SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC21713)

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 BC21713 - A multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled study to assess the efficacy, safety and tolerability of taspoglutide (RO5073031) compared to sitagliptin and placebo in patients with type 2 diabetes mellitus (T2D) inadequately controlled with metformin. Report No [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	666 patients from 124 centers in 20 countries (Argentina, Australia, Canada, France, Germany, Korea, Mexico, Norway, Peru, Poland, Romania, Spain, Slovakia, South Africa, Sweden, Taiwan, Thailand, Turkey, United Kingdom, USA).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	22 September 2008 to 11 January 2011	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** • to assess the efficacy of taspoglutide on glycemic control (as assessed by glycosylated hemoglobin A1c (HbA1c) in patients with T2D inadequately controlled with metformin compared with sitagliptin and placebo, after 24 weeks of treatment. **Secondary Objectives:** • to determine the effects of taspoglutide on additional parameters of diabetes control, body weight, and cardiovascular risk factors • to assess the safety and tolerability of taspoglutide • 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, double-blind, double-dummy, parallel group, placebo- and active-controlled phase 3 study. Stratification based on HbA1c (HbA1c < 8.0% or ⩾ 8.0%).
NUMBER OF SUBJECTS	Planned: 630 patients (180 per taspoglutide 10 mg, taspoglutide 20 mg, sitagliptin arms and 90 per placebo arm) Actual: 666 patients (93 placebo, 190 taspoglutide 10 mg, 198 taspoglutide 20 mg, 185 sitagliptin)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Diagnosed with T2D, and treated with 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) ⩾ 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.	Sitagliptin 100 mg hard gelatine capsules for oral administration. Batch numbers [redacted] Placebo ($ZnCl_2$) matching taspoglutide 10 mg injections: batch numbers [redacted] Placebo ($ZnCl_2$) matching taspoglutide 20 mg injections: batch numbers [redacted] Placebo matching sitagliptin capsules: batch numbers [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Sitagliptin: Once daily (QD) oral administration of 100 mg. Placebo matching sitagliptin: QD oral administration. Placebo matching taspoglutide: QW subcutaneous injection.

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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 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 24-week core phase: • adverse events (AEs), laboratory tests, vital signs, and 12-lead electrocardiogram (ECG), Safety during 28-week extension phase (placebo switch groups): • AEs, laboratory tests, and anti-taspoglutide antibodies Safety during the entire study period (24-week core phase, 28-week extension phase, and 104-week long-term [LT] extension phase) for the continuous treatment groups (i.e., subjects randomly assigned to taspoglutide or sitagliptin groups): • AEs, laboratory tests, vital signs, and 12-lead 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 sitagliptin 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 sitagliptin. 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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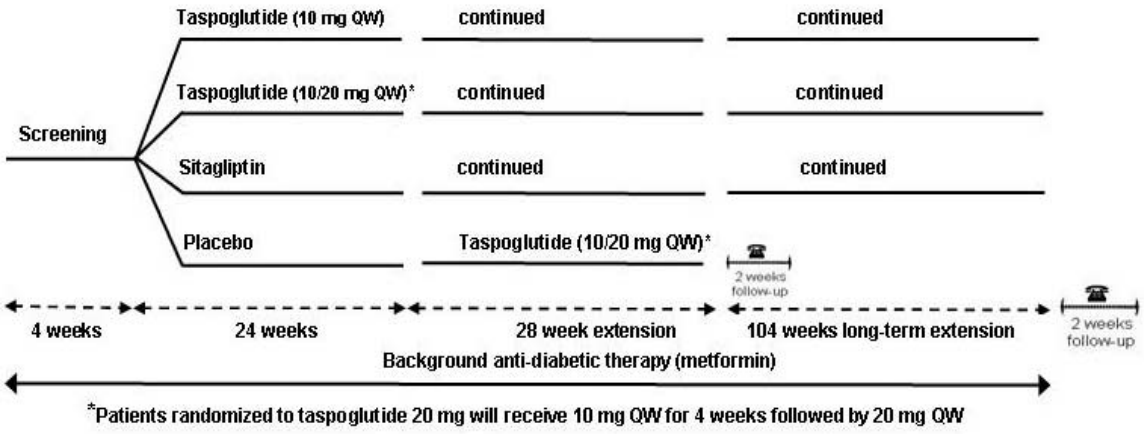
METHODOLOGY:

This was a multicenter, randomized, parallel group double-blind, double-dummy, placebo- and 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 2:2:2:1 ratio to receive either taspoglutide 10 mg QW (plus placebo matching sitagliptin capsules), taspoglutide 20 mg QW (plus placebo matching sitagliptin capsules), sitagliptin 100 mg QD (plus $ZnCl_2$ injections), or placebo (capsules matching sitagliptin plus $ZnCl_2$ injections) in addition to their continued treatment with metformin. Patients in the taspoglutide or sitagliptin treatment groups remained on the same study medication that they had been randomized to throughout the study. At the end of the core phase, patients assigned to the placebo group were switched to taspoglutide ('placebo switch patients'), with approximately one-half of the placebo patients receiving taspoglutide 10 mg and the other half receiving taspoglutide 20 mg during the extension phase. Participation in the 104-week LT extension phase was voluntary and limited to those who completed the core and extension phases in the taspoglutide or sitagliptin groups. Patients were required to sign a separate informed consent if they elected to continue treatment in the LT extension phase.

Figure 1 Overview of Study Design and Dosing Regimen



EFFICACY RESULTS

Results of the changes from baseline at week 24 in HbA1c, FPG, and body weight are shown for each treatment group in Table 1. 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 noninferior to that for patients treated with sitagliptin, using the pre-established limit of 0.4% in patients with T2D receiving background therapy with metformin. Furthermore, under closed test procedures, superiority was also achieved for both of the taspoglutide doses relative to sitagliptin. 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 (using the noninferiority limit of 3 kg) and superiority was established for both doses of taspoglutide to sitagliptin.

The efficacy responses at Week 24 for the taspoglutide groups compared with sitagliptin 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)

	Placebo N=90	Taspoglutide 10 mg N = 182	Taspoglutide 20 mg N=187	Sitagliptin 100 mg N=177
HbA1c (%)				
LS mean	-0.100	-1.231	-1.300	-0.889
95% CI	(-0.255,0.054)	(-1.341, -1.121)	(-1.410, -1.191)	(-1.001, -0.778)
Diff from placebo				
LS mean		-1.131	-1.220	
p-value[a]		<0.0001	<0.0001	
Diff from sitagliptin				
LS mean		-0.342	-0.411	
p-value[a]		<0.0001	<0.0001	
FPG (mmol/L)				
LS mean	-0.074	-2.159	-2.335	-1.351
95% CI	(-0.465, 0.316)	(-2.437, -1.880)	(-2.612, -2.058)	(-1.634, -1.067)
Diff from placebo				
LS mean		-2.085	-2.261	
p-value[a]		<0.0001	<0.0001	
Diff from sitagliptin				
LS mean		-0.808	-0.984	
p-value[a]		<0.0001	<0.0001	
Body weight (kg)				
LS mean	-0.488	-1.837	-2.565	-0.891
95% CI	(-1.259, 0.283)	(-2.386, -1.289)	(-3.115, -2.015)	(-1.449, -0.334)
Diff from placebo				
LS mean		-1.349	-2.077	
p-value[a]		0.0036	<0.0001	
Diff from sitagliptin				
LS mean		-0.946	-1.674	
p-value[a]		0.0127	<0.0001	

[a] Adjusted.

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

During the 24-week core phase, the incidences of overall AEs and AEs leading to withdrawal were higher in the taspoglutide 10 mg and 20 mg groups than in the placebo or sitagliptin groups (Table 2). The higher incidences in the taspoglutide groups were mainly due to a higher occurrence of gastrointestinal AEs such as nausea and vomiting, decreased appetite, and injection site reactions.

The incidence of SAEs during the 24-week core phase was similar in each active treatment group and higher than that in the placebo group. No individual SAE (preferred term) occurred in more than one patient per treatment group.

There were no deaths, no reports of pancreatitis, and no reports of thyroid neoplasm during the 24-week core phase. Systemic allergic reactions, consisting mainly of hypersensitivity, were reported in a similar percentage of patients in the taspoglutide 10 mg or 20 mg groups and sitagliptin group (1-2%). No systemic allergic reactions were reported during the core phase in patients in the placebo group.

No clinically relevant effects of taspoglutide were observed on laboratory parameters, ECG parameters, or vital signs measured at week 24.

Table 2 Summary of Adverse Events, Deaths, and Withdrawals During Double-blind Core Phase (Week 24 Safety Population)

Protocol(s): BC21713 Analysis: SAFETY POPULATION Center: ALL CENTERS Phase: Core

	Placebo N = 93 No. (%)	Taspoglutide 10 mg N = 187 No. (%)	Taspoglutide 20 mg N = 192 No. (%)	Sitagliptin N = 184 No. (%)
Total Pts with at Least one AE	60 (64.5)	149 (79.7)	166 (86.5)	119 (64.7)
Total Number of AEs	147	479	626	310
Deaths #	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study withdrawals due to an AE #	4 (4.3)	32 (17.1)	31 (16.1)	3 (1.6)
Patients with at least one				
AE leading to Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	2 (2.2)	11 (5.9)	8 (4.2)	10 (5.4)
AE leading to withdrawal from treatment	6 (6.5)	34 (18.2)	35 (18.2)	5 (2.7)

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' also includes patients who completed the Core Phase but then shortly
thereafter discontinued treatment due to an AE which was ongoing at the time of Core Phase completion, patients who terminated early due to Insufficient Therapeutic Response and patients who Withdrew Consent.
AEs which began on the first day of the Extension Phase are excluded.
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SAFETY RESULTS IN THE EXTENSION PHASE (WEEKS 24 TO 52) – PLACEBO SWITCH PATIENTS:

At the end of the 28-week extension phase, 69% patients in the placebo switch taspoglutide 10 mg group and 72% patients in the placebo switch taspoglutide 20 mg group reported one or more AEs. The most frequently reported AEs were gastrointestinal disorders (mainly nausea and vomiting) and injection site reactions. AEs leading to withdrawal were reported for 11% of patients in both placebo switch groups.

During the extension phase, there was a single death due to an unrelated injury (placebo/taspoglutide 20 mg group), two other patients with SAEs assessed as unrelated to study treatment, and one report of hypersensitivity that was severe and resulted in treatment withdrawal (placebo/taspoglutide 10 mg group). There were no reports of pancreatitis or thyroid neoplasm in placebo switch patients during the extension phase, although one patient in the placebo/taspoglutide 20 mg group had blood calcitonin increased reported as an AE.

SAFETY RESULTS DURING ENTIRE STUDY: CONTINUOUS TREATMENT PATIENTS

During the entire study treatment period (core, extension, and LT extension phases), the overall incidence of AEs was higher for the taspoglutide 20 mg group than for the taspoglutide 10 mg or sitagliptin groups (Table 3). While gastrointestinal disorders were among the most frequently reported AEs in all three continuous treatment groups, these were reported at a higher rate in the taspoglutide groups (68% and 70% in 10 and 20 mg groups, respectively) than in the sitagliptin group (37%). This treatment difference was due to higher reporting rates in the taspoglutide groups for gastrointestinal AEs (e.g., nausea, vomiting, diarrhea, dyspepsia, constipation, and gastroesophageal reflux disease) and injection site reactions. Infection-related AEs (e.g., nasopharyngitis and upper respiratory tract infection) were more common with sitagliptin treatment (45%) than with taspoglutide (35% and 34% in 10 mg and 20 mg groups, respectively).

No clear difference in incidence of SAEs was observed between sitagliptin and taspoglutide-treated patients across the entire study period (Table 3). There was one death in a continuous treatment patient (taspoglutide 20 mg group) due to cerebral ischemia that was assessed by the investigator to be due to the patient's underlying chronic obstructive pulmonary disease and not

related to study treatment.

More patients in the taspoglutide 10 mg and 20 mg groups had an AE(s) that led to withdrawal compared with sitagliptin group (Table 3). The higher incidence of AEs leading to withdrawal in the taspoglutide groups was primarily due to more patients in these groups discontinuing due to gastrointestinal AEs (mainly nausea and vomiting), hypersensitivity, and injection-site reaction AEs.

Systemic allergic reactions (predominately hypersensitivity) were more common in the taspoglutide 10 mg (4%) and 20 mg (7%) groups than in the sitagliptin group (<1%) across the entire study period. None of the systemic allergic reaction was serious, although most resulted in treatment withdrawal.

There were no reports of pancreatitis in any patient treated with taspoglutide or sitagliptin during the study. Prespecified thyroid neoplasm-related AEs occurred at a similar rate in the taspoglutide 10 mg (2%), 20 mg (1%), and sitagliptin (2%) groups. The majority of these AEs consisted of the reported laboratory abnormality, increased blood calcitonin, and goiter. There were three reports of thyroid neoplasm (i.e., nodules), one in the taspoglutide 20 mg group and two in the sitagliptin group. The thyroid nodules in the taspoglutide group were too small to biopsy.

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 post-baseline for 46% of patients in the taspoglutide groups.

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

f_ae24_u Protocol(s): BC21713
Analysis: SAFETY POPULATION Center: ALL CENTERS Phase: LTE

	TASPOGLUTIDE 10 MG N = 187 No. (%)	TASPOGLUTIDE 20 MG N = 192 No. (%)	SITAGLIPTIN N = 184 No. (%)
Total Pts with at Least one AE	160 (85.6)	183 (95.3)	149 (81.0)
Total Number of AEs	737	931	643
Deaths #	1 (0.5)	0 (0.0)	0 (0.0)
Study withdrawals due to an AE #	51 (27.3)	71 (37.0)	11 (6.0)
Patients with at least one			
AE leading to Death	1 (0.5)	0 (0.0)	0 (0.0)
Serious AE	18 (9.6)	18 (9.4)	19 (10.3)
AE leading to withdrawal from treatment	52 (27.8)	69 (35.9)	13 (7.1)

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.
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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 sitagliptin 100 mg QD in patients with T2D inadequately controlled with metformin. Both noninferiority and superiority of both doses of taspoglutide versus sitagliptin 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), hypersensitivity, injection site

reactions, and AEs leading to withdrawal when compared with sitagliptin-treated patients. The treatment difference in AEs leading to withdrawal was primarily due to higher rates of discontinuation due to gastrointestinal-related AEs, hypersensitivity, and injection-site reactions. No clinically relevant adverse effects of taspoglutide or sitagliptin were identified on laboratory safety parameters, vital signs or ECGs.