Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

Effects of Taspoglutide on Glycemic Control and Body Weight in Obese Patients With Type 2 Diabetes (T-Emerge 7 Study)

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Objective: Therapies that lower blood glucose and provide weight loss may provide meaningful benefits for obese patients with type 2 diabetes mellitus (T2DM). This study assessed the efficacy of taspoglutide compared with placebo on glycemic control and weight in obese patients with T2DM inadequately controlled with metformin monotherapy.

Design and Methods: In a 24-week, randomized, double-blind, placebo-controlled, multicenter trial, obese adults with T2DM were randomized (1:1) to weekly subcutaneous taspoglutide 20 mg (10 mg for first 4 weeks) ($n = 154$) or placebo ($n = 151$) for 24 weeks. Efficacy measures included hemoglobin A1c (HbA1c) levels, body weight, percentage of patients achieving HbA1c $\leq$6.5 and $\leq$7.0%, and fasting plasma glucose (FPG). Adverse events (AEs) were assessed.

Results: Mean baseline HbA1c was 7.55% and mean baseline BMI was 36.7 kg/m^2. HbA1c reductions from baseline were significantly greater with taspoglutide than placebo (least square mean [LSMean], -0.81% vs. -0.09%; $P < 0.0001$). Weight loss at week 24 was significantly greater with taspoglutide than placebo (LSMean, -3.16 vs. -1.85 kg; $P < 0.01$). In the taspoglutide and placebo groups, target HbA1c levels ($\leq$6.5%) were achieved by 49 and 16% of patients, respectively, while 72 and 36% achieved HbA1c levels $\leq$7%. Decreases in FPG were significantly greater with taspoglutide than placebo (-23.59 vs. 0.09 mg/dl; $P < 0.0001$). Nausea and vomiting were the most common AEs associated with taspoglutide, but tended to be transient and generally mild or moderate.

Conclusions: In obese patients with T2DM, once-weekly taspoglutide provided the combined benefits of glycemic control and weight loss.

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Introduction

The prevalence of both obesity and diabetes has increased dramatically over the last three decades. Approximately 1 billion people worldwide are overweight or obese, and it is estimated that 439 million adults will have diabetes by the year 2030 (1,2). Furthermore, the majority of newly diagnosed cases of diabetes can be directly attributed to obesity (3), and patients with both obesity and type 2 diabetes are at high risk for cardiovascular disease since obesity exacerbates pre-existing cardiometabolic abnormalities (4-6).

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Therefore, although achieving glycemic control is paramount in patients with diabetes, decreasing weight is also imperative, as it has been shown to improve glycemic control, dyslipidemia, hypertension, and long-term outcomes (5,7,8). While weight-loss programs have proven beneficial in improving long-term glycemic control and health outcomes (7,8), they have a low rate of success (7,9). Furthermore, several commonly used antidiabetes therapies (e.g., insulin, sulfonylureas, and thiazolidinediones) are associated with weight gain, which compromises their benefits on glycemic control and renders their use in this population problematic (10-12). Therapies such as insulin and sulfonylureas are also associated with hypoglycemia and fail to preserve β-cell function, which may lead to a further decline in glycemic control over time (12). Therapies that lower blood glucose and provide weight loss with a low risk of hypoglycemia may thus offer higher overall combined benefits for obese patients with type 2 diabetes.

Taspoglutide (RO5073031) is a new, long-acting, human analog of glucagon-like peptide (GLP-1) that produces a long-lasting incretin effect (13). In Phase 2 trials in patients with type 2 diabetes, once-weekly taspoglutide demonstrated good glycemic control with minimal hypoglycemic risk and favorable weight loss (14,15). The primary objective of this study was to assess the efficacy of taspoglutide compared with placebo after 24 weeks of treatment on glycemic control in obese patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy. Safety and tolerability were also assessed, as were the effects of taspoglutide on body weight, additional parameters of diabetes control, and cardiovascular risk factors.

Subjects and Methods

Study design

T-emerge 7 was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (NCT00823992) of obese patients with type 2 diabetes mellitus conducted at 63 centers in eight countries. The study comprised an initial 2-week screening period followed by 24 weeks of double-blind treatment (the results of which are described herein). The study also included a 28-week open-label extension phase, during which patients on taspoglutide continued on the same dose, while patients in the placebo group were switched to taspoglutide 20 mg once weekly (after 4 weeks of taspoglutide 10 mg once weekly). All patients who received at least one dose of study drug were followed up for 2 weeks after their last clinic visit.

Patients were stratified by body mass index (BMI) into two groups (<40 kg/m^2 and ≥ 40 kg/m^2) and randomized in a 1:1 ratio. Patients received a subcutaneous injection in the abdomen of either a sustained-release formulation taspoglutide 20 mg once weekly (following 10 mg once weekly for the first 4 weeks) or placebo (zinc chloride solution 2.7 mg/ml) on the same day each week for 24 weeks. The titration scheme (first 4 weeks of treatment with taspoglutide 10 mg once weekly followed by 20 mg once weekly) was chosen to improve gastrointestinal tolerability (15). All patients continued their prestudy metformin treatment regimen. Patients were provided glucose monitoring devices (ACCU-CHEK®, Roche) for blood glucose self-monitoring. During the study, if glycemic control deteriorated to prespecified levels, additional antihyperglycemic rescue medication was prescribed (first choice was a sulfonylurea [preferably glimepride or glipizide extended release]) and patients continued in the study. Those patients who had contraindications to sulfonylureas received other approved antidiabetes treatments as rescue medication. The investigator or study personnel were instructed to confirm that all patients were following an appropriate dietary and exercise regimen throughout the study.

Randomization was achieved by use of a central randomization system (by site); the randomization code was not broken until the end of the study. All efficacy parameter data were blinded to the investigators during the 24-week double-blind treatment period.

To assess adherence to study interventions, patients were asked to return all used and unused drug supply at each dispensing visit. Patients who missed a dose were instructed to take that dose within the next 3 days of the scheduled date for drug administration. Failing to administer a dose within 10 days from the previous dose was regarded as a missed dose. If a missed dose occurred, patients were instructed to resume the regular treatment schedule with the next scheduled dose.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. In addition, all local regulatory requirements were followed including, in particular, those affording greater protection to the safety of trial participants. The relevant independent ethics committees or independent institutional review boards at each study site approved the study design prior to commencement, and all subjects gave written informed consent before participation.

Patients

Consenting patients were eligible for the study if they were aged 18-75 years with a diagnosis of type 2 diabetes mellitus that was inadequately controlled with diet, exercise, and metformin ($\geq$1,500 mg/day or individually maximally tolerated daily dose) for $\geq$12 weeks prior to screening. Patients were also required to have hemoglobin A1c (HbA1c) $\geq$6.5 and $\leq$9.5% at screening, to be obese (defined as a BMI $\geq$30 and $\leq$50 kg/m^2 at screening), and to have stable weight $\pm$5% for $\geq$12 weeks prior to screening. Patients had to agree to follow a diet and exercise plan during the course of the study, and women of childbearing potential were required to use one medically approved method of contraception during the course of the trial.

Exclusion criteria included diagnosis or history of type 1 diabetes, acute or clinically significant diabetes complications, clinically symptomatic gastrointestinal disease, bariatric surgery, chronic pancreatitis or idiopathic acute pancreatitis, myocardial infarction, coronary artery bypass or stroke within the past 6 months, abnormalities in clinical laboratory tests or electrocardiogram (ECG), blood pressure >170/105 mm Hg, or clinically relevant QT prolongation. The following medications were prohibited: other oral antihyperglycemic agents, weight-lowering drugs, herbal/over-the-counter medications, or corticosteroids within 12 weeks prior to screening and during the trial; insulin within 6 months; or another GLP-1 mimetic or analog at any time prior to screening and during the trial. Antihypertensive, lipid lowering, and thyroid medications were required to be at stable doses for at least 4, 8, and 12 weeks prior to baseline, respectively. Pregnant and nursing women were ineligible for this study.

Efficacy assessments

The primary efficacy endpoint was mean absolute change from baseline in HbA1c at end of treatment (week 24). Secondary efficacy

endpoints included changes in body weight, anthropometric measurements (waist and hip circumference, and waist-to-hip ratio), and HbA1c response rates (percentage of patients with HbA1c $\leq$6.5 and $\leq$7%). Additional secondary efficacy endpoints were absolute and relative changes from baseline in fasting plasma glucose (FPG), β-cell function (indexed by fasting proinsulin concentration, fasting proinsulin/insulin ratio, homeostasis model assessment of β-cell function [HOMA-B]), plasma C-peptide levels, and plasma lipid levels (triglycerides, total cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol). Exploratory efficacy endpoints were changes from baseline in high-sensitivity C-reactive protein (hsCRP), blood pressure, time to glycemic rescue medication, and change from baseline in eating habits.

Safety and tolerability assessments

Data pertaining to adverse events (AEs), vital signs, routine clinical laboratory evaluations (hematology, biochemistry, and urinalysis), ECGs, and plasma calcitonin levels were collected at preplanned intervals throughout the study. All AEs were classified according to the medical dictionary for regulatory activities (MedDRA) terminology. AEs of special interest in this study included hypoglycemia, immunogenicity, pancreatitis, and thyroid tumors. Hypoglycemic episodes were reported as follows: all reported (symptoms with or without confirmation by measured plasma glucose concentration), confirmed (symptoms accompanied by measured plasma glucose concentration $\leq$55 mg/dl), or severe (requiring assistance to actively administer carbohydrate, glucagon, or other resuscitative actions).

Relationships between study medications and AEs were evaluated by the investigators at the site. All AEs, especially those deemed related to study medication, were followed up until relieved or judged to be no longer clinically significant or until they became chronic to the extent that they could be fully characterized.

Statistical analysis

This study was conducted to assess the efficacy of taspoglutide compared with placebo on glycemic control with respect to mean change in HbA1c. It was estimated that 130 patients per treatment arm would provide 90% power to detect: (1) a 0.6% difference in HbA1c change from baseline (assuming an underlying standard deviation [s.d.] of 1.2%) and (2) a 3-kg difference in body weight change from baseline (assuming an underlying s.d. of 6.5 kg) between the taspoglutide and placebo treatment arms at a two-sided significance level of $\alpha = 0.05$, assuming a patient dropout rate of 20%.

Efficacy analyses were conducted on the intent-to-treat (ITT) population, defined as all randomized patients who received at least one dose of study medication and had an evaluable HbA1c measurement at baseline ($\leq$day 1) and at least one post-baseline measurement. Missing data were imputed using the last observation carried forward method. Analysis of covariance (ANCOVA) was used to assess differences in absolute change from baseline in HbA1c between treatment groups. Fixed sequential testing procedures, which controlled for multiplicity across parameters, were used to test whether taspoglutide was significantly better than placebo. HbA1c was tested first, and if taspoglutide was significantly better than placebo, then FPG was tested. If FPG was significantly better for taspoglutide than placebo, then body weight was tested.

Secondary endpoints were also analyzed using ANCOVA, except for responder analyses; responder rates and related 95% confidence intervals (CIs) were calculated according to Pearson-Clopper. Approximate 95% CIs for the pairwise comparisons vs. placebo were calculated. To assess the robustness of the results, primary analyses were repeated using the per-protocol population, defined as ITT patients with no major protocol violations who completed 24 weeks of treatment, were compliant with study medication, and had an evaluable HbA1c at baseline (day 7 to day 1) and at week 24. Safety analyses were performed in the safety population, defined as all randomized patients who received at least one dose of study medication and had at least one post-baseline safety follow-up.

Results

Patient disposition and baseline characteristics

Of the 305 adult patients randomized to the study, 304 patients were included in the safety population and 292 (96%) in the ITT population; 256 patients (84% of the safety population) completed the study and 210 (72% of the ITT population) patients had no major protocol violations (per protocol population). Patient disposition is shown in Figure 1. In all, 66% (101/150) of patients in the taspoglutide group and 79% (119/154) of patients in the placebo group received the 24 planned injections. Injection dosing compliance was similar in both treatment groups (0.94 and 0.97 injections/week in the taspoglutide and placebo groups, respectively).

Baseline demographics and clinical characteristics were similar across treatment groups (Table 1). Mean (s.d.) baseline HbA1c was 7.55% (0.84), mean duration of diabetes was 5.08 years (4.22), mean body weight was 102.5 kg (18.1), and mean baseline BMI was 36.7 kg/m^2 (4.9); 22% of patients had a BMI $\geq$40 kg/m^2. Most patients were women (59%), white (93%), and nonsmokers (84%). Slightly greater proportions of taspoglutide-treated patients had a baseline HbA1c $\geq$8% (30% vs. 27% for taspoglutide and placebo, respectively) and had a history of lipid disorders (51% vs. 43%), whereas slightly more placebo patients had hypertension (69% vs. 76% for taspoglutide and placebo, respectively). Similar proportions of patients were recruited from Europe and North America.

Primary efficacy outcomes

In obese patients with relatively low baseline HbA1c ($\sim$7.5%) who had not achieved glycemic control on diet, exercise, and metformin monotherapy, taspoglutide 20 mg once weekly produced a significantly greater HbA1c decrease from baseline at week 24 compared with placebo (least square mean [LSMean] [standard error (s.e.)]), $-$0.81% (0.06) vs. $-$0.09% (0.06), respectively; unadjusted $P < 0.0001$). Significant reductions in HbA1c from baseline were seen at week 8 in the taspoglutide group and continued to decrease up to week 12, and were then maintained to week 24 (Figure 2A). The LSMean (s.e.) difference of taspoglutide from placebo in HbA1c change from baseline at 24 weeks was $-$0.72% (0.08%; 95% CI, $-$0.88, $-$0.55; unadjusted $P < 0.0001$). Reductions in HbA1c at week 24 were generally similar regardless of baseline BMI; HbA1c decreases in taspoglutide-treated patients were $-$0.83% (0.07) and $-$0.73% (0.12) in patients with baseline BMIs $<$40 and $\geq$40 kg/m^2, respectively. However, taspoglutide-treated patients with a baseline HbA1c $\geq$8% appear to have greater reductions in HbA1c than those

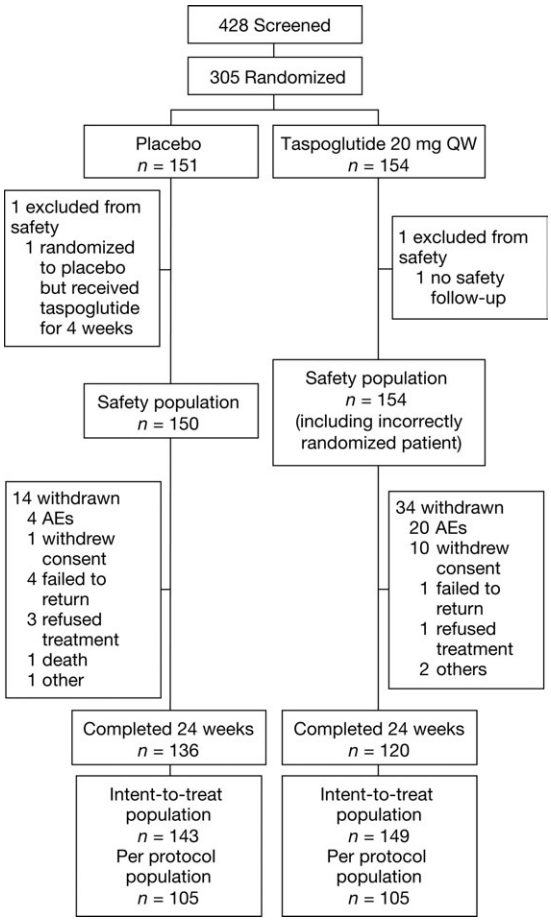

FIGURE 1 Patient disposition*. AEs, adverse events; QW, once weekly. *Patients from 63 centers in eight countries participated in the study.

with a baseline HbA1c <8% (−1.30% [0.14] vs. −0.60% [0.06], respectively) (Figure 2B).

Secondary efficacy outcomes

Body weight and anthropometric assessments. Taspoglutide induced a statistically significant weight loss compared with placebo. At week 24, LSMean (s.e.) weight loss was 3.16 kg (0.30) with taspoglutide compared with 1.85 kg (0.31) in the placebo group (unadjusted $P = 0.0027$) (Figure 3A). The largest decreases in weight were observed over the first 12 weeks of treatment; weight loss continued from week 12 to week 24 in both groups but at a slower rate. Almost one-third of patients (32.9% [95% CI, 25.4, 41.0]) in the taspoglutide group had lost ≥5% of their baseline body weight at week 24 (Figure 3B); a ≥10% loss of baseline body weight was observed with taspoglutide in a small proportion of patients (4% [95% CI, 1.5, 8.6]).

Modest decreases in waist circumference were observed in both treatment groups (LSMean [s.e.], −2.68 cm [0.43] and −2.01 cm [0.45] for taspoglutide 20 mg and placebo, respectively; unadjusted P = NS). A significant decrease in hip circumference was observed at week 24 with taspoglutide compared with placebo (−2.28 cm [0.40] and 0.65 cm [0.41], respectively; unadjusted $P = 0.0047$). At week 24, no differences in waist-to-hip ratio were observed between treatment groups (LSMean [s.e.], −0.003 [0.004] and −0.012 [0.004] for taspoglutide 20 mg and placebo, respectively; unadjusted P = NS).

HbA1c response rates. Higher proportions of taspoglutide-treated patients reached target HbA1c levels of ≤7% (72.5% [95% CI, 64.6, 79.5]) and ≤6.5% (49.0% [95% CI, 40.7, 57.3]) compared with placebo-treated patients (36% [95% CI, 28.5, 44.8] and 16% [95% CI, 10.5, 23.1], respectively) (Figure 3C).

A relationship between the change in glycemic control (HbA1c) and change in body weight was observed (Figure 3D). A greater proportion of patients in the taspoglutide group (75.2%) experienced both a reduction in HbA1c and loss in body weight than those in the placebo group (44.1%).

Fasting plasma glucose. FPG reductions from baseline were observed as early as week 4 in the taspoglutide group and remained greater than placebo until study end. At week 24, LSMean (s.e.) changes from baseline in FPG were significantly greater with

TABLE 1 Patient demographics and clinical characteristics at baseline in the intent-to-treat population

Variables	Placebo ($n = 143$)	Taspoglutide 20 mg QW ($n = 149$)
Sex		
Women, *n* (%)	87 (61)	86 (58)
Age, years (s.d.)	54 (10)	53 (10.0)
Race, *n* (%)		
White	134 (94)	137 (92)
Black	4 (3)	9 (6)
Asian	4 (3)	2 (1)
Other	1 (1)	1 (1)
Ethnicity, *n* (%)		
Hispanic	27 (19)	23 (15)
Weight, kg (s.d.)	101.4 (16.4)	103.6 (19.5)
BMI, kg/m^2(s.d.)	36.5 (4.8)	36.9 (5.0)
BMI ≥40 kg/m^2, *n* (%)	32 (22)	33 (22)
Waist circumference (cm (s.d.))	114.0 (12.1)	115.0 (14.1)
Hip circumference, cm (s.d.)	117.9 (11.4)	119.7 (12.0)
HbA1c, % (s.d.)	7.55 (0.84)	7.54 (0.84)
HbA1c baseline ≥8.0%, *n* (%)	39 (27)	44 (30)
FPG, mg/dl (s.d.)	158 (33)	163 (41)
Diabetes duration, years (s.d.)	4.9 (4.1)	5.2 (4.3)
Comorbid conditions, *n* (%)		
History of dyslipidemia	61 (43)	76 (51)
History of hypertension	108 (76)	103 (69)
Geographic region, *n* (%)		
Europe	73 (51)	81 (54)
North America	70 (49)	68 (46)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; s.d., standard deviation.

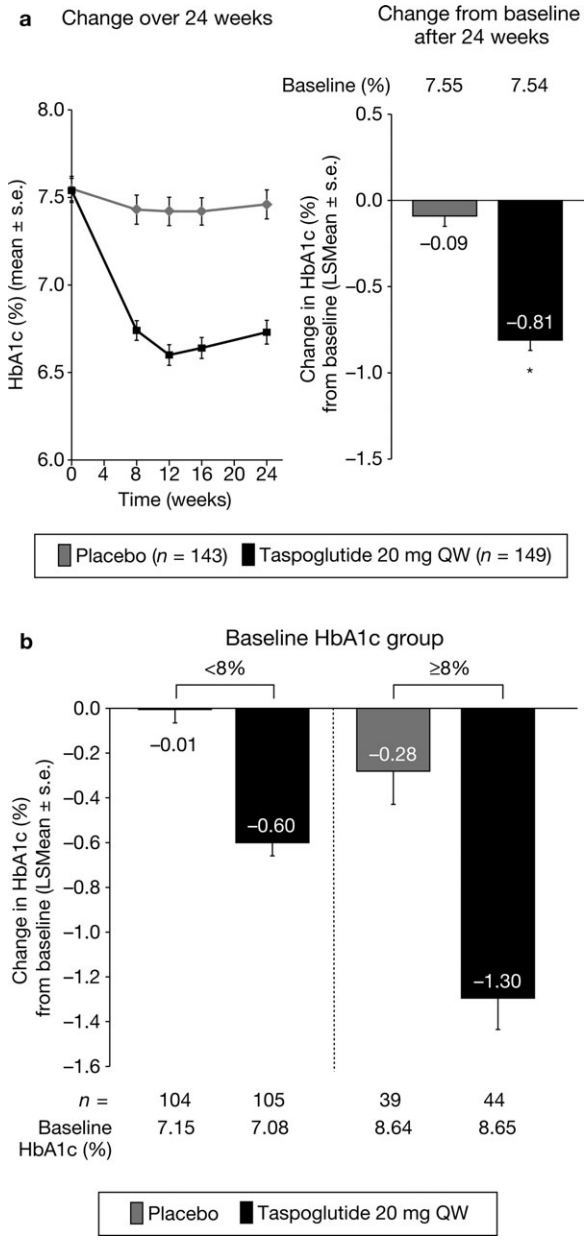

FIGURE 2 Primary efficacy outcomes: glycemic control. Obese patients with type 2 diabetes inadequately controlled with metformin monotherapy received either taspoglutide 20 mg once weekly (QW) or placebo for 24 weeks (last observation carried forward analysis, intent-to-treat population). (a) Mean hemoglobin A1c (HbA1c) values over time and absolute change from baseline at week 24. (b) Absolute change in HbA1c from baseline stratified by baseline HbA1c value. *$P < 0.0001$ vs. placebo. LSMean, least square mean; s.e., standard error.

taspoglutide 20 mg (−23.59 [3.21] mg/dl [−1.31 mmol/l]) than with placebo (0.09 [3.27] mg/dl [0.01 mmol/l]; unadjusted $P < 0.0001$) (Figure 4).

β-cell function and C-peptide levels. An LSMean (s.e.) increase from baseline in HOMA-B score was observed in both treatment groups after 24 weeks of treatment, but was significantly greater with taspoglutide (40.02 [5.60]) compared with placebo (2.67 [6.17]; unadjusted $P < 0.0001$). A greater decrease in C-peptide concentrations was observed in the placebo group compared with the taspoglutide group (LSMean [s.e.] change from baseline: −173.20 [35.12] pmol/l and −5.98 [32.78] pmol/l, respectively; unadjusted $P = 0.0006$). The changes from baseline in fasting insulin, proinsulin, and proinsulin:insulin ratio did not differ between the taspoglutide and placebo groups.

Lipid parameters. Modest improvements from baseline were observed at week 24 for all lipid parameters in both treatment groups (Figure 5). Total cholesterol, LDL cholesterol, the LDL/HDL ratio, and triglycerides showed reductions from baseline, whereas HDL cholesterol showed an increase.

Exploratory efficacy endpoints. In patients treated with taspoglutide, a significant reduction from baseline was observed with hsCRP (−2.05 [0.41]) compared with placebo (−0.84 [0.44]); unadjusted $P < 0.05$. Small improvements compared with baseline were observed in taspoglutide-treated patients at week 24 for systolic blood pressure, and appetite assessments improved (decrease in hunger, increase in fullness, and decrease in desire and quantity to eat), but these changes were not significant (results not shown). Five (3.4%) and 18 (12.6%) patients from the taspoglutide and placebo groups, respectively, received glycemic rescue medication. The time to the first occurrence of glycemic rescue medication was after 12 weeks in both treatment groups.

Sensitivity analyses in the per-protocol population confirmed results of the primary analyses in the ITT population.

Safety and tolerability

AEs were reported by 79 and 59% of patients receiving taspoglutide and placebo, respectively, and tended to be mild to moderate in severity. AEs considered by the investigator to be related to treatment were more frequently reported in the taspoglutide group compared with placebo (57.8% vs. 24.7%). Overall, 23 (14.9%) patients in the taspoglutide 20-mg group and five (3.3%) patients in the placebo group experienced AEs or laboratory abnormalities that led to withdrawal from study treatment. Approximately one-half of the AEs that led to withdrawal from treatment with taspoglutide were due to general disorders and administration site reactions, including fatigue, injection site erythema, injection site hypersensitivity, and injection site nodule.

AEs that occurred at incidences ≥5% are summarized in Table 2. Gastrointestinal AEs and injection site reactions were the most commonly reported AEs associated with taspoglutide. Nausea and vomiting occurred in approximately one-third and one-quarter of taspoglutide-treated patients, respectively. Both events were mild to moderate in intensity, occurred predominantly as a single episode on the day of injection, infrequently led to discontinuation, and tended to last for no more than 1 day (Figures 6A and 6B). No patients in the placebo group and 3.9% of patients in the taspoglutide group withdrew from the study due to nausea or vomiting.

The two most commonly reported injection site reactions were injection site erythema and injection site nodule, which occurred in 11.7% of patients each in the taspoglutide group, and in 2% and 1.3% of patients in the placebo group, respectively. The majority of injection site reactions were mild to moderate; nine (5.7%) patients

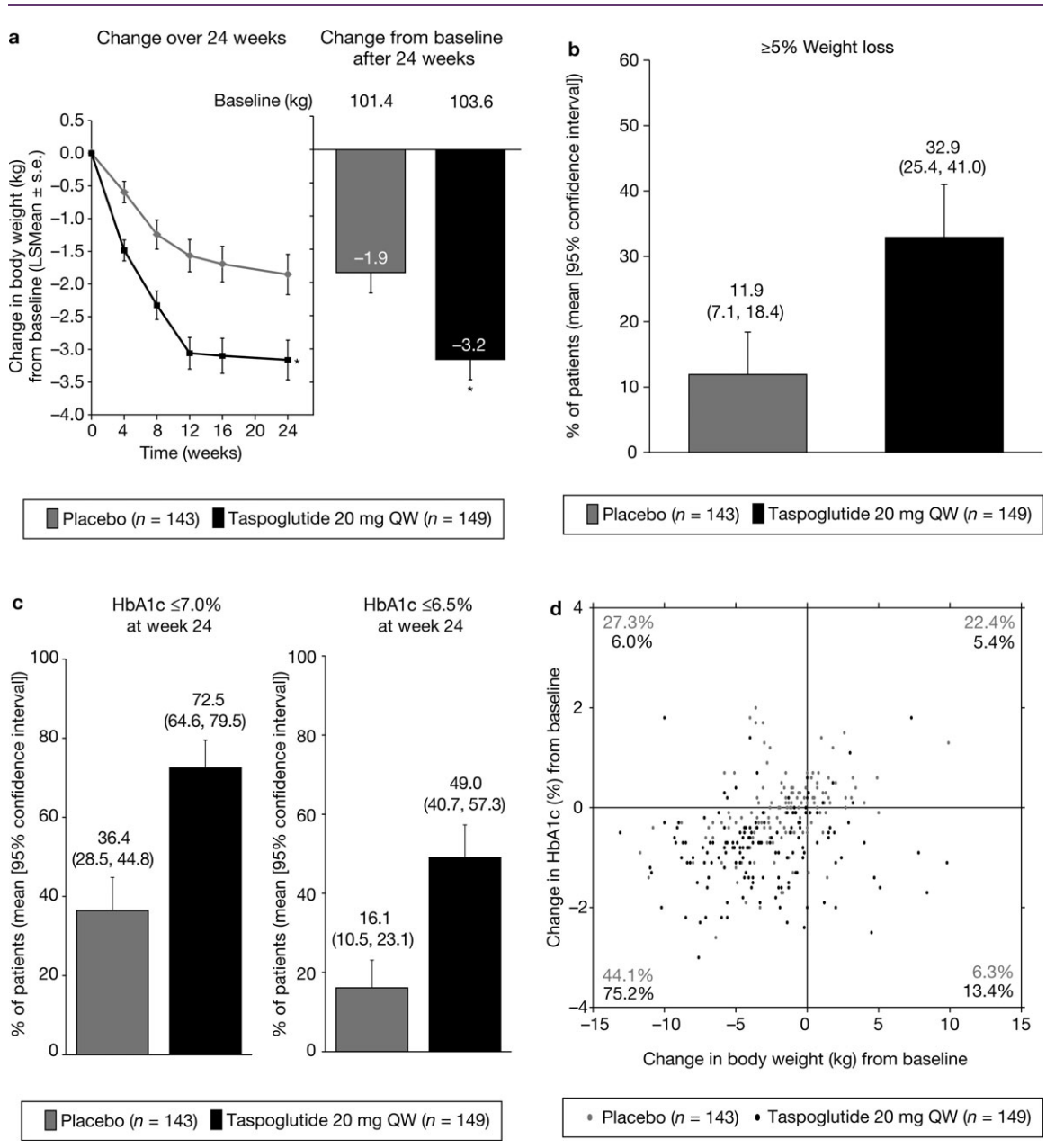

FIGURE 3 Secondary efficacy outcomes: change in body weight and patients achieving target hemoglobin A1c (HbA1c). Obese patients with type 2 diabetes inadequately controlled with metformin monotherapy received either taspoglutide 20 mg once weekly (QW) or placebo for 24 weeks (last observation carried forward analysis, intent-to-treat population). (a) Mean change from baseline in body weight over time and absolute change from baseline at week 24. (b) Percentage of patients achieving target weight loss at week 24. (c) Percentage of patients achieving target HbA1c levels at week 24. (d) Relationship between the change in body weight and change in HbA1c: glycemic control. Values represent proportion of each treatment group within each quadrant. *$P = 0.0027$ vs. placebo. LSMean, least square mean; s.e., standard error.

in the taspoglutide group had injection site reactions that led to discontinuation.

The overall incidence of hypoglycemic events was low (9.7% in the taspoglutide group and 2.7% in the placebo group). All hypoglycemic events were mild or moderate and resolved without sequelae, and no confirmed (i.e., having a glucose value $\leq$55 mg/dl) or severe hypoglycemia was reported in the taspoglutide group. There were no clinically significant abnormalities in vital signs, ECG reports, hematology, biochemistry, urinalysis, and calcitonin values. No events of pancreatitis or thyroid cancer were reported.

A total of 16 patients (10 in the taspoglutide group and 6 in the placebo group) experienced serious AEs. Events in the taspoglutide group included anaphylactic reaction, acute myocardial infarction, bladder prolapse, malignant melanoma, syncope, cellulitis,

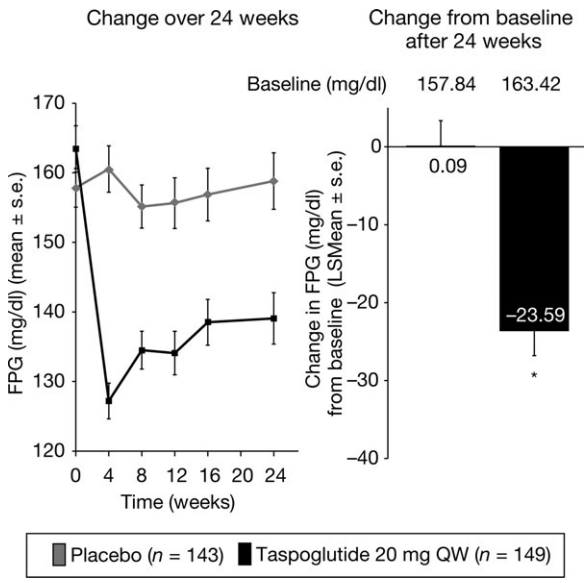

FIGURE 4 Secondary efficacy outcome: change in fasting plasma glucose (FPG). Obese patients with type 2 diabetes inadequately controlled with metformin monotherapy received either taspoglutide 20 mg once weekly or placebo for 24 weeks (last observation carried forward analysis, intent-to-treat population). Mean FPG values over time and absolute change in FPG from baseline at week 24. *$P < 0.0001$ vs. placebo. LSMean, least square mean; s.e., standard error.

arthralgia, foot deformity, sciatica, and abdominal pain (in one patient each). The anaphylactic reaction was considered by the investigator to be treatment-related and severe, and it resulted in early withdrawal of the patient from the study. This reaction fully resolved after treatment with prednisone. All other events were considered to be unrelated to study treatment and patients continued on study. Seven events occurred among the six patients in the placebo group and included coronary artery disease, hematuria, nephrolithiasis, pneumonia, foot fracture, tibia fracture, and varicose veins. One death occurred in the placebo arm during the 24-week treatment period.

Discussion

The results of this study demonstrated that taspoglutide 20 mg once weekly for 24 weeks provided both glycemic control and weight loss for obese patients already receiving maximal dosages of metformin and participating in a diet and exercise plan. After 24 weeks of treatment, taspoglutide demonstrated a robust HbA1c reduction of −0.81% in obese patients with a low baseline HbA1c (~7.5%) who had not achieved glycemic control on metformin monotherapy. Almost one-half of patients achieved an HbA1c ≤6.5% after 24 weeks of taspoglutide treatment, as is reflected by the fact that 49% of patients had an HbA1c level ≤6.5%. Furthermore, marked reductions in HbA1c were observed in patients regardless of baseline body weight or BMI, including those with BMI ≥40 kg/m^2 at baseline, demonstrating that even extremely obese subjects derived benefit from taspoglutide.

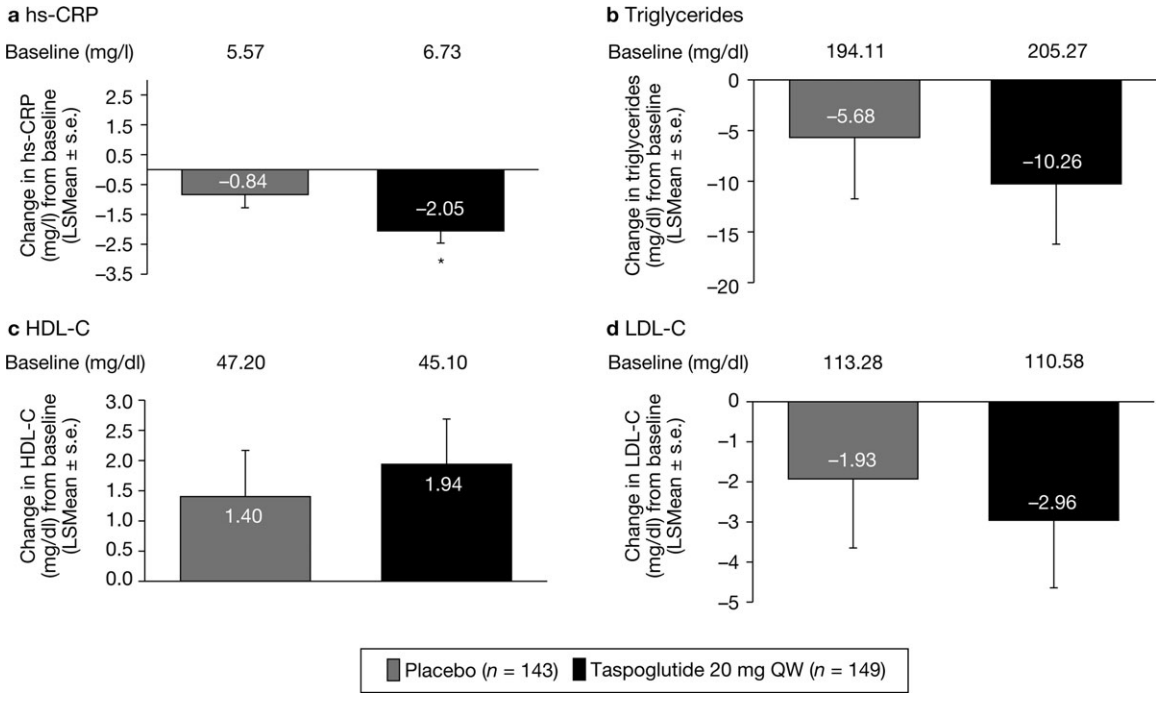

FIGURE 5 Change in lipid parameters and C-reactive protein. Obese patients with type 2 diabetes inadequately controlled with metformin monotherapy received either taspoglutide 20 mg once weekly or placebo for 24 weeks (last observation carried forward analysis, intent-to-treat population). Change from baseline in: (a) high-sensitivity C-reactive protein (hsCRP); (b) triglycerides; (c) high-density lipoprotein cholesterol (HDL-C); and (d) low-density lipoprotein cholesterol (LDL-C) at week 24. *$P < 0.05$ vs. placebo. LSMean, least square mean; s.e., standard error.

TABLE 2 Adverse events (AEs) reported in the safety population, including the overall incidence of AEs occurring in ≥5% of patients

Description/body system, *n* (%)	Placebo (*n* = 150)	Taspoglutide 20 mg QW (*n* = 154)
Total patients with ≥1 AE	89 (59.3)	122 (79.2)
Serious AEs	6 (4.0)	10 (6.5)
Withdrawals due to AEs[a]	5 (3.3)	23 (14.9)
Withdrawals due to nausea and vomiting	-	6 (3.9)
Deaths (*n*)	1	-
Gastrointestinal disorders		
Nausea	8 (5.3)	54 (35.1)
Vomiting	5 (3.3)	37 (24.0)
Diarrhea	16 (10.7)	16 (10.4)
Constipation	3 (2.0)	10 (6.5)
Dyspepsia	3 (2.0)	10 (6.5)
General disorders and administration site conditions		
Injection site erythema	3 (2.0)	18 (11.7)
Injection site nodule	2 (1.3)	18 (11.7)
Injection site pruritus	1 (0.7)	15 (9.7)
Injection site pain	4 (2.7)	8 (5.2)
Injection site reaction	1 (0.7)	11 (7.1)
Injection site mass	1 (0.7)	8 (5.2)
Metabolism and nutrition disorders		
Hypoglycemia	4 (2.7)	15 (9.7)
Confirmed (glucose ≤55 mg/dl^{-1})	1 (0.7)	-
Severe hypoglycemia	-	-
Decreased appetite	5 (3.3)	9 (5.8)
Musculoskeletal and connective tissue disorders		
Back pain	5 (3.3)	8 (5.2)
Nervous system disorders		
Headache	8 (5.3)	9 (5.8)
Dizziness	6 (4.0)	9 (5.8)

[a]Includes patients who completed the 24-week core phase but then shortly thereafter discontinued due to AEs that were ongoing at time of completion.

The efficacy of taspoglutide was also compared in patients with HbA1c ≥8% and those with HbA1c <8% at baseline. Although HbA1c reductions were twice as great in patients with a baseline HbA1c ≥8% compared with patients with baseline HbA1c <8% (−1.30% vs. −0.60%), the latter patients achieved HbA1c levels of ≤6.5% after taspoglutide treatment, since baseline HbA1c in the <8% group was ∼7.0%. This observation suggests that patients who have near-normal HbA1c levels may derive benefit from taspoglutide.

In contrast to other antidiabetes medications, such as insulin, sulfonylureas, and thiazolidinediones, which are associated with weight gain (10-12), taspoglutide treatment was associated with significant weight loss as well as a trend for decreases in waist and hip circumference, although the latter did not reach significance. As expected, patients who were classified as obese at baseline lost over 3 kg of their body weight following taspoglutide treatment and one-third of patients lost <5%. It is noteworthy that the information regarding diet and exercise provided to patients consisted of periodic reinforcement of a healthy lifestyle behavior from a healthcare professional at each visit. This limited intervention resulted in reduction in body weight in the placebo group. As weight loss has been shown to improve glycemic control, dyslipidemia, and hypertension, as well as long-term outcomes (5,7,8), these results, when taken together with the significant improvements in glycemic control, suggest that taspoglutide may provide enhanced benefits for obese patients with type 2 diabetes; however, long-term studies are needed to confirm these results.

Overall, these results are similar to those reported in a study of overweight patients (mean [s.d.] BMI 34 [6] kg/m^2) with type 2 diabetes treated with exenatide twice daily as add-on therapy to metformin and/or a sulfonylurea; HbA1c levels decreased by 0.9% and patients lost ∼2 kg body weight following exenatide treatment (16). Other studies of the GLP-1 receptor agonists exenatide and liraglutide as add-on therapy to metformin and/or sulfonylurea therapy have demonstrated similar HbA1c decreases (17,18). A recent retrospective study of patient records found that patients treated with exenatide twice daily lost a mean (s.d.) of 3.0 kg (7.3) (19), although these studies were not specific to overweight or obese patients. Although the exact mechanism underlying this weight loss is unclear, one study has shown that weight loss in patients treated with liraglutide is associated with a reduction in fat mass and relative total body fat (20).

Taspoglutide once weekly significantly decreased FPG and improved insulin release, which are consistent with its prolonged incretin response (13). Taspoglutide also improved β-cell function, as evidenced by the significant improvement in HOMA-B levels. Traditional agents, including metformin, sulfonylureas, or insulin, do not affect β-cell function, and patients treated with these agents generally lose glycemic control over time (21). The increase in HOMA-B score, an index of insulin secretion, seen with taspoglutide treatment is consistent with the results in other studies (14,22). Taspoglutide prevented the significant decline in fasting C-peptide concentrations observed in the placebo group (−5.98 pmol/l vs. −173.20 pmol/l, respectively). This result was consistent with other taspoglutide clinical studies (14; F. Hoffmann-La Roche Ltd, unpublished data) and might be related to a decline in β-cell function in the placebo group vs. relative β-cell stimulation in the taspoglutide group as shown by the relationship between insulin and FPG (14). The robust suppression in FPG with taspoglutide may be explained by increased sensitivity with taspoglutide treatment in this obese population. Although glucagon was not measured in this study, taspoglutide has been shown to suppress inappropriately elevated glucagon levels (14; F. Hoffmann-La Roche Ltd, unpublished data).

Taspoglutide treatment was also associated with modest improvements in blood lipid parameters and clinically meaningful reduction in systolic blood pressure. When taken together with its favorable effects on blood glucose and weight, it suggests that taspoglutide treatment provides well-rounded glycemic control with favorable cardiometabolic effects.

Nausea and vomiting were the most frequently reported AEs, although these events were predominantly single episodes that tended to occur on the day of injection and infrequently led to

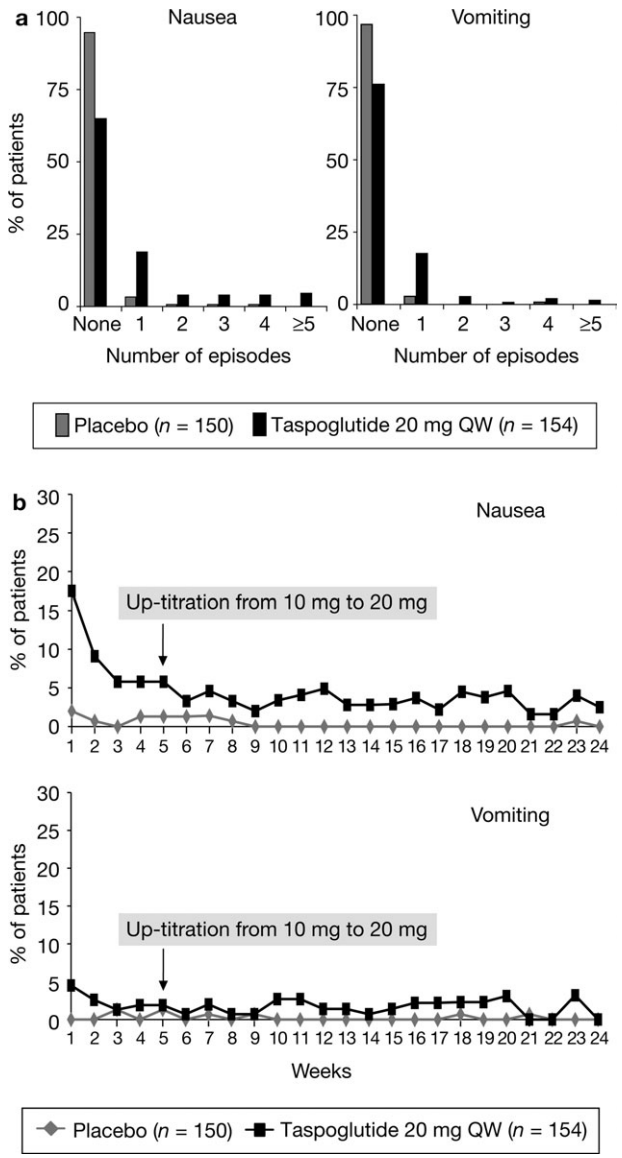

FIGURE 6 Incidence of nausea or vomiting. In the safety population, (a) number of episodes of nausea and vomiting; (b) proportion of patients affected by nausea or vomiting throughout the 24-week study. Up-titration for taspoglutide group only. QW, once weekly.

discontinuation. The weight loss observed in the study was not correlated with nausea and vomiting. In contrast to traditional antidiabetes agents, which are associated with hypoglycemia (21), there was a low risk of hypoglycemia with taspoglutide treatment, and no severe hypoglycemia. Although acute pancreatitis has been associated with the use of the GLP-1 receptor agonist exenatide (23), no cases of pancreatitis were reported among taspoglutide-treated patients in this study. Taken together, these results suggest that taspoglutide provides significant glycemic control in obese patients (even those with low baseline HbA1c levels) without increasing the risk of hypoglycemia or pancreatitis.

The T-emerge Phase 3 clinical trial program was designed to assess the safety and efficacy of taspoglutide in a diverse range of patients with type 2 diabetes. To our knowledge, T-emerge 7 was the first multinational, randomized, controlled, double-blind study of a GLP-1 receptor agonist conducted exclusively in obese patients with type 2 diabetes. This study included one of the largest cohorts of extremely obese patients with type 2 diabetes reported in clinical trials (22% had a BMI $\geq$40 kg/m^{-2}), a target population often excluded from clinical trials. Limitations of the study included its relatively short duration, the lack of an active comparator, and a lack of standardization of the diet and exercise regimen throughout the trial.

In conclusion, in this study of obese patients with type 2 diabetes, taspoglutide once weekly provided combined benefits of substantial HbA1c lowering, target HbA1c control, and low risk of hypoglycemia, with a favorable effect on weight loss. An antidiabetes therapy such as taspoglutide that achieves favorable blood glucose-lowering control and weight loss may provide a better approach for glycemic control with cardiometabolic benefits.* O

Acknowledgments

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*In September 2010, Roche decided to stop dosing patients in the taspoglutide Phase 3 trials because higher than expected discontinuation rates of taspoglutide-treated patients were observed, mainly due to gastrointestinal tolerability 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.

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