Efficacy and Safety of Taspoglutide Monotherapy in Drug-Naive Type 2 Diabetic Patients After 24 Weeks of Treatment

Results of a randomized, double-blind, placebo-controlled phase 3 study (T-emerge 1)

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OBJECTIVE—To evaluate the efficacy and safety of taspoglutide monotherapy in drug-naive patients with type 2 diabetes inadequately controlled.

RESEARCH DESIGN AND METHODS—In this 24-week double-blind, placebo-controlled, multicenter trial, 373 patients with type 2 diabetes naive to antihyperglycemic medication were randomized to weekly subcutaneous taspoglutide 10 or 20 mg or placebo.

RESULTS—HbA_{1c} reductions from baseline were greater with taspoglutide 10 and 20 mg than placebo (least squares mean [SE] changes: –1.01% [0.07], –1.18% [0.06], and –0.09% [0.07], respectively; both $P < 0.0001$ vs. placebo). Decreases in bodyweight were greater with taspoglutide 10 mg (–1.45 kg [0.32]) and with 20 mg (–2.25 kg [0.30]) than placebo (–1.23 kg [0.31]; $P = 0.61$ and $P = 0.02$ for taspoglutide 10 and 20 mg vs. placebo, respectively). Gastrointestinal adverse events and injection site reactions were more common with taspoglutide than placebo.

CONCLUSIONS—In drug-naive patients, once-weekly taspoglutide improved glycemic control, reduced body weight, and was generally well tolerated.

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Taspoglutide is a human glucagon-like peptide 1 analog with a pharmacokinetic profile suitable for once-weekly subcutaneous administration (1). In a phase 2 clinical trial, once-weekly taspoglutide added to metformin lowered HbA_{1c} by up to 1%, reduced body weight, and was generally well tolerated (2). The efficacy and safety of taspoglutide monotherapy as a first-line agent was investigated in a phase 3 trial in patients with early type 2 diabetes who were inadequately controlled with diet and exercise and naive to antihyperglycemic therapy.

RESEARCH DESIGN AND METHODS

This 24-week, randomized, double-blind, placebo-controlled study (clinical trial reg. no. NCT00744926) was conducted at 53 centers internationally and in accordance with the principles of the Declaration of Helsinki. An institutional review/ethics board at each center approved the protocol, and written informed consent was obtained from all patients.

Eligible patients were adults (aged ≥18 and ≤80 years) with type 2 diabetes naive to antihyperglycemic therapy and uncontrolled with diet and exercise (HbA_{1c} 6.5−10%; BMI 25−45 kg/m^2).

Patients were excluded if they had significant complications associated with type 2 diabetes, symptomatic gastrointestinal diseases, history of bariatric surgery, pancreatic disease, cardiac disease within the past 6 months, history of unstable hypertension, treatment with chronic corticosteroids within the past month, and treatment with weight-lowering agents within the past 12 weeks.

Patients were randomly assigned (1:1:1) to subcutaneous taspoglutide 10 mg weekly, taspoglutide 20 mg weekly (after 10 mg weekly for the initial 4 weeks), or placebo. Patients were stratified by baseline HbA_{1c} (<8.0 or ≥8.0%). If glycemic control deteriorated, additional antihyperglycemic rescue medication was prescribed and the patient could continue in the study.

The primary efficacy end point was absolute change from baseline in HbA_{1c} after 24 weeks. Secondary efficacy end points included HbA_{1c} response rates (≤6.5 and ≤7%) and changes in fasting plasma glucose (FPG), fructosamine, body weight, fasting proinsulin, fasting proinsulin-to-insulin ratio, and homeostasis model

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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.

Table 1—*AEs (safety population)*

	Placebo (*n* = 123)	Taspoglutide 10 mg (*n* = 116)	Taspoglutide 20 mg (*n* = 129)
Serious AEs			
Unstable angina	1	0	0
Benign prostatic hypertrophy	1	1	0
Hypersensitivity	0	1	1
Abdominal pain	0	1	0
Ischemic stroke	0	1	0
Hypertension	0	1	0
Angina pectoris	0	0	1
Neck pain	0	0	1
AEs leading to withdrawal			
Vomiting	0	4 (3.4)	2 (1.6)
Nausea	0	1 (0.9)	5 (3.9)
Diarrhea	1 (0.8)	2 (1.7)	0
Other gastrointestinal events	0	0	4 (3.1)
Injection site reaction	0	2 (1.7)	4 (3.1)
Hyperglycemia	2 (1.6)	2 (1.7)	0
Hypersensitivity	0	1 (0.9)	1 (0.8)
Liver enzyme elevations	1 (0.8)	0	0
Palpitations	0	0	1 (0.8)
Headache	0	1 (0.9)	0
Total patients withdrawn	4	13	17
Treatment-emergent AEs*			
Total gastrointestinal events	13 (10.6)	44 (37.9)	58 (45.0)
Nausea	5 (4.1)	30 (25.9)	40 (31.0)
Vomiting	0	20 (17.2)	23 (17.8)
Diarrhea	5 (4.1)	16 (13.8)	12 (9.3)
General disorders and administration site conditions	13 (10.6)	42 (36.2)	44 (34.1)
Injection site nodule	1 (0.8)	14 (12.1)	12 (9.3)
Injection site reaction	0	8 (6.9)	9 (7.0)
Injection site in duration	1 (0.8)	6 (5.2)	7 (5.4)
Injection site pruritis	0	5 (4.3)	7 (5.4)
Total nervous system disorders	6 (4.9)	19 (16.4)	15 (11.6)
Headache	2 (1.6)	13 (11.2)	8 (6.2)
Dizziness	2 (1.6)	6 (5.2)	8 (6.2)
Total metabolism and nutrition	4 (3.3)	14 (12.1)	7 (5.4)
Hypoglycemia	1 (0.8)	6 (5.2)	5 (3.9)

Data are *n* or *n* (%). *Data are *n* (%) of the safety population (*n* = 368) for AEs that began during study treatment and occurred in ≥5% of patients in any treatment group.

assessment of β-cell function (HOMA-B). Exploratory end points are listed in Supplementary Table 1.

Safety assessments included adverse events (AEs), vital signs, physical examinations, clinical laboratory tests, electrocardiograms, and hypoglycemia.

Statistical analysis

Approximately 130 patients per treatment arm were needed to detect a difference from placebo in HbA_{1c} of 0.6% between groups with a power of 90%, assuming an SD of change from baseline of 1.2. Primary efficacy analyses were conducted using intention-to-treat population. The primary end point was analyzed using ANCOVA with treatment, region, and baseline value of the end point as the covariate. Missing data were imputed using the last observation carried forward method. HbA_{1c} was tested in each of the two active arms versus placebo using the two-sided 95% CI for treatment difference.

RESULTS—Of 373 randomized patients, 368 received at least one dose of study medication and had at least one follow-up safety measurement, and 354 received at least one dose of study medication and had an evaluable baseline and at least one postbaseline measurement of HbA_{1c} (Supplementary Fig. 1). Treatment groups were well matched at baseline, and mean duration of diabetes was 2.1−2.8 years (Supplementary Table 2).

Least squares mean HbA_{1c} decreased from baseline by −0.09 ± 0.07, −1.01 ± 0.07, and −1.18 ± 0.06% with placebo, taspoglutide 10 mg, and taspoglutide 20 mg, respectively (both $P < 0.0001$ vs. placebo). Reductions were greater with taspoglutide (10- and 20-mg groups, respectively) in patients with HbA_{1c} ≥8% (–1.69 and –1.72%) vs. <8% (–0.69 and –0.93%) at baseline. A greater proportion of patients in the taspoglutide 10- and 20-mg groups, respectively, achieved HbA_{1c} of ≤6.5% (60 and 66%) and ≤7.0% (80 and 83%) versus placebo (17 and 40%) (Supplementary Fig. 2*A* and *B*).

Least squares mean changes from baseline in FPG were –0.08 ± 0.17, –1.55 ± 0.17, and –1.90 ± 0.16 mmol/L with placebo, taspoglutide 10-mg, and 20-mg groups, respectively (both $P <$ 0.001 vs. placebo). Weight loss occurred progressively in all groups and was greater in the taspoglutide 20-mg group versus placebo (–2.25 ± 0.30 kg; $P = 0.02$).

Significant improvements in HOMA-B were seen with both doses of taspoglutide versus placebo (59 and 65 vs. 2; $P = 0.01$ and $P < 0.01$ for taspoglutide 10 mg and 20 mg, respectively). Proinsulin-to-insulin ratios significantly decreased with taspoglutide 10 and 20 mg versus placebo (Supplementary Table 3).

Treatment-emergent AEs were reported in 44.7, 69.0, and 75.2% of patients in the placebo, taspoglutide 10-mg, and taspoglutide 20-mg groups, respectively. Serious AEs were reported in 10 patients (Table 1). Hypersensitivity reactions were reported in two patients receiving taspoglutide 10 mg (one moderate rash on left forearm, which occurred shortly after the first injection of trial medication, and one moderate systemic urticaria, which occurred on study day 163 after the last injection) and in two patients receiving taspoglutide 20 mg (one case of face redness moderate in intensity that started on study day 29 immediately after the patient had received the fifth dose of taspoglutide and one severe edema of the larynx and tongue that occurred shortly after the first dose of taspoglutide 10 mg and resolved 1 h after prednisone administered). No deaths occurred and no cases of pancreatitis were reported.

Gastrointestinal complaints were the most frequently reported AEs (Table 1). Injection site reactions occurred at a higher frequency in patients receiving taspoglutide

than placebo. No cases of severe hypoglycemia were reported.

Withdrawal from treatment as a result of AEs occurred in 3.3, 11.2, and 13.2% of the placebo, taspoglutide 10-mg, and taspoglutide 20-mg groups, respectively (Table 1).

CONCLUSIONS—Once-weekly taspoglutide monotherapy improved HbA_{1c}, FPG, and HOMA-B and reduced body weight during a 24-week period in patients with newly diagnosed type 2 diabetes who were naive to antihyperglycemic agents. Notable findings included a mean reduction in HbA_{1c} of nearly 1.2% in patients with a mean baseline of 7.7% treated with taspoglutide 20 mg. In patients with baseline HbA_{1c} of ~7.0%, patients achieved an HbA_{1c} of 6.1% with 20 mg and 6.3% with 10 mg after 24 weeks of treatment with taspoglutide.

Taspoglutide monotherapy was generally well tolerated; the most frequently reported AEs were nausea and vomiting. Hypersensitivity reactions occurred in four patients; two patients withdrew. In summary, once-weekly taspoglutide given as monotherapy was efficacious and generally well tolerated in patients with type 2 diabetes naive to treatment with antidiabetic agents.

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