) monotherapy or SU + metformin combination therapy. **Secondary Objectives:** • to determine the effects of taspoglutide and pioglitazone on additional parameters of diabetes control and body weight • to assess the safety and tolerability of taspoglutide versus pioglitazone up to 104 weeks of treatment • 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 contributes significantly to the between-patient differences in PK parameters of taspoglutide. *Data are not reported.*		

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STUDY DESIGN	Multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled phase 3 study. Stratification based on HbA1c (HbA1c < 8.0% or ⩾ 8.0%) and background diabetes therapy (SU alone or SU + metformin).
NUMBER OF SUBJECTS	Planned: 648 patients (216 per treatment group) Actual: 760 patients (248 taspoglutide 10 mg, 251 taspoglutide 20 mg, 261 pioglitazone)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Diagnosed with T2D, and treated with a stable dose of SU monotherapy or SU plus metformin combination therapy for at least 12 weeks prior to screening. The SU dosage was to have been the maximum effective dose (defined as at least half the maximum country-specific labeled dose, except for cases in which the highest individually tolerated dose was less), and the metformin dose was to have been ≥ 1500 mg/day. • 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.	Pioglitazone 30 and 45 mg tablets over-encapsulated for oral administration. Placebo ($ZnCl_2$) matching taspoglutide 10 mg injections: batch numbers [redacted] Placebo ($ZnCl_2$) matching taspoglutide 20 mg injections: batch numbers [redacted] Placebo matching pioglitazone capsules.

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DOSE / ROUTE / REGIMEN / DURATION	Pioglitazone: Once daily (QD) oral administration of 30 mg before breakfast for the first 4 weeks followed by 45 mg QD starting at week 5. Placebo matching pioglitazone: QD oral administration. Placebo matching taspoglutide: QW subcutaneous injection.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint:** • the absolute change from baseline in HbA1c after 24 weeks of treatment. **Secondary endpoints**: • the absolute change from baseline in fasting plasma glucose (FPG) at end of treatment; • the absolute change from baseline in body weight at end of treatment. *Because of the termination of the clinical development program for taspoglutide, the secondary endpoints were analyzed for week 24 time point rather than at the end of treatment.* 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 52-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 pioglitazone 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. If noninferiority was met for both treatment comparisons, a closed testing procedure was used to test for the superiority of taspoglutide to pioglitazone. 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.

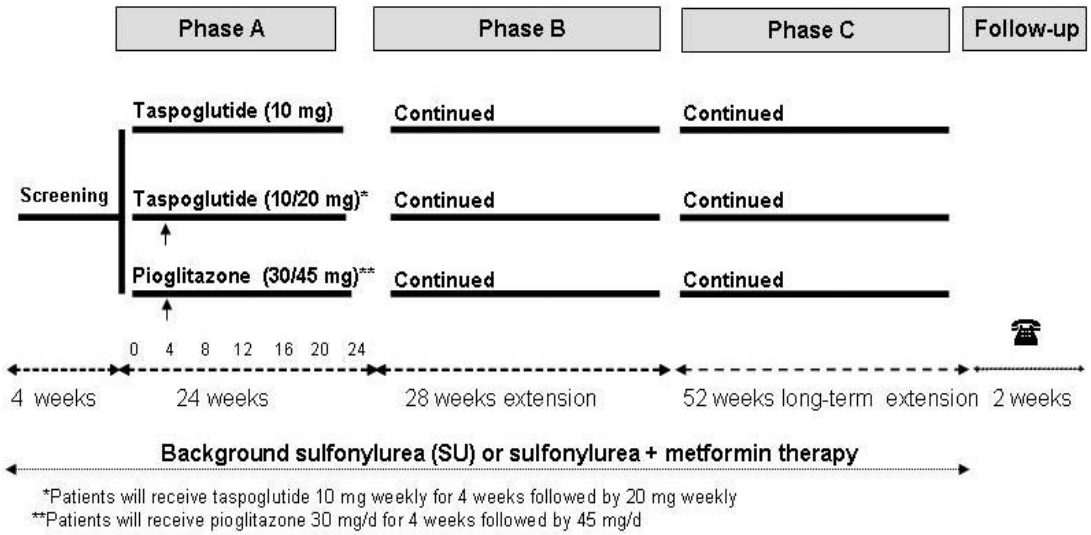
Safety Analyses

Presented in individual patient listings and summary tables as appropriate.

METHODOLOGY:

This was a multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled phase 3 study with a 24-week core phase, a 28-week extension phase, and 52-week long-term (LT) extension phase (see Figure 1). Stratification was based on HbA1c at screening (< 8.0% or ⩾ 8.0) and background diabetes therapy (SU alone or SU + metformin). On day 1 of the core phase, patients were randomized to one of the following three treatment arms: taspoglutide 10 mg QW (plus placebo matching pioglitazone capsules), taspoglutide 20 mg QW (plus placebo matching pioglitazone capsules), or pioglitazone 45 mg QD (plus $ZnCl_2$ injections) in a ratio of 1:1:1, in addition to their continued treatment with SU alone or in combination with metformin. Patients remained on the same study medication that they had been randomized to throughout the study.

Figure 1 Overview of Study Design and Dosing Regimen



EFFICACY RESULTS

Compared with pioglitazone 45 mg QD, treatment with taspoglutide 10 mg or 20 mg QW resulted in a noninferior reduction from baseline in HbA1c at week 24 (based on noninferiority margin of 0.4%) in patients with T2D inadequately controlled with SU with or without metformin therapy. Under closed test procedures, superiority compared to pioglitazone was not achieved at either taspoglutide dose.

Improvement in FPG at week 24 was observed in all groups, and noninferiority to pioglitazone was shown for the 20 mg dose. Superiority to pioglitazone was not achieved for either taspoglutide dose group.

Treatment with taspoglutide resulted in a decrease in body weight of approximately 1 kg at week 24 compared with pioglitazone where a mean increase in body weight of approximately 3.5 kg was seen; the treatment difference was statistically significant for both taspoglutide groups.

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

	Taspoglutide 10 mg N = 240	Taspoglutide 20 mg N = 245	Pioglitazone N = 255
HbA1c (%)			
LS mean	-1.183	-1.363	-1.299
95% CI	(-1.335,-1.031)	(-1.514, -1.211)	(-1.451, -1.146)
Diff from pioglitazone			
LS mean	0.116	0.064	
p-value[a]	0.2133	0.3721	
FPG (mmol/L)			
LS mean	-1.915	-2.139	-2.173
95% CI	(-2.338, -1.491)	(-2.559, -1.720)	(-2.597, -1.750)
Diff from pioglitazone			
LS mean	0.259	0.034	
p-value[a]	0.3904	0.8637	
Body weight (kg)			
LS mean	-0.769	-0.957	3.595
95% CI	(-1.381, -0.158)	(-1.562, -0.352)	(2.985, 4.205)
Diff from pioglitazone			
LS mean	-4.364	-4.552	
p-value[a]	<0.0001	<0.0001	

[a] Adjusted.

SAFETY RESULTS DURING ENTIRE STUDY

The mean total cumulative injection dose of taspoglutide was 397 mg for the taspoglutide 10 mg group (equivalent to approximately 40 weekly injections) and 711 mg for the taspoglutide 20 mg group (equivalent to approximately 38 weekly). The mean total cumulative dose of pioglitazone was 11805 mg (equivalent to approximately 39 weeks of QD dosing).

During the entire study treatment period (core, extension, and LT extension phases), the incidences of overall AEs were similar for the taspoglutide 10 mg and 20 mg groups (92% and 93%, respectively) and pioglitazone group (87%). Gastrointestinal AEs, such as nausea and vomiting, were the most common AEs reported in patients treated with taspoglutide and occurred at a higher frequency in the 10 mg and 20 mg groups (61-62%) than in the pioglitazone group (29%). Injection site-related AEs were also more common in patients receiving taspoglutide injections and oral placebo than in patients treated with oral pioglitazone and weekly $ZnCl_2$ injections. Gastrointestinal AEs are a known side effect of GLP-1 analogues such as taspoglutide. Common AEs that were reported at least twice as frequently in the pioglitazone group than in one or both taspoglutide groups were oedema peripheral, hypertension, weight increased, bronchitis, and pain in extremity.

Adverse events leading to discontinuation of study treatment were more frequent in the taspoglutide groups (19% each) than in the pioglitazone group (6%). This difference was mainly due to a higher occurrence of gastrointestinal AEs, such as nausea and vomiting, hypersensitivity, injection site reactions, and dizziness. Weight increased and oedema peripheral were the most common AEs leading to discontinuation in the pioglitazone group.

The incidence of SAEs during the study was highest in the taspoglutide 10 mg group (11%) and similar for the taspoglutide 20 mg (6%) and pioglitazone (5%) groups. Almost all individual SAEs (preferred terms) reported among patients receiving taspoglutide were reported in no more than one patient.

There were no deaths during the study.

Systemic allergic reactions (predominately hypersensitivity) were more common in the taspoglutide 10 mg (2%) and 20 mg (2%) groups than in the pioglitazone group (< 1%) across the entire study period. All seven reports of hypersensitivity in the taspoglutide groups resulted in treatment withdrawal, and four of these reports were serious.

There were two reports of pancreatitis in patients treated with taspoglutide (both in 10 mg group); both of these events were serious and resulted in discontinuation although neither was associated with a marked abnormality in serum lipase or amylase concentrations.

Prespecified thyroid-related AEs occurred in a similar small number of patients in the taspoglutide (n=2) and pioglitazone (n=2) groups. Neither of the single reports of thyroid neoplasm (nodules) in the taspoglutide 10 mg and pioglitazone groups were malignant.

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 (BLQ, real or ALQ) was reported postbaseline for 50% of patients in the taspoglutide groups.

Table 3 Summary of Adverse Events, Deaths, and Withdrawals During Entire Study (Safety Population)

f_ae24 Protocol(s): BC21893 Analysis: SAFETY POPULATION Center: ALL CENTERS
Phase: LTE

	TASPOGLUTIDE 10 MG N = 243 No. (%)	TASPOGLUTIDE 20 MG N = 251 No. (%)	PIOGLITAZONE N = 257 No. (%)
Total Pts with at Least one AE	223 (91.8)	234 (93.2)	224 (87.2)
Total Number of AEs	1106	1169	1006
Deaths #	0 (0.0)	0 (0.0)	0 (0.0)
Study withdrawals due to an AE #	44 (18.1)	47 (18.7)	14 (5.4)
Patients with at least one			
AE leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	27 (11.1)	15 (6.0)	13 (5.1)
AE leading to withdrawal from treatment	47 (19.3)	48 (19.1)	15 (5.8)

Investigator text for Adverse Events encoded using MedDRA version 14.0.
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 16JUN2011:11:41:18 (1 of 1)

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 comparable to that of pioglitazone 45 mg QD in patients with T2D inadequately controlled with SU therapy with or without metformin. The specified criterion for statistical noninferiority of the two taspoglutide dose groups to pioglitazone was also met for HbA1c.

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