SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC20965)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: Taspoglutide NAME OF ACTIVE SUBSTANCE(S): Glucagon-like peptide-1 analoque	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A multi-center, randomized, open-label, active-controlled study to compare the efficacy, safety and tolerability of taspoglutide (RO5073031) versus insulin glargine in insulin-naive type 2 diabetic patients inadequately controlled with metformin and sulphonylurea combination therapy/[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	1049 patients from 186 centers in 25 countries (Austria, Australia, Belgium, Brazil, Canada, Czech Republic, Finland, France, Germany, Great Britain, Greece, Hong Kong, Hungary, Italy, Mexico, New Zealand, Peru, Portugal, Poland, Republic of Korea, Russia, Serbia/Montenegro, Spain, Thailand, USA)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL (first patient screened to last patient last visit)	9 October 2008 to 15 December 2010	CLINICAL PHASE	3
OBJECTIVES	**Primary objective:** • To demonstrate the non-inferiority of taspoglutide to insulin glargine on glycemic control (as assessed by HbA1c) after 24 weeks of treatment. **Secondary objectives:** • To assess the effects of taspoglutide versus insulin glargine on additional parameters of glycemic control after 24 weeks. • To assess the effects of taspoglutide versus insulin glargine on body weight and cardiovascular (CV) risk factors (lipid profile) after 24 weeks. • To assess the safety and the tolerability of taspoglutide versus insulin glargine after 24 weeks.		

	• To assess the efficacy, safety, and tolerability of taspoglutide of taspoglutide versus insulin glargine after 52 and 156 weeks. • To describe the pharmacokinetics of taspoglutide using a population PK approach including the influence of covariates on the PK parameters of taspoglutide after 24 weeks. Due to the termination of the clinical development program for taspoglutide, only key efficacy results from the 24 week open-label active controlled core period and data from the 28 week extension period (52 weeks) are presented in this report. For the long term extension period, the focus was on safety data up to LPLV only.
STUDY DESIGN	Multi-center, randomized, open-label, parallel group, active-controlled study. Stratification will be based on HbA1c (HbA1c < 8.0% or ≥ 8.0%).
NUMBER OF SUBJECTS	Planned: 990 patients randomized into three active arms (330:330:330) Actual: 1049 patients (367 taspoglutide 10 mg, 350 taspoglutide 20 mg, 332 insulin glargine)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	1. Diagnosed with T2D and treated with a stable dose of metformin and sulphonylurea (including immediate or extend-release fixed combination) for at least 12 weeks prior to screening. The dose of metformin must be ≥ 1500 mg/day (or individual maximally tolerated dose), but no more than the maximum dose specified in the label; sulphonylurea can be at any dose. 2. Agreement that the sulphonylurea treatment must be stopped 5 days (+/- 1 day) before the start of the treatment period (Day 1). 3. Men and women aged 18 - 75 years at screening. 4. HbA1c: ≥ 7.0% and ≤ 10% at screening. 5. Fasting serum C-peptide ≥ 1 ng/mL (≥ 333 pmol/L). 6. Body mass index (BMI) ≥ 25 (> 23 for Asians) and ≤ 45 kg/m^2 at screening. 7. Stable weight ± 5% for at least 12 weeks prior to screening.
TRIAL DRUG / STROKE (BATCH) No.	Taspoglutide: provided in 10% sustained release formulation of taspoglutide for subcutaneous injection via a pre-filled syringe: • Taspoglutide 10 mg: batch numbers [redacted] • Taspoglutide 20 mg: [redacted]

DOSE / ROUTE / REGIMEN / DURATION	Sustained release formulation of taspoglutide for once weekly (QW) subcutaneous injection in the abdomen before breakfast via a pre-filled syringe: • Taspoglutide 10 mg QW for the entire duration of the study; • Taspoglutide 10 mg QW for 4 weeks, followed by 20 mg QW for the rest of the study.
REFERENCE DRUG / STROKE (BATCH) No.	Insulin glargine, self-administered once daily via a multi-dose pen as a subcutaneous injection in the abdomen, thigh, or upper arm. Batch: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Insulin glargine will be self-administered once daily by subcutaneous injection in the abdomen, thigh, or upper arm at bedtime. The starting dose for insulin-naive subjects will be 10 IU/day and will be titrated to a FPG ≤ 110 mg/dL (6.1 mmol/L)
CRITERIA FOR EVALUATION	
EFFICACY:	Key endpoints were assessed at the end of the 24 weeks treatment period and at the end of the 52 weeks treatment period. **Primary endpoint** • Absolute change from baseline in HbA1c. **Secondary endpoints** • Absolute and percentage change from baseline in fasting plasma glucose (FPG). • Absolute and percentage change from baseline in body weight. 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, an the LT extension up to final visit) include: Adverse events, vital signs, physical examination, clinical laboratory tests, ECG, fundus oculi, and anti-taspoglutide antibodies (only in patients randomized to taspoglutide).
STATISTICAL METHODS	**Efficacy** Analysis of variance will be used to assess possible differences in the absolute change in HbA1c (%), FPG, and body weight between the different treatment groups at Week 24 and Week 52. An assessment of non-inferiority of each taspoglutide group to the insulin glargine group was to be made using non-inferiority limits of 0.4% for the treatment difference in the mean change from baseline in HbA1c. 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** Presented in individual patient listings and summary tables as appropriate.

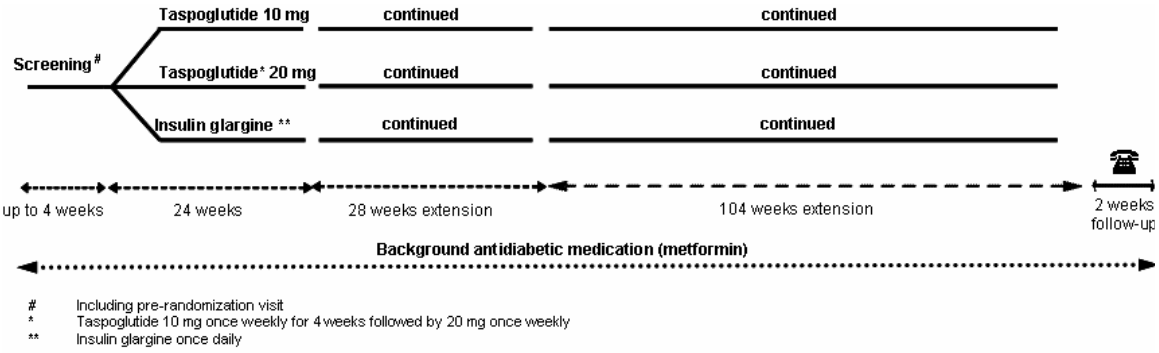
METHODOLOGY:

This was a multi-center, randomized, open-label, parallel group, active-controlled, phase 3 study originally consisting of five phases (Figure 1):

1. **Screening period** (up to 4 weeks, including a prerandomization visit). During this period, eligible patients discontinued sulphonylurea treatment 5 days (+/- 1 day) before randomization.
2. **Core treatment period (24-week open-label active-controlled):** Eligible patients were randomized on day 1 to one of three active treatment arms with a ratio 1:1:1; taspoglutide 10 mg once weekly (QW), taspoglutide 20 mg QW, or insulin glargine QD, all in addition to background metformin treatment.
3. **Extension**: 28-week open-label active-controlled treatment extension.
4. **Long-term extension:** 104-week open-label active-controlled treatment extension (optional).
5. **Follow-up**. All patients who received at least one dose of study drug had a follow-up visit (via telephone call) 2 weeks after their last visit. This applied both to patients who completed the study and to patients who discontinued at any time during the study (unless consent was withdrawn).

All patients consented to participate for the duration of the study of one year (24-week core treatment period and 28-week extension period), but could opt out of the 104-week long-term extension period. Separate consent was required in order to continue in the long-term extension. In both extension periods, patients continued with the treatment they were originally assigned to. Efficacy results from the 24-week core treatment and 28-week extension phases are reported to give a total of 52 weeks of treatment results. Safety results are reported up to final visit at study end.

Figure 1 Study Design



EFFICACY RESULTS:

After 24 weeks of treatment, the absolute change from baseline in HbA1c for patients treated with taspoglutide (10 mg and 20 mg) was non-inferior to that of patients treated with insulin glargine at both taspoglutide doses in the ITT populations. Also, compared to baseline values, a reduction in FPG was observed at the end of the 24-week treatment period in all three treatment groups. However, as expected, the absolute change from baseline in FPG at Week 24 for patients treated with taspoglutide (both doses) was smaller than that observed for patients treated with insulin glargine in the ITT population. The absolute change from baseline in body weight at Week 24 for patients treated with taspoglutide (both doses) was superior to that of patients treated with insulin glargine in the ITT population. Compared with the small reduction in body weight observed in the insulin glargine group, the weight loss in taspoglutide-treated patients was statistically significant and superior at both taspoglutide doses (Table 1).

The efficacy responses at Week 24 were maintained at the end of the 28-week extension phase (i.e., at Week 52).

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

	Taspoglutide 10 mg n = 361	Taspoglutide 20 mg n = 348	Insulin glargine n = 319
HbA1c (%)			
LS mean	-0.765	-0.977	-0.835
95% CI	(-0.866, -0.664)	(-1.079, -0.875)	-0.940, -0.731)
Diff from insulin glargine			
LS mean	0.071	-0.141	
p value[a]	0.2974	0.0800	
FPG (mmol/L)			
LS mean	-2.144	-2.509	-4.055
95% CI	(-2.428, -1.860)	(-2.798, -2.220)	(-4.350, -3.759)
Diff from insulin glargine			
LS mean	1.911	1.546	
p value[a]	<.0001	<.0001	
	Taspoglutide 10 mg n = 361	**Taspoglutide 20 mg n = 348**	**Insulin glargine n = 319**
Body weight (kg)			
LS mean	-3.260	-4.089	-0.422
95% CI	(-3.623, -2.896)	(-4.457, -3.721)	(-0.800, -0.044)
Diff from insulin glargine			
LS mean	-2.837	-3.667	
p value[a]	<.0001	<.0001	

a: unadjusted.

PHARMACODYNAMIC RESULTS:

NA

PHARMACOKINETIC RESULTS:

NA

SAFETY RESULTS:

During the entire study treatment period (core, extension, and LT extension phases), the overall incidence of AEs was higher for the taspoglutide 10 mg (89%) and taspoglutide 20 mg (94%) groups versus the insulin glargine (82%) group (Table 2). Adverse events of special interest (cardiovascular AEs, gastrointestinal AEs, pancreatitis, thyroid neoplasms, hypoglycemia, systemic allergic reactions, and injection site reactions) were defined based on the known safety profile for GLP-1 analogues, the available data for taspoglutide from phase 1 and 2 studies, and the epidemiological background data for the T2D population. Due to the nature of the comparator in the study, incidence and prevalence of hypoglycemia were also secondary end-points. 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 (67% and 74% in the 10 mg and 20 mg groups, respectively) compared to the insulin glargine group (25%). This treatment difference was most apparent for the gastrointestinal AEs of nausea, vomiting, dyspepsia, and constipation. Hypoglycemic events were the most common in the insulin glaring arm; significantly fewer patients experienced hypoglycemia with taspoglutide 10 mg (12%) or taspoglutide 20 mg (11%) than with insulin glargine (46%).

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): BC20965
Analysis: SAFETY POPULATION Center: ALL CENTERS
Phase: LTE

	TASPOGLUTIDE 10 MG N = 364 No. (%)	TASPOGLUTIDE 20 MG N = 351 No. (%)	INSULIN GLARGINE N = 322 No. (%)
Total Pts with at Least one AE	323 (88.7)	329 (93.7)	264 (82.0)
Total Number of AEs	1499	1561	1084
Deaths #	2 (0.5)	2 (0.6)	2 (0.6)
Study withdrawals due to an AE #	65 (17.9)	107 (30.5)	4 (1.2)
Patients with at least one			
AE leading to Death	2 (0.5)	2 (0.6)	2 (0.6)
Serious AE	39 (10.7)	49 (14.0)	38 (11.8)
AE leading to withdrawal from treatment	76 (20.9)	117 (33.3)	8 (2.5)

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 03JUN2011:08:08:37 (1 of 1)

A total of 126 patients across the three treatment groups experienced at least one SAE during the study: 39 (11%) patients in the taspoglutide 10 mg group, 49 (14%) patients in the taspoglutide 20 mg group, and 38 (12%) patients in the insulin glargine group. In each treatment group, most of the SAEs were assessed as not related to study drug. The most common type of SAEs in all treatment groups were 'Cardiac Disorders', with an incidence of approximately 2% in all three treatment groups. For six patients, the SAE resulted in death; two in the taspoglutide 10 mg (respiratory failure and cerebrovascular accident), two in the taspoglutide 20 mg (acute myocardial infarction and cardiac arrest—acute myocardial infarction according to the death certificate), and two in the insulin glargine (pneumonia and cerebral haemorrhage) groups. None of these deaths were considered related to trial treatment.

More patients in the taspoglutide 10 mg and 20 mg groups had an AE(s) that led to withdrawal (21% and 33%, respectively) compared with insulin glargine group (3%).The higher incidence of events leading to withdrawal in the taspoglutide groups was primarily due to GI Disorders (mainly nausea and vomiting), which led to 29/364 (8%) patients in the taspoglutide 10 mg group and 58/351 (17%) patients in the taspoglutide 20 mg group withdrawing prematurely from treatment compared with no patients in the insulin glargine group. Non-GI AEs leading to withdrawal with a higher incidence in the taspoglutide groups (≥ 2%) vs insulin glargine were 'Metabolism and Nutrition Disorders' ([3.0% and 3% vs. >1%], mainly hyperglycemia), 'Immune System Disorders' ([3.8% and 5.4% vs. 0%], mainly hypersensitivity and anaphylactic reactions), 'General Disorders and Administration Site Conditions' ([1% and 3% vs. 0%], mainly injection site AEs).

Cardiac disorders were more frequently reported in patients treated with taspoglutide 10 mg and 20 mg than in patients treated with insulin glargine (10% and 8% vs. 7%, respectively). The most common AEs (preferred term), particularly in the taspoglutide groups, were tachycardia and palpitations.

Three patients experienced pancreatitis during the study, two from the taspoglutide 20 mg group and the other from the insulin glargine group. Two of these cases were considered an SAE. The reported cases in the taspoglutide group were moderate in intensity and considered related to treatment which led to withdrawal from the study.

Thyroid neoplasm-related events were reported for three patients in the taspoglutide 10 mg group, four patients in the taspoglutide 20 mg group, and seven patients in the insulin glargine group. Most cases in the taspoglutide groups were goiter and two events were considered by the investigator to be related to treatment one case of goiter and one of increased blood calcitonin). Three cases of thyroid neoplasm were reported, two in the insulin glargine and one in the taspoglutide 10 mg arm. Two of the events were reported as serious (one in the taspoglutide 20 mg group and one in the insulin glargine group).

The incidence of systemic allergic reaction AEs was higher in the taspoglutide 10 mg and 20 mg groups than in the insulin glargine group (6% and 9% vs. 0.6%, respectively). Five events in the taspoglutide 10 mg group and ten events in the taspoglutide 20 mg group were reported as an SAE, none were reported in the insulin glargine group. The majority of systemic allergic reaction AEs were considered by the investigator to be related to study treatment and all (except one considered unresolved) were resolved without sequel.

The incidence of injection site reactions was higher in patients treated with taspoglutide 10 mg and 20 mg groups than in patients treated with insulin glargine (34% and 37% vs. 3%, respectively). Most injection site reactions were mild to moderate in intensity with only three severe in intensity. One patient in the taspoglutide 20 mg group reported an SAE for injection site reaction. The majority of injection site reactions AEs were considered by the investigator to be related to study treatment.

Overall, no clinically relevant adverse effects of taspoglutide were identified on laboratory safety parameters in terms of mean changes from baseline or marked laboratory abnormalities during the study. The percentage of patients who had a marked abnormality in hematology or blood chemistry parameter at any time during the study was small and generally comparable between the treatment groups (typically < 2% per group). 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 test result (below limit of quantitation, above limit of quantitation, or real) was reported post-baseline for 45% of patients in the taspoglutide groups (41% in 10 mg group; 49% in 20 mg group).

CONCLUSIONS:

After 24 and 52 weeks of treatment, the efficacy of taspoglutide 10 mg and 20 mg (as assessed by absolute change from baseline HbA1c) was shown to be non-inferior to that of patients treated with insulin glargine when added to metformin in patients with advanced T2D inadequately controlled with metformin and sulphonylurea combination therapy.

The safety and tolerability profile of taspoglutide in this study was characterized by higher incidences of gastrointestinal AEs (mainly nausea and vomiting) and of AEs leading to treatment withdrawal compared with insulin glargine patients. The treatment difference in AEs leading to treatment withdrawal in the taspoglutide groups was primarily due to gastrointestinal-related AEs and systemic allergic reactions. Significantly fewer patients experienced hypoglycemia with taspoglutide then with insulin glargine. No clinically relevant adverse effects of taspoglutide were identified on laboratory safety parameters, vital signs, or ECGs.
