SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NC25113)

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 NC25113 - A randomized double blind, placebo-controlled clinical trial to assess the effects of taspoglutide (RO5073031) on cardiovascular outcomes in subjects with inadequately controlled type 2 diabetes (T2D) and established cardiovascular (CV) disease. 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	249 centers in 23 countries (Australia, Brazil, Bulgaria, Canada, Czech Republic, Denmark, Estonia, Germany, Hungary, India, Israel, Lithuania, Malaysia, Mexico, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, Ukraine, United Kingdom, United States, US)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	22 December 2009 to 13 December 2010	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** The primary objective of the study was to determine the effect of taspoglutide in addition to standard of care on CV outcomes in T2D patients with established CV disease in order to rule out an unacceptable (80%) increase in CV events. The primary endpoint of the study was the time to first occurrence of any component of a CV composite endpoint (CV death, myocardial infarction (MI), stroke, or hospitalization for unstable angina) adjudicated by an independent CV Event Adjudication Committee (CV-EAC). **Secondary Objectives:** • To assess the effects of taspoglutide versus placebo added on to standard of care on:: – a secondary CV composite endpoint comprised of time to first occurrence of CV death, acute MI, or stroke – time to first occurrence of each of the individual components of the composite primary endpoint: CV death, acute MI, stroke or hospitalization for unstable angina (*Data are not reported*).		

	– total mortality (*Data are not reported*). • To assess the effects of taspoglutide vs. placebo added on to standard of care on the following tertiary endpoints: – Time to first occurrence of the composite endpoint comprised of: CV death, acute MI, stroke, hospitalization for unstable angina, resuscitated cardiac arrest and hospitalization for heart failure (*Data are not reported*) – Time to first occurrence of the composite endpoint comprised of the primary composite endpoint plus any revascularization procedure (*Data are not reported*) – Time to first occurrence of the composite endpoint comprised of the primary composite endpoint plus any coronary revascularization procedure (*Data are not reported*). • To assess the effects of taspoglutide vs. placebo added on to standard of care on the following exploratory endpoints: – Metabolic and renal function parameters (*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%), age (< 60 or ≥ 60 years), and country.
NUMBER OF SUBJECTS	Planned: 2000 patients (1000 per treatment arm) Randomized: 2118 patients (1061 placebo, 1057 taspoglutide 20 mg) Randomized, Treated: 2010 patients (1057 placebo, 1053 taspoglutide 20 mg)

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Diagnosed with T2D, and receiving standard treatment for T2D (diet and/or any approved glucose-lowering therapies, except for current treatment with exenatide or exendin-4 analogues, GLP-1 or GLP-1 analogues, and insulin or insulin analogues (latter given for more than 7 consecutive days within the 12-week period prior to screening). • Male and female patients ≥ 18 years of age at screening. • HbA1c ≥ 6.5% and ≤ 10.0 % at screening. • Body mass index (BMI) ⩾ 23 kg/m^2 at screening. • Established CV disease, with an onset ⩾ 1 month prior to screening (acute coronary syndromes such as unstable angina and/or acute MI with onset > 2 months prior to screening) that was stable in the investigator's opinion based on the presence of at least one of the following: documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease.
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/[redacted] – batch numbers [redacted] • taspoglutide 20 mg (200 µL) - Ro 507-3031/[redacted] – batch numbers [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Once weekly (QW) subcutaneous (SC) injection of taspoglutide in the abdomen. Taspoglutide 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.	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/[redacted] – batch number [redacted] • placebo to taspoglutide 20 mg (200 µL): Ro 507-3031/[redacted] – batch number [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Patients randomized to placebo received QW SC injections in the abdomen.

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CRITERIA FOR EVALUATION	
EFFICACY:	Percentage of subjects with adjudicated major adverse CV events (MACE), comprised of CV death, non-fatal acute myocardial infarction, and non-fatal stroke, and MACE+, defined as MACE events plus hospitalization for unstable angina. *Since Study NC25113 was terminated prematurely before the planned number of CV events occurred, no analyses of the pre-specified primary or secondary CV endpoints were performed.*
PHARMACODYNAMICS:	Not applicable.
PHARMACOKINETICS:	Not applicable.
SAFETY:	Adverse events (AEs), laboratory tests, vital signs, and 12-lead electrocardiogram (ECG), anti-taspoglutide antibodies.
STATISTICAL METHODS	All data presented in individual patient listings and summary tables as appropriate.

METHODOLOGY:

The study consisted of a screening period, a double-blind placebo-controlled treatment period, and a follow-up phone call. Patients with positive anti-taspoglutide antibodies at the termination of the study and those who experienced a systemic allergic reaction had to perform a safety follow-up visit 8 weeks after the end-of-study visit instead of the telephone visit. The duration of the treatment period was event driven, with double-blind treatment to have continued until the pre-specified number of primary CV events had occurred. On day 1 of the treatment period, patients were randomized in a 1:1 ratio to receive either taspoglutide 20 mg or placebo matching taspoglutide. Both double-blind study treatments were administered once weekly (QW) in addition to standard of care treatment for T2D and CV disease. The dose of the background therapy(ies) could be modified by the investigator at any time during throughout the study, if clinically warranted, including initiation of additional medications or discontinuation of existing background medication(s), consistent with local standard of care.

All available, relevant information on reported CV events occurring in patients enrolled in this study were systematically and objectively reviewed by the CV-EAC to determine if the event(s) met the pre-defined criteria to be classified a CV event. The CV-EAC was blinded to the identity of the study treatment throughout their data review process. The final decision concerning each event was communicated to the sponsor. The CV-EAC was comprised of four physicians who had expertise in the diagnosis and treatment of CV, diabetes, and neurological disorders and are experienced in the medical aspects of clinical trials.

No patient completed this study as it was terminated early by the sponsor. The majority of subjects in both treatment groups completed 8 weeks of study treatment (676/1057, 64% placebo; 607/1053, 58% taspoglutide). Only a small minority of patients in the placebo (5%) and taspoglutide (3%) groups received more than 24 QW injections. Patients who were discontinued from study treatment prematurely were encouraged to remain in the study for continued assessment of CV events. Approximately one-half of subjects in each treatment group (50% placebo; 48% taspoglutide) remained in the study through Week 16; 14 patients (2/1057 placebo, 12/1053 taspoglutide) remained in the study through Week 36.

The mean cumulative dose of taspoglutide was 155.0 mg (equivalent to approximately 10 weekly injections (≈ 4 weekly injections of 10 mg; ≈ 6 weekly injections of 20 mg].

ADJUDICATED CARDIOVASCULAR EVENTS RESULTS:

Based on the CV events onset, a summary of the first adjudicated MACE and MACE+ CV events reported during the study is provided in Table 1; for patients with multiple events, only the first event is included in this table. Two patients in the placebo group had more than one adjudicated CV event (acute myocardial infarction followed by CV death; stroke followed by CV death). Few adjudicated CV events were reported during the double-blind study period, and there was no difference in the number of patients with MACE+ events for the taspoglutide 20 mg and placebo groups.

Table 1 Summary of Adjudicated MACE and MACE+ by Study Treatment Safety Population)

Protocol: E8; Analysis: Safety Population

MACE+	PLACEBO (N=1057)	TASPOGLUTIDE 20 MG (N=1053)
CV death*	3 (0.28%)	3 (0.28%)
Acute Myocardial Infarction*	4 (0.38%)	5 (0.48%)
Stroke*	2 (0.18%)	2 (0.18%)
Hospitalization for unstable angina**	2 (0.18%)	1 (0.10%)

Note: Some patients had multiple adjudicated events.Only their first event is summarized in this table.
*MACE (defined as CV death, non-fatal acute myocardial infarction or non-fatal stroke).
**MACE+ (defined as MACE plus hospitalization for unstable angina).

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SAFETY RESULTS:

An overview of the safety profile in the taspoglutide 20 mg and placebo groups is presented in Table 2.

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

Protocol(s): NC25113; Analysis: SAFETY POPULATION Center: ALL CENTERS

	PLACEBO N = 1057 No. (%)	TASPOGLUTIDE 20 MG N = 1053 No. (%)
Total Pts with at Least one AE	373 (35.3)	591 (56.1)
Total Number of AEs	730	1497
Deaths #	5 (0.5)	4 (0.4)
Study withdrawals due to an AE #	3 (0.3)	27 (2.6)
Patients with at least one		
AE leading to Death	5 (0.5)	4 (0.4)
Serious AE	45 (4.3)	49 (4.7)
AE leading to withdrawal from treatment	25 (2.4)	151 (14.3)

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.
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During the double-blind treatment period, the incidences of overall AEs (35% placebo vs. 56% taspoglutide 20 mg) and of AEs leading to withdrawal (2% vs. 14%) were higher in the

taspoglutide groups than in the placebo group. The higher incidences of AEs in the taspoglutide groups were mainly due to a higher occurrence of gastrointestinal AEs such as nausea and vomiting, hypoglycemia, and decreased appetite. About two-thirds of the AEs that led to discontinuation of treatment in the taspoglutide 20 mg group were gastrointestinal-related; other common AEs that led to discontinuation in this treatment group were injection-site reaction or injection site hypersensitivity.

No difference in the incidences of deaths and non-fatal SAEs was observed between placebo and taspoglutide-treated patients. Each of the nine deaths (five placebo, four taspoglutide), except for one in the taspoglutide 20 mg group, were adjudicated CV deaths. The non-CV death was due to pneumonia. None of the deaths were assessed by the investigator to be related to study treatment.

A total of 94 patients experienced an SAE; 45 (4%) in the placebo group and 49 (5%) in the taspoglutide 20 mg group. As expected in a population with T2D and established CV disease, the most common SAEs in both groups were CV-related ('Cardiac Disorders' plus stroke-related AEs) (22/51 SAEs in placebo group; 30/58 SAEs in taspoglutide group. Most SAEs in both treatment groups were assessed by the investigator as not related to study treatment.

Systemic allergic reactions occurred in a total of seven patients (2 placebo, 5 taspoglutide 20 mg); none were serious. Pancreatitis was reported for two patients in the taspoglutide 20 mg group, both of which were classified as serious and resulted in discontinuation in accord with the protocol. Higher mean changes from baseline in amylase and lipase were observed in the taspoglutide 20 mg group compared with the placebo group. There were no reports of pancreatic cancer.

Three patients in the taspoglutide 20 mg group and two in the placebo group had laboratory abnormalities of blood calcitonin increased, and one patient in each group had a benign thyroid mass (goiter in taspoglutide group). There were no reports of malignant thyroid neoplasm in this study.

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

Of the 1026 patients with a post-baseline test result, 126 (12%) had at least one confirmed positive anti-taspoglutide antibody test result. For 51 patients (5%), the confirmed positive result post-baseline was greater than 230 ng·eq/mL. The percentage of patients with confirmed positive anti-taspoglutide antibody results was 1% (8/1024 patients) at Week 4, 9% (66/697 patients) at Week 12, 26% (99/384 patients) at Week 24, and 36% (20/56 patients) at Week 36.

CONCLUSIONS:

In a patient population characterized by T2D and established CV disease followed for up to 36 weeks, once-weekly administration of taspoglutide 20 mg resulted in reporting rates of adjudicated outcomes of CV death, acute MI, stroke, or hospitalization due to unstable angina which were comparable to those with placebo plus standard of care for T2D.

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). No clinically relevant adverse effects of taspoglutide were identified on laboratory safety parameters, vital signs or ECGs.