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ORIGINAL RESEARCH

Efficacy and Safety of Taspoglutide Versus Sitagliptin for Type 2 Diabetes Mellitus (T-Emerge 4 Trial)

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ABSTRACT

Introduction: The efficacy and safety of taspoglutide, a long-acting human glucagon-like peptide-1 analog, were compared with sitagliptin or placebo, as adjunct to metformin, in patients with inadequately controlled type 2 diabetes.

Methods: In this randomized, double-blind, double-dummy, parallel-group trial, patients were randomized to taspoglutide 10 mg once weekly (QW), 20 mg QW, 100 mg sitagliptin once daily (QD), or placebo for 24 weeks, followed by 28-week short-term and 104-week long-term extension periods. The primary endpoint was change in glycosylated hemoglobin (HbA_{1c}) after 24 weeks.

Results: In this study, 666 patients (baseline HbA_{1c}, 7.96% [SD, 0.87]; fasting plasma glucose, 9.61 mmol/L [2.56]; body weight, 92.4 kg [19.3]) were randomized to taspoglutide 10 mg QW ($n = 190$), 20 mg QW ($n = 198$), 100 mg sitagliptin QD ($n = 185$), or placebo ($n = 93$) for 24 weeks. After 24 weeks, least squares mean (SE) HbA_{1c} reductions were greater with taspoglutide 10 mg (−1.23% [0.06]) and 20 mg (−1.30% [0.06]) versus sitagliptin (−0.89% [0.06]) or placebo (−0.10% [0.08]). Mean treatment differences with taspoglutide 10 mg and 20 mg were −0.34 (95% confidence intervals [CI]: −0.49, −0.19) and −0.41 (−0.56, −0.26) versus sitagliptin; and

For the T-emerge 4 Study Group.

Study investigators listed in the Appendix.

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−1.13 (−1.31, −0.95) and −1.20 (−1.38, −1.02) versus placebo. Weight loss was greater with taspoglutide 10 mg (−1.8 kg [0.3]) and 20 mg (−2.6 kg [0.3]) than sitagliptin (−0.9 kg [0.3]) or placebo (−0.5 kg [0.4]). Effects on HbA_{1c} and weight loss continued through 52 weeks of treatment. No cases of severe hypoglycemia occurred with any active treatment. Gastrointestinal adverse events, and allergic and injection-site reactions were higher in the taspoglutide groups, causing higher discontinuation rates. Anti-taspoglutide antibodies were confirmed in 46% of patients.

Conclusion: Taspoglutide demonstrated better efficacy on glycemic control and weight loss than sitagliptin, but a high incidence of adverse events led to high discontinuation rates. The safety profile of taspoglutide in this trial was similar to other trials in the clinical program, and led to the discontinuation of dosing.

Keywords: Dipeptidyl peptidase-4; Glucagon-like peptide-1; Glycemic control; Metformin; Sitagliptin; Taspoglutide; Type 2 diabetes mellitus; Weight loss

INTRODUCTION

Despite the number of antidiabetes medications currently available, there is still difficulty achieving tight glycemic control in patients with type 2 diabetes [1]. An emerging class of antidiabetes agents, known as incretin-based therapies, enhances or replaces the glucose-dependent glucoregulatory effects of incretin hormones, primarily glucagon-like peptide-1 (GLP-1) [2]. Native GLP-1 regulates the postprandial rise in blood glucose by augmenting insulin release and blunting glucagon secretion, delaying gastric emptying, and improving satiety. These effects are short-lived, as the active hormone is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). To take advantage of the incretin system, two types of incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have been developed and have been shown to improve fasting and postprandial glucose control with minimal hypoglycemia, and to induce weight loss to varying extents based on their relative stimulation of incretin activity [3, 4].

Currently, there are two GLP-1 receptor agonists (liraglutide and exenatide) available for treating type 2 diabetes. Liraglutide, administered as a once-daily (QD) injection, has demonstrated to be effective in improving glycemic control, with a lower risk of hypoglycemia, and appreciable weight loss [5, 6]. Exenatide, available for administration as a twice-daily injection and in some countries as a once-weekly (QW) injection, results in improved glycemic control, without hypoglycemia, and significant weight loss [7, 8]. The most common treatment-emergent adverse events (AEs) observed with GLP-1 receptor agonists are related to gastrointestinal AEs (nausea, vomiting, diarrhea, and upper abdominal pain). These AEs are considered dose-related and typically become less frequent with subsequent dosing over time. Several DPP-4 inhibitors are approved, including sitagliptin, saxagliptin, and linagliptin. These QD agents have the advantage of being oral medications, but offer modest glycemic efficacy and have little effect on body weight [9–11].

Taspoglutide, a human GLP-1 analog, elicits a long-lasting incretin effect through its enhanced enzymatic stability and sustained-release formulation, allowing for QW administration [12]. In phase 2 trials, taspoglutide QW versus placebo in combination with metformin favorably lowered blood glucose and body

weight, and was well tolerated [13, 14]. The present study (T-emerge 4) was designed to compare the efficacy and safety of taspoglutide versus sitagliptin or placebo over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin alone. A short-term extension phase of 28 weeks followed by a long-term extension phase of 52 weeks were planned to follow the core phase of the study to evaluate long-term effects of taspoglutide compared with sitagliptin. The trial was terminated on January 11, 2011 during the long-term extension phase owing to the discontinuation of dosing in the phase 3 trials because of higher than expected rates of study withdrawals of taspoglutide-treated patients. Here, the authors present key efficacy results from the 24-week core phase and 28-week short-term extension phase, and full safety data for the entire study up to the last dose administered.

MATERIALS AND METHODS

Study Design and Interventions

This phase 3 study was a randomized, double-blind, double-dummy, placebo-, and active-controlled four-arm parallel trial undertaken at 149 clinical sites in 23 countries. Patients were randomized to one of the four following treatment groups in a 2:2:2:1 ratio: (1) taspoglutide 10 mg subcutaneously (s.c.) QW plus oral placebo-sitagliptin QD; (2) taspoglutide 20 mg s.c. QW (after 10 mg s.c. for the first 4 weeks) plus oral placebo-sitagliptin QD; (3) sitagliptin 100 mg orally QD plus placebo-taspoglutide s.c. QW; or (4) placebo-sitagliptin orally QD plus placebo-taspoglutide s.c. QW All patients were instructed to maintain their metformin treatment at a stable dose (≥1,500 mg/day as documented at screening) throughout the study period, as well as their diet and exercise habits.

All patients participated in the initial 24-week, double-blind, placebo-, and active-controlled core phase (phase A) of the study (Fig. 1). This was followed by a 28-week, single-blind, active-treatment period (extension phase B) during which patients in group 4 (double placebo group) were switched either to taspoglutide 10 mg or taspoglutide 20 mg s.c. QW (after 10 mg s.c. for the first 4 weeks) plus placebo-sitagliptin orally QD Finally, only those patients randomized at study initiation to the taspoglutide or sitagliptin groups were maintained in a double-blind, active-controlled period and followed for

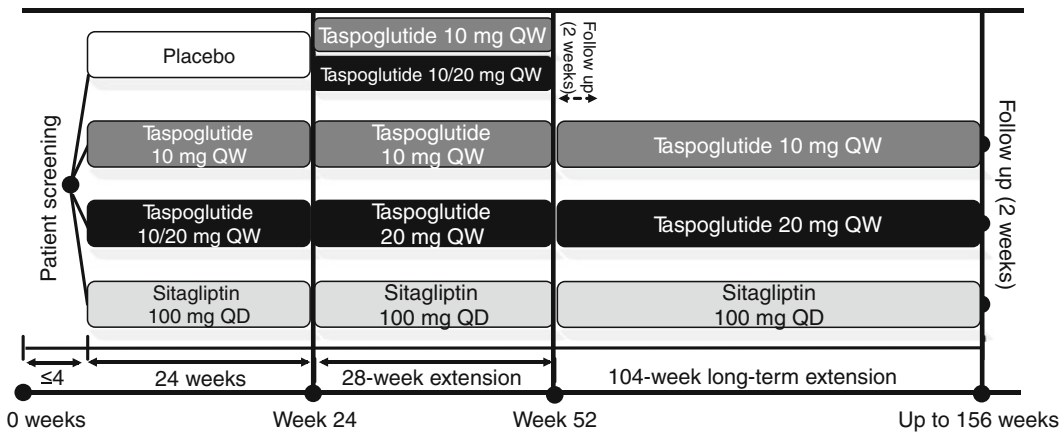

Fig. 1 Study design. Patients randomized to taspoglutide 20 mg QW received taspoglutide 10 mg QW for 4 weeks followed by the 20 mg QW. *QD* once daily, *QW* once weekly

up to an additional 104 weeks; this was the long-term extension phase. Patients originally randomized to the double placebo group did not participate in the long-term extension phase.

Study Participants

Eligible participants were aged 18–75 years with type 2 diabetes, and had inadequate glycemic control (glycosylated hemoglobin [HbA_{1c}] $\geq$7.0% to $\leq$10.0% at screening), a body mass index (BMI) $\geq$25 kg/m^2 (>23 for Asians) to $\leq$45 kg/m^2 (and stable within $\pm$5% for $\geq$12 weeks), and were receiving metformin (stable dose $\geq$1,500 mg/day or maximally tolerated dose for $\geq$12 weeks before screening). Participants were excluded if they had chronic diabetic complications (diabetic nephropathy, neuropathy, and retinopathy), gastrointestinal disease, previous bariatric surgery, pancreatitis, cardiovascular disease, or previous exposure to other oral antihyperglycemic or weight-lowering drugs within 12 weeks, >1 week of insulin within 6 months, or another GLP-1 mimetic or analog at any time.

The trial was conducted in accordance with the Declaration of Helsinki and national regulations, and the protocol was approved by local independent ethics committees or institutional review boards. All participants provided written consent prior to any procedure.

Randomization and Masking

Randomization was stratified by baseline HbA_{1c} (<8.0% or $\geq$8.0%) to prevent imbalances in the treatment arms. Randomization was performed centrally using either a telephone- or web-based system, and patient randomization numbers were generated by the sponsor. Investigators were masked to the results of efficacy assessments during the study, and the sponsor medical review of data avoided systematic unblinding of the treatment code.

Study Endpoints

The primary efficacy endpoint was absolute change in HbA_{1c} (%) from baseline to 24 weeks of treatment. The secondary efficacy endpoints included changes in HbA_{1c}, percentage of patients achieving HbA_{1c} $\leq$6.5% and $\leq$7%, fasting plasma glucose, and body weight at 24 and 52 weeks of treatment, as well as changes in beta-cell function (fasting proinsulin, fasting insulin, fasting proinsulin:insulin ratio, homeostatic model assessment [HOMA]-B), and lipid profile after 52 weeks of treatment. An additional exploratory efficacy endpoint included change in blood pressure after 52 weeks of treatment.

Tolerability/safety assessments included documenting any treatment-emergent AEs or abnormalities in vital signs and physical examination findings, clinical laboratory tests (hematology, biochemistry, and urinalysis), electrocardiogram, or the development of anti-taspoglutide antibodies. Documented hypoglycemia was defined as any episode with or without typical symptoms accompanied by measured plasma-equivalent glucose concentration <3.9 mmol/L. Confirmed (symptomatic or asymptomatic) hypoglycemia was defined by a plasma-equivalent glucose measurement of $\leq$3.1 mmol/L. Severe hypoglycemia was defined as an event requiring assistance of another to administer carbohydrate, glucagon, or other resuscitative actions. Also considered was the need for rescue medications for glycemic control during the study. The following criteria were used to determine the need for rescue medication: if fasting plasma glucose >13.3 mmol/L from

week 4–8, >12.2 mmol/L from week 8–12, and >11.1 mmol/L from week 12–24, and if HbA_{1c} >8% between weeks 24–52, HbA_{1c} >7.5% between weeks 52–104, and HbA_{1c} >7% between weeks 104–156. During the long-term extension phase of the study, a risk mitigation plan was implemented requiring discontinuation of patients with confirmed positive anti-taspoglutide antibody test ≥230 ng-eq/mL, regardless of the presence or absence of allergic AEs and discontinuation of patients with treatment-related systemic allergic reactions.

Statistical Analysis

It was calculated that 630 patients would have to be randomized (180 in the three active treatment groups and 90 in the placebo group). This provided 90% power with a two-sided alpha of 0.05 to detect a difference of 0.6% (SD 1.2%) in change in HbA_{1c} from baseline to 24 weeks for taspoglutide versus placebo (first primary objective), and an 80% power to detect a difference of 0.1% for taspoglutide versus sitagliptin (second primary objective).

Analyses of efficacy endpoints were based on the intent-to-treat population, consisting of all randomized patients who received at least one dose of study drug, and had a baseline and one or more postbaseline evaluable measurements of HbA_{1c}. The safety analysis was based on the safety population that included all patients who received ≥1 dose of study drug and had at least one safety follow-up (or reported any AEs).

Analysis of variance was used to assess the primary endpoint (absolute change in HbA_{1c}) with treatment and region as variables, and baseline HbA_{1c} value as covariate. Missing values were imputed as the last observation carried forward. For testing of taspoglutide versus placebo and sitagliptin, a fixed sequential test procedure was used to control multiplicity across endpoints. HbA_{1c} was tested for significance first, then other secondary endpoints sequentially (starting with fasting plasma glucose and body weight). If significant, the testing continued, but if not, the testing stopped. The Hochberg procedure also was applied to control for multiple comparisons across treatment groups (in HbA_{1c} and other endpoints, if applicable). Analysis of continuous variance was used for the other continuous secondary and exploratory endpoints (but was not part of the testing sequence). The Clopper-Pearson method was used to calculate the HbA_{1c} and body weight response rates as well as related 95% confidence intervals (CI).

RESULTS

Overall, 666 patients were randomized and 656 (98%) qualified for the safety population (i.e., received at least one dose of study medication and had at least one safety assessment). Of those randomized, 542 (81%) patients completed the 24-week core phase and 437 (66%) patients completed the 28-week short-term extension phase (Fig. 2). During the core phase, premature discontinuation occurred in 21%, 28%, 7%, and 11% of patients receiving taspoglutide 10 mg, taspoglutide 20 mg, sitagliptin 100 mg, or placebo, respectively, most frequently resulting from AEs. Across the core phase and short-term extension phase, the greatest number of patients withdrew in the taspoglutide 10 mg (36%) and taspoglutide 20 mg (51%) groups compared with the other groups (placebo/taspoglutide 10 mg [14%], placebo/taspoglutide 20 mg [26%], and sitagliptin 100 mg [14%]). No major differences were seen between treatment groups for baseline

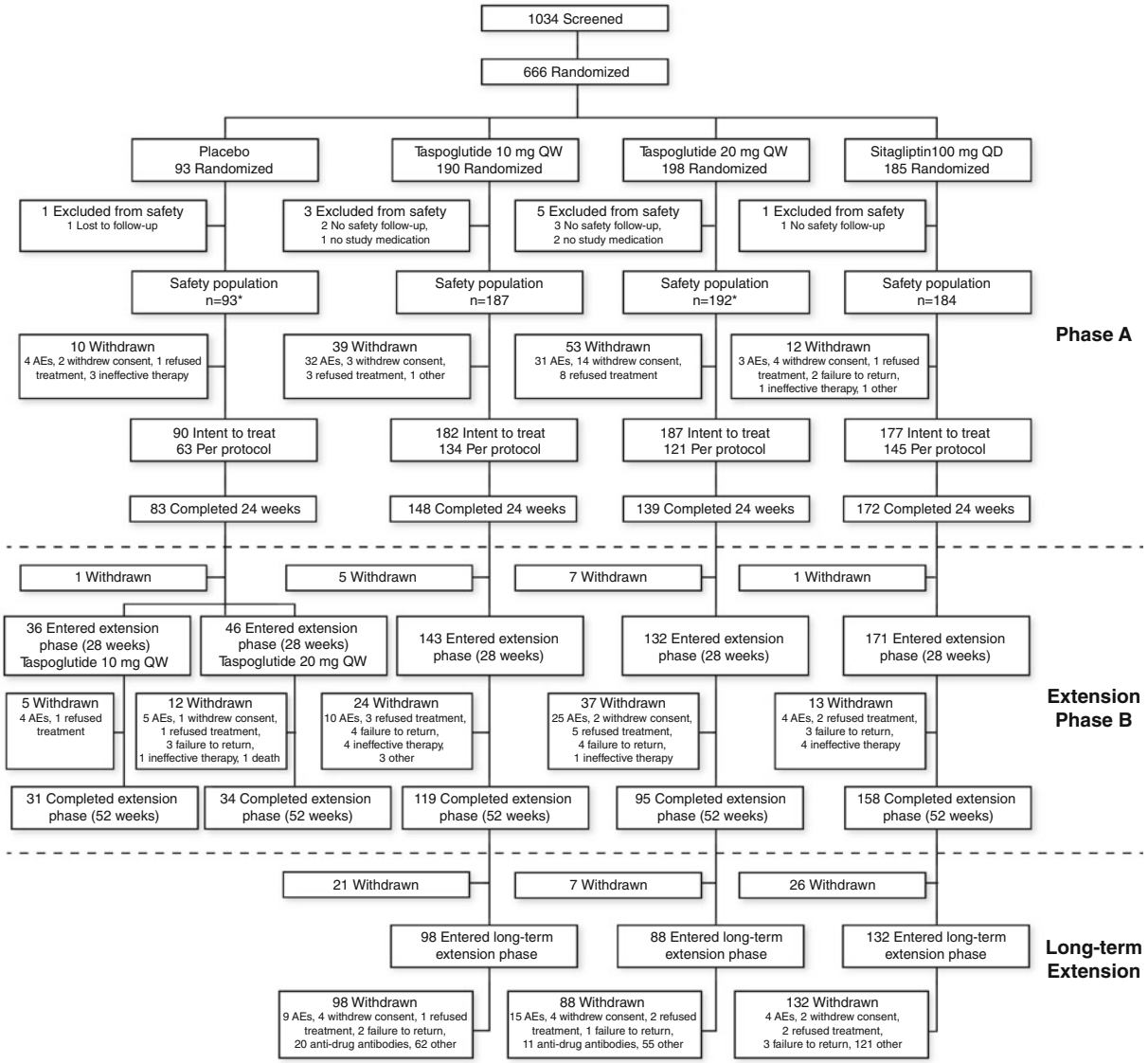

Fig. 2 Patient allocation. *AE* adverse event, *QD* once daily, *QW* once weekly. *One patient randomized to the taspoglutide 20 mg group received placebo for the first 4 weeks of the study and was considered in the placebo group for the safety population

demographics and clinical characteristics (Table 1). The mean age was 55.9 years (SD 9.5), BMI 32.5 kg/m^2 (SD 5.1), HbA_{1c} 7.96% (SD 0.87), and duration of diabetes was 5.9 years (SD 4.7).

Efficacy

After 24 weeks of treatment, taspoglutide had a greater effect on HbA_{1c} compared with sitagliptin (Fig. 3a). Mean HbA_{1c} reductions at week 24 were −1.23% (SE 0.06), −1.30% (0.06), and −0.89% (0.06) for taspoglutide 10 and 20 mg, and sitagliptin 100 mg, respectively, versus −0.1% (0.8) for placebo (Fig. 3b). Mean treatment differences were −0.34 (95% CI −0.49, −0.19) and −0.41 (95% CI −0.56, −0.26) for taspoglutide 10 mg and 20 mg versus sitagliptin (both $P < 0.001$), and −1.13

Table 1 Baseline demographic and clinical characteristics (intent-to-treat population, $n = 636$)

	Placebo ($n = 90$)	Taspoglutide 10 mg ($n = 182$)	Taspoglutide 20 mg ($n = 187$)	Sitagliptin 100 mg ($n = 177$)
Sex				
Male	47 (52)	102 (56)	98 (52)	105 (59)
Female	43 (48)	80 (44)	89 (48)	72 (41)
Age, mean (SD), years	56.1 (10.1)	55.3 (9.5)	56.8 (8.8)	55.5 (9.9)
Race				
White	69 (77)	143 (79)	153 (82)	135 (76)
Asian	9 (10)	15 (8)	14 (7)	19 (11)
Black	5 (6)	13 (7)	8 (4)	10 (6)
Other	7 (8)	11 (6)	12 (6)	13 (7)
Ethnicity				
Non-Hispanic	80 (89)	150 (82)	152 (81)	148 (84)
Hispanic	10 (11)	32 (18)	35 (19)	29 (16)
Weight, mean (SD), kg	91.1 (19.0)	93.6 (20.4)	91.8 (18.0)	92.5 (19.7)
Body mass index, mean (SD), kg/m^2	32.5 (5.5)	32.7 (5.2)	32.3 (5.0)	32.4 (5.0)
HbA_{1c}, mean (SD), %	8.03 (0.83)	7.95 (0.93)	7.97 (0.86)	7.94 (0.85)
HbA_{1c} baseline category				
<8.0%	46 (51)	103 (57)	106 (57)	100 (56)
≥8.0%	44 (49)	79 (43)	81 (43)	77 (44)
Fasting plasma glucose, mean (SD), mmol/L	9.66 (2.60)	9.74 (2.48)	9.64 (2.68)	9.40 (2.50)
Duration of diabetes, mean (SD), years	5.5 (3.9)	6.1 (4.8)	5.7 (4.7)	6.0 (5.0)

Data are *n* (%) unless otherwise indicated
HbA_{1c} glycosylated hemoglobin

(95% CI −1.31, −0.95) and −1.20 (95% CI −1.38, −1.02) for taspoglutide 10 and 20 mg versus placebo (both $P < 0.001$). At 52 weeks, these reductions were still significant with a mean change in HbA_{1c} of −1.03 (95% CI −1.15, −0.91), −1.18 (95% CI −1.30, −1.06), and −0.66 (95% CI −0.78, −0.54) for taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin 100 mg, respectively. After 52 weeks of treatment, a greater proportion of patients achieved HbA_{1c} targets of ≤6.5% or ≤7.0% with taspoglutide 10 and 20 mg than with sitagliptin (HbA_{1c} ≤6.5%: 37.9% and 41.2% vs. 17.5%, respectively; HbA_{1c} ≤7.0%: 57.7% and 67.9% vs. 47.5%).

At 24 weeks, both doses of taspoglutide achieved significantly greater reductions in fasting plasma glucose than sitagliptin or placebo (Fig. 4a). The mean reductions from baseline in fasting plasma glucose were −2.16 mmol/L (SE 0.14), −2.34 mmol/L (SE 0.14), −1.35 mmol/L (SE 0.14), and −0.07 mmol/L (SE 0.20) for taspoglutide 10 mg, taspoglutide 20 mg, sitagliptin 100 mg,

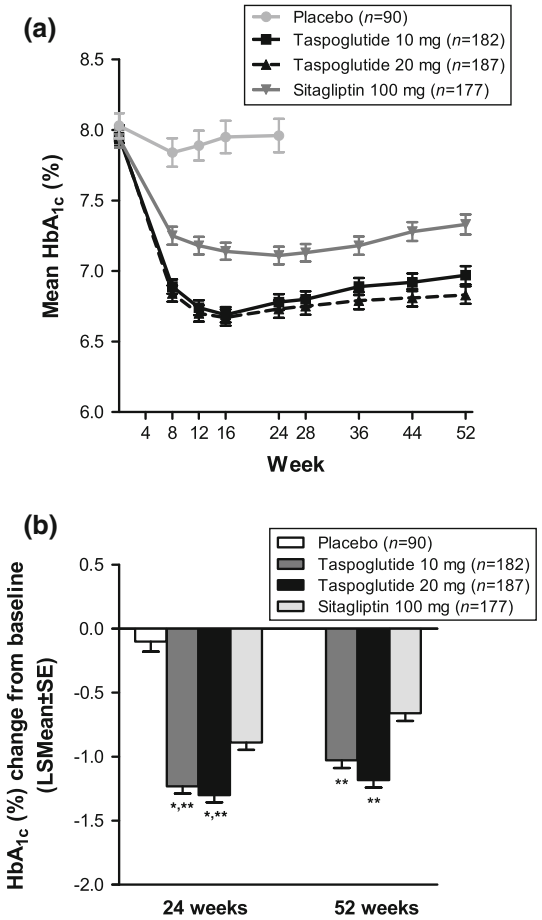

Fig. 3 Effects of treatments on HbA_{1c}. **a** Changes in HbA_{1c} (%) during 52 weeks of treatment. **b** Changes in HbA_{1c} (%) from baseline after 24 and 52 weeks of treatment. *HbA_{1c}* glycosylated hemoglobin, *LSMean* least squares mean. $^{*}P < 0.001$ vs. placebo, $^{**}P < 0.001$ vs. sitagliptin

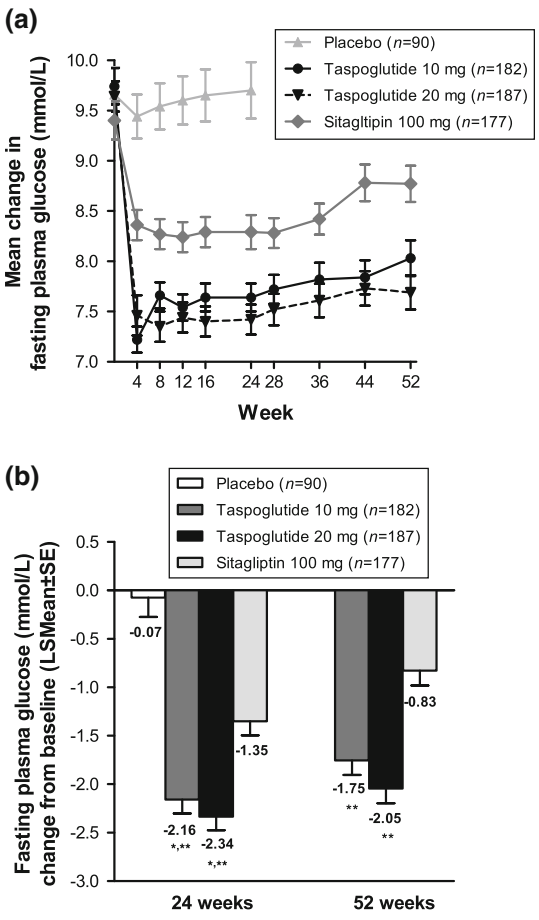

Fig. 4 Effects of treatments on fasting plasma glucose. **a** Changes in fasting plasma glucose (mmol/L) during 52 weeks of treatment. **b** Changes in fasting plasma glucose (mmol/L) from baseline after 24 and 52 weeks of treatment. *LSMean* least squares mean. $^{*}P < 0.001$ vs. placebo, $^{**}P < 0.001$ vs. sitagliptin

and placebo, respectively (Fig. 4b). Mean treatment differences were −0.81 mmol/L (95% CI −1.19, −0.43) and −0.98 mmol/L (95% CI −1.36, −0.61) for taspoglutide 10 mg and 20 mg versus sitagliptin (both $P < 0.001$), and −2.09 mmol/L (95% CI −2.55, −1.62) and −2.26 mmol/L (95% CI −2.72, −1.80) for taspoglutide 10 and 20 mg versus placebo (both $P < 0.001$). Reductions persisted at 52 weeks with fasting plasma glucose mean changes from baseline of −1.75 mmol/L (95% CI −2.05, −1.45), −2.05 mmol/L (95% CI −2.34, −1.75), and −0.83 mmol/L (95% CI −1.13, −0.52) for taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin 100 mg, respectively. During the 24-week core study phase, a higher percentage of patients treated with placebo (16.7%) required rescue medication than those treated with taspoglutide 10 and 20 mg (3.8% and 1.6%, respectively), and sitagliptin (5.1%). Among those patients receiving treatment for 52 weeks, a lower percentage of patients required rescue medication in the taspoglutide

10 and 20 mg groups (11.5% and 6.4%, respectively) than in the sitagliptin group (18.6%).

Taspoglutide produced greater reductions in mean body weight than those observed for sitagliptin or placebo (Fig. 5a): −1.8 kg (SE 0.3), −2.6 kg (SE 0.3), −0.9 kg (SE 0.3), and −0.5 kg (SE 0.4) for taspoglutide 10 mg, taspoglutide 20 mg, sitagliptin 100 mg, and placebo, respectively (Fig. 5b). At 52 weeks, the following reductions were similar to those observed at 24 weeks: −1.6 kg (SE 0.3), −2.4 kg (SE 0.3), and −0.5 kg (SE 0.3) for taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin 100 mg, respectively.

Improvements in HOMA-B were observed at 24 weeks with taspoglutide 10 and 20 mg (23.5% [95% CI 17.54, 29.53] and 32.1% [95% CI 26.11, 38.04], respectively) versus placebo (–3.2% [95% CI –11.67, 5.26]; both $P < 0.001$) and versus sitagliptin (10.3% [95% CI 4.14, 16.42]; taspoglutide 10 mg, $P < 0.005$ and 20 mg, $P < 0.001$). At 52 weeks, taspoglutide 10 mg and 20 mg significantly increased HOMA-B by 21.8% (95% CI 14.27, 29.34; $P < 0.05$) and 31.3% (95% CI 23.80, 38.88; $P < 0.001$), respectively, versus sitagliptin by 10.2% (95% CI 2.40, 17.91) (Table 4 of Appendix). Proinsulin and proinsulin:insulin ratio results, as well as results related to cardiovascular outcomes, are presented in the online Tables 4 and 5 in the Appendix.

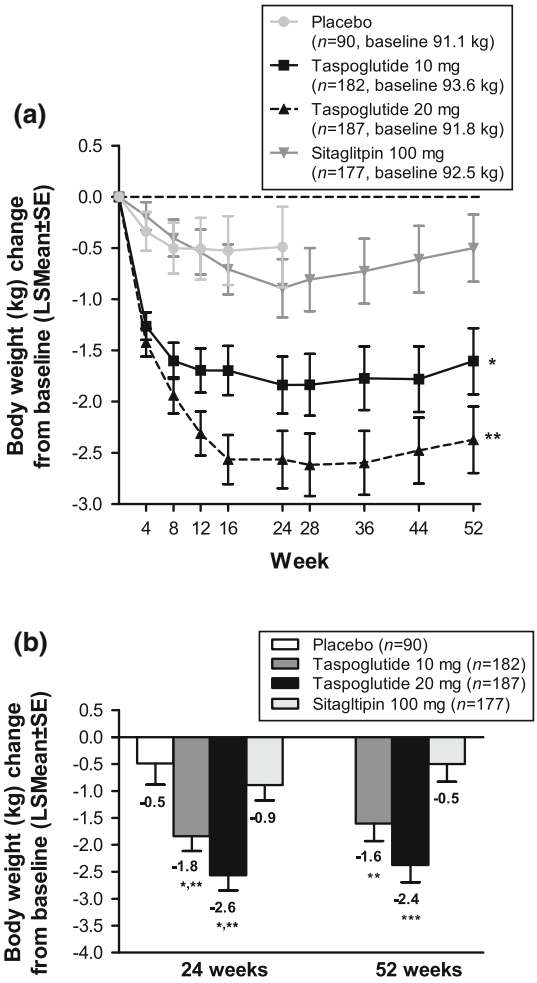

Fig. 5 Effects of treatments on body weight. **a** Changes in body weight (kg) from baseline over 52 weeks of treatment. *LSMean* least squares mean. $^{*}P < 0.05$ vs. sitagliptin, $^{**}P < 0.001$ vs. sitagliptin. **b** Changes in body weight (kg) from baseline after 24 and 52 weeks of treatment. $^{*}P < 0.01$ vs. placebo, $^{**}P < 0.05$ vs. sitagliptin, $^{***}P < 0.001$ vs. sitagliptin

Safety and Tolerability

A majority of patients receiving taspoglutide or sitagliptin experienced at least one AE during the entire study period with most being reported as mild-to-moderate in intensity (Table 2). The most common AEs observed in the taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin groups, respectively, were nausea (51.3%, 57.8%, 17.4%), vomiting (29.4%, 40.1%, 6.5%), diarrhea (17.1%, 15.1%, 5.4%), injection-site nodule (7.5%, 17.2%, 1.6%), injection-site pruritus (7.0%, 17.2%, 2.2%), injection-site erythema (6.4%, 13.5%, 1.6%), nasopharyngitis (7.5%, 7.8%, 15.2%), and upper respiratory tract infection (2.1%, 5.7%, 10.3%). Upper abdominal pain was more common with sitagliptin than with taspoglutide, occurring in 5.4% of subjects

Table 2 Summary of adverse events and withdrawals during the entire study period (up to 156 weeks)

	Taspoglutide 10 mg ($n = 187$)	Taspoglutide 20 mg ($n = 192$)	Sitagliptin 100 mg ($n = 184$)
Patients with at least one AE	160 (85.6)	183 (95.3)	149 (81.0)
Total number of AEs, *n*	737	931	643
Patients with at least one serious AE	18 (9.6)	18 (9.4)	19 (10.3)
Treatment-related serious AEs, %[a] (*n*/*n* serious AEs)	11 (2/18)	19 (5/27)	0 (0/22)
Death	1 (0.5)	0 (0.0)	0 (0.0)
AEs leading to withdrawal in >1%			
Total patients with ≥1 AE	53 (28.3)	69 (35.9)	13 (7.1)
Serious AEs	2 (1.1)	6 (3.1)	2 (1.1)
Gastrointestinal disorders	34 (18.2)	39 (20.3)	3 (1.6)
Nausea	14 (7.5)	21 (10.9)	0 (0)
Vomiting	15 (8.0)	13 (6.8)	1 (0.5)
Diarrhea	2 (1.1)	1 (0.5)	0 (0.0)
General disorders and administration-site conditions	5 (2.7)	7 (3.6)	1 (0.5)
Hypersensitivity[b]	4 (2.1)	8 (4.2)	1 (0.5)
AEs reported by >5% of patients			
Nausea	96 (51.3)	111 (57.8)	32 (17.4)
Vomiting	55 (29.4)	77 (40.1)	12 (6.5)
Diarrhea	32 (17.1)	29 (15.1)	10 (5.4)
Dyspepsia	18 (9.6)	15 (7.8)	4 (2.2)
Constipation	9 (4.8)	15 (7.8)	3 (1.6)
Gastroesophageal reflux disease	11 (5.9)	11 (5.7)	5 (2.7)
Abdominal pain upper	4 (2.1)	6 (3.1)	10 (5.4)
Injection-site nodule	14 (7.5)	33 (17.2)	3 (1.6)
Injection-site pruritus	13 (7.0)	33 (17.2)	4 (2.2)
Injection-site erythema	12 (6.4)	26 (13.5)	3 (1.6)
Injection-site pain	2 (1.1)	7 (3.6)	16 (8.7)
Injection-site mass	7 (3.7)	13 (6.8)	1 (0.5)
Nasopharyngitis	14 (7.5)	15 (7.8)	28 (15.2)
Urinary tract infection	8 (4.3)	15 (7.8)	12 (6.5)
Upper respiratory tract infection	4 (2.1)	11 (5.7)	19 (10.3)
Influenza	8 (4.3)	10 (5.2)	13 (7.1)
Hypoglycemia	21 (11.2)	15 (7.8)	18 (9.8)

Table 2 continued

	Taspoglutide 10 mg ($n = 187$)	Taspoglutide 20 mg ($n = 192$)	Sitagliptin 100 mg ($n = 184$)
Decreased appetite	20 (10.7)	23 (12.0)	5 (2.7)
Headache	15 (8.0)	10 (5.2)	11 (6.0)
Dizziness	11 (5.9)	14 (7.3)	9 (4.9)
Hypertension	5 (2.7)	14 (7.3)	18 (9.8)
Arthralgia	7 (3.7)	6 (3.1)	11 (6.0)
Cough	3 (1.6)	6 (3.1)	10 (5.4)
Hypersensitivity[b,c]	5 (2.7)	10 (5.2)	2 (1.1)

Data are n (%) of the safety population unless otherwise indicated ($n = 563$). AEs are reported as system organ class or preferred terms (Medical Dictionary for Regulatory Activities [MedDRA] version 14.0)

AEs adverse events

[a] Serious AEs related to study treatment: taspoglutide 10 mg ($n = 2$: gastritis and inflammatory bowel); taspoglutide 20 mg ($n = 5$: malaise, head injury and cardiac arrest/lactic acidosis/renal failure acute [in single patient]); and none for sitagliptin

[b] Hypersensitivity refers to the Preferred Term of MedDRA coding dictionary and refers to systemic allergic reactions

[c] Systemic hypersensitivity was reported in 16 patients: taspoglutide 10 mg ($n = 5$), taspoglutide 20 mg ($n = 10$), and sitagliptin ($n = 1$)

compared with 2.1% and 3.1% for taspoglutide 10 mg and taspoglutide 20 mg.

Similar proportions of patients in the taspoglutide 10 mg (11.2% [$n = 21$]), taspoglutide 20 mg (7.8% [$n = 15$]), and sitagliptin (9.8% [$n = 18$]) groups experienced hypoglycemia. None of these were reported as serious or resulted in treatment discontinuation.

Severe AEs were reported in 7%, 10%, and 4% of patients in the taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin groups, respectively. In taspoglutide-treated patients, the most common severe AEs were gastrointestinal (33%), such as nausea and vomiting as well as injection-site reactions (6%). The frequency of serious AEs (SAEs) was similar across treatment groups (taspoglutide 10 mg [9.6% ($n = 18$)], taspoglutide 20 mg [9.4% ($n = 18$)], and sitagliptin [10.3% ($n = 19$)]). In the taspoglutide groups, seven of the following SAEs were deemed treatment-related: two in the taspoglutide 10 mg group, gastritis and inflammatory bowel disease; and five in the taspoglutide 20 mg group, malaise, head injury, and cardiac arrest/lactic acidosis/renal failure acute (in a single patient). No treatment-related SAEs were observed in the sitagliptin group. One death occurred in the taspoglutide 10 mg group, which was not considered treatment-related, but due to underlying chronic obstructive pulmonary disease.

Withdrawals resulting from AEs were more common among patients receiving taspoglutide compared with sitagliptin. In the taspoglutide groups, the most common AEs leading to withdrawal were nausea, vomiting, hypersensitivity, and injection-site-related AEs. In the taspoglutide groups, 18.2–20.3% of patients withdrew because of gastrointestinal AEs compared with 1.6% of those in the

sitagliptin group. Hypersensitivity reactions accounted for 2.1% and 4.2% of withdrawals in patients receiving taspoglutide 10 mg and taspoglutide 20 mg, respectively, compared with 0.5% in patients receiving sitagliptin.

Nearly all systemic allergic reactions observed ($n = 23$) were experienced by patients receiving taspoglutide: eight (4%), 14 (7%), and one (1%) for taspoglutide 10 mg, taspoglutide 20 mg, and sitagliptin, respectively. Systemic hypersensitivity was the most common of these, reported in five and ten patients in the taspoglutide 10 and 20 mg groups, and in one patient in the sitagliptin group. Most systemic allergic reactions led to treatment discontinuation, but none were considered SAEs.

Positive postbaseline anti-taspoglutide antibody results were reported in 41% (71/172) and 51% (91/178) of taspoglutide 10 mg and taspoglutide 20 mg patients, respectively (Table 3). As a result of the implemented risk mitigation plan, 30% (106/350) of patients with a confirmed positive anti-taspoglutide antibody test of $\geq$230 ng-eq/mL were discontinued during the long-term extension phase of the study.

Prespecified thyroid-related AEs were reported in four (2%) patients in the taspoglutide 10 mg group, two (1%) patients in the taspoglutide 20 mg group, and four (2%) patients in the sitagliptin group. Goitre was reported in three patients receiving taspoglutide and two patients receiving sitagliptin. Increased blood calcitonin levels were identified in two patients receiving taspoglutide (taspoglutide 10 mg, 3.42 pmol/L; taspoglutide 20 mg, 3.98 pmol/L); however, no thyroid ultrasound or biopsy data were available. A thyroid neoplasm was identified in three patients: one patient receiving taspoglutide 10 mg and two patients receiving sitagliptin. In the patient treated with taspoglutide 10 mg, the thyroid neoplasm consisted of multiple nodules with no confirmatory biopsy with onset on day 186 of the study. In the two sitagliptin-treated patients, one had bilateral thyroid nodules too small for biopsy initially observed on day 177 and the other patient underwent a partial thyroidectomy for a Hürthle cell benign tumor observed on day 436. There were no cases of acute or chronic pancreatitis.

DISCUSSION

This head-to-head comparative study showed that taspoglutide 10 and 20 mg QW improved glycemic control more effectively than sitagliptin and placebo without increased risk of hypoglycemia, and it was associated with significantly greater weight loss over 24 weeks in patients inadequately controlled on metformin. Both doses of taspoglutide achieved similar reductions in HbA_{1c} at 24 weeks of -1.23% and -1.30% from a baseline of approximately 8.0%. The reduction from baseline in HbA_{1c} with sitagliptin was significantly smaller at -0.89%. Reductions in HbA_{1c} from baseline in taspoglutide-treated patients were observed as early as week 4 and continued to decrease until weeks 12–16, and were generally maintained at 52 weeks. Likewise, improvements in fasting plasma glucose and body weight were statistically significant compared with sitagliptin at weeks 24 and 52. Thus, taspoglutide treatment not only achieved noninferiority, but more importantly achieved superiority relative to sitagliptin for measures of efficacy. Moreover, a greater percentage of taspoglutide-treated patients achieved HbA_{1c} targets of $\leq$6.5% or $\leq$7.0% than those treated with sitagliptin. Despite similar reductions in HbA_{1c} for the two doses of taspoglutide, greater weight loss was seen with the 20 mg dose, suggesting that

Table 3 Summary of confirmed anti-taspoglutide antibody results (taspoglutide safety population, $n = 379$)

	Taspoglutide		Pooled ($n = 379$)
	10 mg ($n = 187$)	20 mg ($n = 192$)	
Baseline, n[a]	172	173	345
Confirmed positive, n (%)	0 (0)	2 (1)	2 (1)
Week 24, n	157	166	323
Confirmed positive, n (%)	43 (27)	64 (39)	107 (33)
Week 52, n	128	116	244
Confirmed positive, n (%)	48 (38)	55 (47)	103 (42)
Week 64, n	74	62	136
Confirmed positive, n (%)	20 (27)	20 (32)	40 (29)
Week 76, n	78	66	144
Confirmed positive, n (%)	0 (0)	1 (2)	1 (1)
Week 88, n	33	29	62
Confirmed positive, n (%)	15 (45)	11 (38)	26 (42)
Week 104, n	3	5	8
Confirmed positive, n (%)	0 (0)	2 (40)	2 (25)
Postbaseline, n	172	178	350
≥1 confirmed positive, n (%)	71 (41)	91 (51)	162 (46)[b]

All percentages are calculated using "n" from the associated scheduled time as the denominator. If a patient had antibody results from more than 1 day in the scheduled time of baseline, weeks 12, 24, 52, and 104, the worst result is summarized. A confirmed (positive) antibody response necessitated additional antibody testing at all subsequent planned study visits until the antibody test result returned to pretreatment values

[a] The number of patients who had at least one antibody test during the time windows for the scheduled time

[b] Per the implemented risk mitigation plan, 30% (106/350) of patients with a confirmed positive anti-taspoglutide antibody test of ≥230 ng-eq/mL were discontinued during the long-term extension phase of the study

doses higher than necessary for glycemic control may further reduce body weight.

These results are consistent with other studies of incretin-based therapies in similar populations failing to achieve glycemic control with metformin. In comparative studies, liraglutide QD and exenatide QW achieved greater glycemic efficacy than sitagliptin. Liraglutide achieved HbA_{1c} reductions of −1.24% to −1.50% versus −0.90% with sitagliptin, while exenatide QW achieved −1.5% versus −0.9% [8, 15]. In other phase 3 trials, GLP-1 receptor agonists have achieved generally comparable HbA_{1c} reductions, although some variability in the treatment responses may have been due to differences in background therapies and baseline HbA_{1c} [5, 6, 8, 15–18]. The efficacy of sitagliptin in recent comparative trials, including the present study, was similar to previous studies with HbA_{1c} improvements of −0.67% to −1.0% in metformin-treated patients [9, 10].

Previous studies have also demonstrated greater effects on weight loss with GLP-1 receptor agonists when compared with

sitagliptin. Liraglutide QD reduced body weight by 2.86 and 3.38 kg with 1.2 and 1.8 mg liraglutide, respectively, versus 0.96 kg for sitagliptin [15]. Exenatide QW achieved a weight loss of 2.3 kg compared with 0.8 kg for sitagliptin [8]. In other studies, sitagliptin has demonstrated only minimal reductions in body weight of 0.5–0.7 kg [9, 10].

In general, the overall safety profile of taspoglutide was notably worse than sitagliptin primarily because of gastrointestinal events, systemic allergic reactions, and injection-site reactions. However, there was a higher incidence of nasopharyngitis and upper respiratory tract infections reported with sitagliptin than with taspoglutide. The incidence of overall AEs was higher in the taspoglutide 10 mg (85.6%) and taspoglutide 20 mg (95.3%) groups than in the sitagliptin (81.0%) group. The AEs leading to withdrawal were approximately four-to-five-times higher in the taspoglutide 10 mg (27.8%) and taspoglutide 20 mg (35.9%) groups than in the sitagliptin (7.1%) group.

The greater frequency of gastrointestinal events, primarily nausea, vomiting, and dyspepsia, observed in patients treated with taspoglutide is consistent with that of other GLP-1 receptor agonists [5, 6, 8, 15–18]. In this study, although the gastrointestinal events were usually mild-to-moderate, 19.3% of patients in the taspoglutide groups experienced gastrointestinal events that led to withdrawals during the course of the study.

Although systemic allergic reactions to protein-based therapies do occur, the incidence observed with taspoglutide treatment is notably higher than what has been reported with other GLP-1 receptor agonists [19]. The most frequent allergic reactions to occur were hypersensitivity. As a result of the risk mitigation plan implemented during the long-term extension phase of the study, patients with a systemic allergic reaction were discontinued from the study.[1]

Anti-taspoglutide antibodies were confirmed positive in 41% and 51% of taspoglutide 10 and 20 mg patients, respectively. Previous studies have shown positive antibody production in patients treated with the other GLP-1 receptor agonists, exenatide and liraglutide [19]. Antibody formation to the respective GLP-1 receptor agonist has been reported in 32% and 45% of patients treated with exenatide twice-daily and exenatide QW, respectively [20], and 4–13% of patients treated with liraglutide q.d [21, 22].

Taspoglutide was associated with high rates of injection-site events, such as erythema, pruritus, and nodules. In two exenatide studies, injection-site reactions, such as bruising were rarely reported [7, 23].

In the present study, hypoglycemia was a rare occurrence and the number of events was generally comparable between taspoglutide and sitagliptin groups. Similar low rates of hypoglycemia have been observed for the other GLP-receptor agonists, exenatide and liraglutide [5, 6, 16–18].

This study provides long-term follow-up beyond the standard 24-week endpoint; however, longer-term evaluations outside of the clinical trial setting are needed to determine durability of the response and clinical benefit in this highly prevalent, chronic disease.

[1] In September 2010, Roche decided to stop dosing patients in the taspoglutide phase III trials because higher than expected discontinuation rates of taspoglutide-treated patients were observed, mainly due to gastrointestinal intolerability, and as a result of the implementation of the risk-mitigation plan to address serious hypersensitivity reactions. Since this time, Roche has worked on the root cause analysis and on the modified taspoglutide formulations with the input of Ipsen. After further analysis, Roche has now made the decision to stop the development of taspoglutide and to return the product to the originator, Ipsen, which is currently pursuing further investigations.

Limitations of this study should be considered when extrapolating the findings to a population beyond those in this study, such as participants with relatively new-onset diabetes, monotherapy limited to metformin, and majority of participants being non-Hispanic whites. In addition, although patients were advised to maintain pre-study diet and exercise habits, there was a lack of rigor with standardization of patients' diet and exercise regimens during the study, which could have compromised the true weight loss potential of taspoglutide.

In conclusion, the current findings showed that taspoglutide QW has several key advantages over sitagliptin, as adjunct to metformin, including superior glycemic control and increased weight loss without increased risk of hypoglycemia. However, treatment with taspoglutide was associated with substantial rates of gastrointestinal intolerability and allergic reactions, and led to high subsequent rates of discontinuation.

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Conflict of interest. Dr. Bergenstal has acted as a consultant for and received grants from Abbott Diabetes Care, Amylin, Bayer, Becton–Dickinson, Boehringer Ingelheim, Calibra, Eli Lilly, Halozyme, Helmsley Trust, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, ResMed, Roche, Sanofi Aventis, and Takeda; has acted as a consultant for Valeritas; and received grants from DexCom, Intracia, Merck and National Institutes of Health (all money paid to institution for consultancies and grants); inherited stock in Merck. Dr. Forti has board membership for Sanofi Aventis, Boeringer Ingelheim, Eli Lilly; has acted as a consultant for Novartis and Novo Nordisk; has received grants and speaker bureaus/lectureships from Novo Nordisk, Roche, Novartis, Servier, Boeringer Ingelheim, Sanofi Aventis, Eli Lilly, and Merck Sharp & Dohme (money paid to institution for grants). Dr. Chiasson has no conflicts of interest declared. Dr. Woloschak was an employee of Roche Pharmaceuticals at the time of this study, and is now affiliated with Novartis Pharmaceuticals, Inc. Dr. Boldrin is employed by F. Hoffman-La Roche. Dr. Balena was an employee of F. Hoffmann-La Roche AG at the time of this study, and is now affiliated to Eli Lilly and Company Ltd.

Table 4 Changes from baseline in beta-cell function at 24 and 52 weeks

	Placebo (n = 90)		Taspoglutide 10 mg (n = 182)		Taspoglutide 20 mg (n = 187)		Sitagliptin 100 mg (n = 177)	
	24 weeks	52 weeks	24 weeks	52 weeks	24 weeks	52 weeks	24 weeks	52 weeks
HOMA-B, %, baseline (SE)	45.3 (4.5)	–	45.0 (3.2)	45.0 (3.3)	44.2 (3.2)	44.2 (3.3)	48.2 (3.3)	48.2 (3.4)
Change from baseline (95% CI)	−3.2 (−11.67, 5.26)	–	23.5 (17.54, 29.53)*,***	21.8 (14.27, 29.34)***	32.1 (26.11, 38.04)*,*****	31.3 (23.80, 38.88)****	10.3 (4.14, 16.42)	10.2 (2.40, 17.91)
Insulin, μU/mL, baseline (SE)	11.97 (0.98)	–	12.44 (0.70)	12.44 (0.72)	11.97 (0.69)	11.97 (0.72)	12.19 (0.71)	12.19 (0.74)
Change from baseline (95% CI)	−1.50 (−3.08, 0.09)	–	0.54 (−0.57, 1.65)*****	0.35 (−0.94, 1.63)	0.80 (−0.30, 1.91)*****	1.05 (−0.23, 2.34)	−0.08 (−1.22, 1.06)	0.25 (−1.07, 1.57)
Proinsulin, μU/mL, baseline (SE)	6.05 (0.45)	–	5.75 (0.32)	5.75 (0.32)	5.58 (0.31)	5.58 (0.31)	5.82 (0.32)	5.82 (0.32)
Change from baseline (95% CI)	0.29 (−0.43, 1.00)-	–	−1.05 (−1.55, −0.55)******	−0.81 (−1.34, −0.28)	−1.06 (−1.55, −0.57)******	−0.59 (−1.11, −0.07)	−0.88 (−1.39, −0.38)	−0.46 (−1.00, −0.08)
Proinsulin:insulin ratio, baseline (SE)	0.56 (0.03)	–	0.56 (0.02)	0.56 (0.02)	0.54 (0.02)	0.54 (0.02)	0.55 (0.02)	0.55 (0.02)
Change from baseline (95% CI)	0.04 (−0.01, 0.08)	–	−0.12 (−0.15, −0.09)*	−0.11 (−0.14, −0.08)	−0.14 (−0.18, −0.11)*	−0.12 (−0.15, −0.09)	−0.11 (−0.14, −0.07)	−0.09 (−0.13, −0.06)

HOMA homeostatic model assessment, *CI* confidence intervals

* $P < 0.001$ vs. placebo, ** $P < 0.005$ vs. sitagliptin, *** $P < 0.05$ vs. sitagliptin, **** $P < 0.001$ vs. sitagliptin, ***** $P < 0.05$ vs. placebo, ****** $P < 0.005$ vs. placebo

Table 5 Changes from baseline in blood pressure and lipid profile at 24 and 52 weeks

	Placebo (n = 90)		Taspoglutide 10 mg (n = 182)		Taspoglutide 20 mg (n = 187)		Sitagliptin 100 mg (n = 177)	
	24 weeks	52 weeks	24 weeks	52 weeks	24 weeks	52 weeks	24 weeks	52 weeks
Blood pressure								
Systolic blood pressure, mmHg, baseline (SE)	132.3 (1.4)	–	131.9 (1.0)	131.9 (1.0)	133.2 (1.0)	133.2 (1.0)	131.7 (1.0)	131.7 (1.0)
Change from baseline (95% CI)	−0.9 (−3.44, 1.57)	–	−4.0 (−5.84, −2.25)*	−2.8 (−4.65, −0.89)	−3.3 (−5.09, −1.54)	−2.7 (−4.56, −0.83)	−2.8 (−4.66, −1.02)	−1.7 (−3.56, 0.25)
Diastolic blood pressure, mmHg, baseline (SE)	80.5 (0.9)	–	80.1 (0.6)	80.1 (0.6)	80.1 (0.6)	80.1 (0.6)	79.5 (0.6)	79.5 (0.6)
Change from baseline (95% CI)	−0.4 (−1.88, 1.14)	–	−1.5 (−2.54, −0.38)	−1.0 (−2.19, 0.16)	−1.6 (−2.67, −0.53)	−1.8 (−2.93, −0.60)	−1.4 (−2.50, −0.31)	−0.9 (−2.06, 0.32)
Lipid profile								
Total cholesterol, mmol/L, baseline (SE)	4.94 (0.12)	–	4.99 (0.08)	4.99 (0.08)	4.88 (0.08)	4.88 (0.08)	5.04 (0.09)	5.04 (0.08)
Change from baseline (95% CI)	−0.16 (−0.32, 0.01)	–	−0.26 (−0.37, −0.14)	−0.17 (−0.29, −0.05)	−0.29 (−0.40, −0.18)	−0.27 (−0.39, −0.15)	−0.22 (−0.33, −0.10)	−0.18 (−0.30, −0.06)
HDL, mmol/L, baseline (SE)	1.26 (0.04)	–	1.23 (0.02)	1.23 (0.03)	1.22 (0.02)	1.22 (0.02)	1.19 (0.03)	1.19 (0.03)
Change from baseline (95% CI)	0.04 (−0.01, 0.08)	–	0.01 (−0.02, 0.04)	−0.01 (−0.04, 0.02)	0.01 (−0.02, 0.04)	0.00 (−0.03, 0.03)	0.04 (0.01, 0.08)	0.01 (−0.02, 0.04)
LDL, mmol/L, baseline (SE)	2.88 (0.10)	–	2.89 (0.07)	2.89 (0.07)	2.69 (0.07)	2.69 (0.07)	2.91 (0.07)	2.91 (0.07)
Change from baseline (95% CI)	−0.11 (−0.24, 0.03)	–	−0.14 (−0.24, −0.04)	0.00 (−0.11, 0.10)	−0.16 (−0.25, −0.06)	−0.11 (−0.21, −0.01)	−0.10 (−0.20, −0.01)	−0.02 (−0.12, 0.09)
LDL:HDL ratio, mmol/L, baseline (SE)	2.35 (0.10)	–	2.46 (0.07)	2.46 (0.07)	2.32 (0.07)	2.32 (0.07)	2.58 (0.07)	2.58 (0.07)
Change from baseline (95% CI)	−0.10 (−0.23, 0.04)	–	−0.08 (−0.18, 0.02)	0.06 (−0.04, 0.17)	−0.15 (−0.24, −0.05)	−0.07 (−0.17, 0.03)	−0.18 (−0.27, −0.08)	−0.05 (−0.16, 0.05)
Triglycerides, mmol/L, baseline (SE)	2.02 (0.14)	–	2.17 (0.10)	2.17 (0.10)	2.36 (0.09)	2.36 (0.10)	2.35 (0.10)	2.35 (0.10)
Change from baseline (95% CI)	−0.06 (−0.28, 0.16)	–	−0.22 (−0.37, −0.07)	−0.22 (−0.40, −0.05)	−0.17 (−0.32, −0.02)	−0.14 (−0.31, 0.03)	−0.22 (−0.37, −0.06)	−0.12 (−0.30, 0.05)

* $P < 0.05$ vs. placebo

CI confidence intervals, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

APPENDIX

See Tables 4 and 5.

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