SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC22092)

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 BC22092 - A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of taspoglutide (RO5073031) compared to placebo in obese patients with type 2 diabetes mellitus (T2D) inadequately controlled with metformin monotherapy. Report No. [redacted]. May 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	63 centers in 8 countries (Canada, Germany, Italy, Macedonia, Poland, Russia, United Kingdom, USA)		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL (first patient randomized to last patient last observation)	2 April 2009 to 19 May 2010	CLINICAL PHASE	3
OBJECTIVES	Primary: • To assess the efficacy of taspoglutide on glycemic control (as assessed by HbA1c) in obese patients with T2D inadequately controlled with metformin monotherapy compared to placebo after 24 weeks of treatment. Secondary: • To assess the effects of taspoglutide versus placebo on body weight. • To assess the effects of taspoglutide versus placebo on additional parameters of diabetes control and cardiovascular risk factors including lipid profile. • 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. *Data are not reported.*		
STUDY DESIGN	Multicenter, randomized, double-blind, parallel group, placebo-controlled phase 3 study. Stratification based on BMI (<40 or ⩾40 kg/m²).		
NUMBER OF SUBJECTS	Planned: 260 patients (130 per treatment arm)		

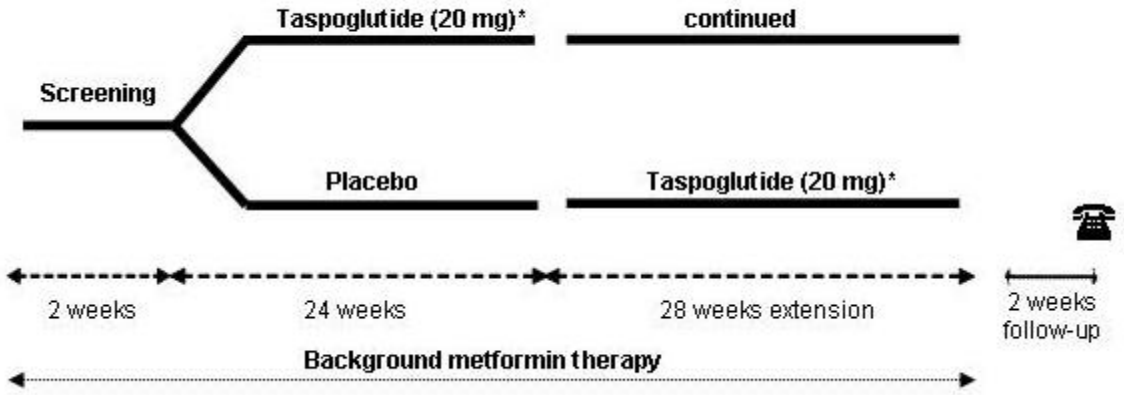
	Actual: 305 patients (151 placebo, 154 taspoglutide 20 mg)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The target population was obese male and female patients with T2D whose disease was not adequately controlled with metformin monotherapy. Key inclusion criteria were: • Aged 18 to 75 years at screening. Women of childbearing potential had to use one medically approved method of contraception during the course of the trial. • Stable dose of metformin ⩾ 1500 mg/day (or individually maximally tolerated dose) for at least 12 weeks prior to screening. • HbA1c: ⩾ 6.5% and ⩽ 9.5% at screening. • BMI ⩾30 and ⩽50 kg/m2 at screening. • Stable weight ± 5% for at least 12 weeks prior to screening. • Agreement to follow a diet and exercise plan during the course of the study.
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	Taspoglutide 20 mg QW. Once weekly (QW) subcutaneous injection of taspoglutide in the abdomen before breakfast. 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 20 mg received QW injections throughout the 52-week treatment period.
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	Placebo QW QW subcutaneous injection in the abdomen before breakfast; 100 µL for the first 4 weeks then 200 µL thereafter. Patients randomized to placebo received placebo during the 24-week core phase and switched to taspoglutide 20 mg QW from week 25 onwards.
CRITERIA FOR EVALUATION	
EFFICACY:	Primary endpoint: • the absolute change from baseline in HbA1c (%) at week 24

	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 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	<u>Efficacy</u> 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 two 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. <u>Safety Analyses</u> 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 period), a 28-week open-label extension (extension phase), and a follow-up phone call (Figure 1). On day 1 of the core phase, eligible patients were randomized in a 1:1 ratio to receive either taspoglutide 20 mg QW (after 4 weeks of taspoglutide 10 mg QW) or placebo QW, both in addition to background metformin treatment, for 24 weeks. At the end of week 24, patients in the taspoglutide 20 mg group continued taking the same dose of taspoglutide for a further 28 weeks ('continuous treatment patients') whereas patients in the placebo group were switched to taspoglutide 20 mg QW for the remainder of the study ('placebo switch patients').

Figure 1 Overall Study Design



*Patients received taspoglutide 10 mg QW for the first 4 weeks followed by 20 mg QW.

EFFICACY RESULTS:

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

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

	Placebo N=143	Taspoglutide 20 mg N=149
HbA1c (%)		
LS mean	-0.087	-0.806
95% CI	-0.205, 0.030	-0.921, -0.690
Diff from placebo		
LS mean		-0.718
p-value [a]		<0.0001
FPG (mmol/L)		
LS mean	0.005	-1.310
95% CI	-0.353, 0.362	-1.660, -0.959
Diff from placebo		
LS mean		-1.314
p-value [a]		<0.0001
Body weight (kg)		
LS mean	-1.854	-3.162
95% CI	-2.462, -1.247	-3.758, -2.566
Diff from placebo		
LS mean		-1.307
p-value [a]		0.0027

a Unadjusted.

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

During the 24-week double-blind core treatment period, the incidences of overall AEs (59% vs. 79% in placebo and taspoglutide 20 mg groups, respectively) and of AEs leading to withdrawal (3% vs. 15%, respectively) were higher in the taspoglutide 20 mg group than in the placebo group (Table 1). The higher incidences in the taspoglutide group were mainly due to a higher occurrence of gastrointestinal AEs such as nausea and vomiting, as well as injection site reactions such as erythema, nodules, and pruritus. The incidence of hypoglycemia (3% vs. 10%, respectively) was also higher in the taspoglutide 20 mg group, but most cases were mild or moderate, resolved without sequelae, did not lead to withdrawal from treatment, and were considered to be unrelated to study treatment.

SAEs were reported for 6/150 (4%) patients in the placebo group and 10/154 (7%) patients in the taspoglutide group. No individual SAE (preferred term) occurred in more than one patient. Only one SAE in the taspoglutide group, a severe anaphylactic reaction, was considered to be related to treatment. The reaction, which led to withdrawal from treatment, resolved without sequelae following treatment with prednisone.

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 taspoglutide-treated patients, and no reports of pancreatitis or thyroid tumors. The one death in the study occurred in the placebo group.

Table 1 Summary of Adverse Events, Deaths, and Withdrawals – Double-blind Core Period (Week 24, Safety Population)

ae24 Summary of Adverse Events, Deaths and Withdrawals
Protocol(s): BC22092
Analysis: SAFETY POPULATION Center: ALL CENTERS
Phase: Core

	Placebo N = 150 No. (%)	Taspoglutide 20 mg N = 154 No. (%)
Total Pts with at Least one AE	89 (59.3)	122 (79.2)
Total Number of AEs	231	472
Deaths #	1 (0.7)	0 (0.0)
Study withdrawals due to an AE #	4 (2.7)	20 (13.0)
Patients with at least one		
AE leading to Death	1 (0.7)	0 (0.0)
Serious AE	6 (4.0)	10 (6.5)
AE leading to withdrawal from treatment	5 (3.3)	23 (14.9)

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, a patient who withdrew consent, and a patient who died.
AEs which began on the first day of the Extension Phase are excluded.
AE24 08FEB2010:22:04:15 (1 of 1)

SAFETY RESULTS UP TO WEEK 52 – CONTINUOUS TREATMENT PATIENTS

At week 52, 139/154 (90%) patients in the taspoglutide 20 mg continuous treatment safety population had experienced at least one AE, 13 (8%) patients had experienced an SAE and 29 (19%) patients had experienced an AE that led to premature withdrawal from treatment. As observed at week 24, the most frequently reported individual AEs at week 52 included gastrointestinal disorders (nausea, vomiting and diarrhea), injection site reactions (nodules, erythema, and pruritus), and hypoglycemia. The majority of patients who experienced at least one gastrointestinal or injection site AE experienced their first event during the 24-week core period.

A total of 53/140 (38%) continuous treatment patients had at least one confirmed positive anti-taspoglutide antibody result post-baseline. 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 tumors.

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

The safety profile of taspoglutide in the placebo switch patients during the 28 week open label extension phase was similar to that observed in the taspoglutide 20 mg group during the 24-week double-blind core phase. The incidences of overall AEs, SAEs and of AEs leading to withdrawal were 74% (100/136 patients), 2% (2 patients), and 14% (19 patients), respectively. As observed in the taspoglutide 20 mg group, the most frequently reported individual AEs were nausea (37%), vomiting (24%) and injection site reactions such as nodules (10%) and pruritus (10%).

A total of 42/126 (33%) placebo switch patients had a confirmed positive anti taspoglutide antibody result after receiving taspoglutide for up to 28 weeks.

CONCLUSIONS:

After 24 weeks of treatment, the efficacy of taspoglutide 20 mg QW (as assessed by the absolute change from baseline in HbA1c) was shown to be superior to that of placebo in obese patients with T2D inadequately controlled with metformin. Treatment with taspoglutide 20 mg also resulted in clear improvements compared to placebo in FPG concentrations and body weight.

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.