Long-term safety and efficacy of a novel once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in patients with type 2 diabetes mellitus: A 52-week open-label, phase 3 study

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ABSTRACT

Aims/Introduction: Trelagliptin is a novel once-weekly oral dipeptidyl peptidase-4 inhibitor for type 2 diabetes mellitus that was first approved in Japan. We evaluated long-term safety and efficacy of trelagliptin in Japanese patients with type 2 diabetes mellitus.

Materials and Methods: This was a phase 3, multicenter, open-label study to evaluate long-term safety and efficacy of trelagliptin. Patients with type 2 diabetes mellitus inadequately controlled despite diet/exercise or treatment with one of the existing oral antidiabetic drugs along with diet/exercise received trelagliptin 100 mg orally once weekly for 52 weeks as monotherapy or combination therapies. The primary end-points were the safety variables, and the secondary end-points were glycosylated hemoglobin and fasting plasma glucose.

Results: A total of 680 patients received the following antidiabetic therapies: trelagliptin monotherapy ($n = 248$), combination with a sulfonylurea ($n = 158$), a glinide ($n = 67$), an α-glucosidase inhibitor ($n = 65$), a biguanide ($n = 70$), or a thiazolidinedione ($n = 72$). During the study, 79.8% of the patients experienced at least one adverse event for monotherapy, 87.3% for combination with a sulfonylurea, 77.6% for a glinide, 81.5% for an α-glucosidase inhibitor, 64.3% for a biguanide, and 84.7% for a thiazolidinedione, respectively. Most of the adverse events were mild or moderate. The change in glycosylated hemoglobin from baseline at the end of the treatment period was −0.74 to −0.25% for each therapy.

Conclusions: Once-weekly oral trelagliptin provides well-tolerated long-term safety and efficacy in both monotherapy and combination therapies in Japanese patients with type 2 diabetes mellitus.

INTRODUCTION

As hyperglycemia is the key determinant factor in micro- and macrovascular complications of type 2 diabetes mellitus, it is important to maintain long-term glycemic control to prevent and delay the onset and development of complications[1–3]. Adherence to treatment is often poor in patients with chronic, potentially asymptomatic diseases, such as type 2 diabetes

mellitus[4–7]. Drug regimens with reduced dosing frequency are often preferred by patients, and could result in improved treatment compliance[5–9]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are prescribed to patients with type 2 diabetes mellitus, with administration once or twice a day.

Trelagliptin succinate (trelagliptin) is a novel long-acting, highly selective DPP-4 inhibitor that is available as a once-weekly oral dosing regimen[10–12]. In a phase 1 study, the profile of single doses of trelagliptin supported once-weekly

dosing, and showed sustained inhibition of DPP-4 for 7 days[10]. The results of a phase 2 placebo-controlled study showed that trelagliptin once a week for 12 weeks produced a dose-dependent improvement in glycemic control[11]. In a phase 3 study, 24-week treatment with once-weekly oral tre-lagliptin at a dose of 100 mg showed non-inferiority of tre-lagliptin to once-daily DPP-4 inhibitor alogliptin with favorable safety and tolerability profiles, which were also comparable with those of alogliptin[12].

The present study was designed to evaluate the long-term safety and efficacy of once-weekly oral trelagliptin when administered alone or in combination with an existing oral antidiabetic drug for 52 weeks in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study design and patients
This was a long-term, multicenter, open-label phase 3 study to evaluate the safety and efficacy of once-weekly oral trelagliptin as monotherapy or in combination with an existing oral antidiabetic drug in Japanese patients with type 2 diabetes mellitus with inadequate glycemic control despite diet and exercise therapies or treatment with one of the existing oral antidiabetic drugs along with diet and exercise therapies. Patients considered eligible according to the inclusion and exclusion criteria during the 2-week screening period received one tablet of trelagliptin 100 mg orally once weekly before breakfast for 52 weeks during the treatment period.

We enrolled patients aged 20 years and older who had been given a diagnosis of type 2 diabetes mellitus; who had glycosylated hemoglobin (HbA$_{1c}$) values between 6.9% and 10.5% at the beginning of the screening period; who had been on specific diet and exercise therapies for at least 10 weeks before the start of screening. The inclusion criteria for the patients who only received long-term combination therapy included the following: use of an existing oral antidiabetic drug at a stable dose and a regimen from at least 10 weeks (14 weeks for thiozolidinedione) before the start of screening. In the present study, the basal antidiabetic drug was defined as an existing oral antidiabetic drug that the patient was receiving at the beginning of the screening period and continued to use concomitantly until the end of the study.

Patients were excluded if they had signs of hepatic impairment (e.g., alanine aminotransferase or aspartate aminotransferase ≥2.5-fold the upper limit of normal, or total bilirubin ≥34.2 μmol/L), or if they had clinically significant electrocardiogram (ECG) abnormalities (e.g., QT interval corrected for heart rate [QTcF interval] >450 ms at the start of screening).

The study was approved by the institutional review board of each study site, and was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization Harmonized Tripartile Guideline for Good Clinical Practice. All patients provided written informed consent.

Procedures
After a 2-week screening period, eligible patients received 100 mg of oral trelagliptin once a week. For the combination therapy group, patients who had been using an existing oral antidiabetic drug according to the package insert of the drug at a stable dose and regimen for at least 10 weeks (14 weeks for thiozolidinedione) before the start of the screening period were enrolled and continued to receive the same antidiabetic drug in addition to trelagliptin until the end of the study. We monitored the patients' compliance with diet and exercise throughout the study by assigning all patients to one of the following categories of compliance with diet and exercise sessions: fully complied (≥90% for diet and exercise sessions); almost complied (≥70%); occasionally complied (≥50%); and rarely complied (<50%). We assessed drug compliance through analysis of the records of the administration date of trelagliptin, and the number of drugs prescribed and collected for each basal oral antidiabetic drug. No rescue therapy was planned.

Patients were assessed for safety and efficacy parameters at 2-week intervals from the end of screening (i.e., baseline, week 0) to week 4, and then every 4 weeks until the end of treatment (week 52), with a final follow-up visit 1 week later. At each assessment, we measured the following: safety variables, including adverse events (AEs); vital signs; 12-lead ECG findings; clinical laboratory test data and self-measured blood glucose (only for patients who received combination therapy with a sulfonylurea); HbA$_{1c}$, fasting plasma glucose (FPG); fasting insulin; fasting glucagon; glycoalbumin; weight; homeostasis model assessments of insulin resistance (HOMA-IR) and β-cell function (HOMA-β); and DPP-4 activity. All samples for clinical laboratory tests were obtained before drug dosage.

All clinical laboratory tests were carried out at an independent central laboratory (LSI Medience Corporation, Tokyo, Japan). HbA$_{1c}$ was converted from Japan Diabetes Society values (%) into National Glycohemoglobin Standardization Program values (%) using the following calculation: National Glycohemoglobin Standardization Program HbA$_{1c}$ (%) = 1.02 × Japan Diabetes Society HbA$_{1c}$ (%) + 0.25%. DPP-4 activity was measured with the enzyme activity measurement method by enzyme-linked immunosorbent assay[13]. HOMA-IR was calculated with the equation HOMA-IR = insulin concentration × FPG/405; HOMA-β with the equation HOMA-β = insulin concentration × 360/(FPG − 63).

An interim analysis was planned to be carried out using the data up to week 4 of the treatment period from the first 300 patients who received the study drug without database lock to evaluate the risk of QT/QTc interval prolongation that trelagliptin might pose, and to decide whether to continue or discontinue the study or even revise the protocol. An Independent Safety Monitoring Committee was set to recommend to the sponsor whether the study should be terminated or continued, or whether the protocol should be revised, on the basis of the results of the interim analysis.

Outcome

The primary end-points were safety variables, including AEs, vital signs, 12-lead ECG findings, clinical laboratory test data and self-measured blood glucose (only for patients who received combination therapy with a sulfonylurea). The secondary end-points were efficacy variables, such as HbA_{1c} and FPG. Other efficacy measures included fasting insulin, fasting glucagon, glycoalbumin, weight, HOMA-IR and HOMA-β, and DPP-4 activity.

Statistical analysis

To fulfil the requirement of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents[14], and Questions and Answers regarding the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents regarding the number of patients and assuming discontinuation rates of approximately 7% during 24-week treatment for trelagliptin monotherapy, a total of 227 patients who received trelagliptin monotherapy were required in the present study. According to the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents[14], and assuming discontinuation rates of approximately 30% for combination with sulfonylurea and 20% for combination with each of the other antidiabetic drugs, it was necessary to enrol 143 patients in the combination therapy with sulfonylurea arm and 63 in each of the other combination therapy arms.

Safety evaluation was carried out on the safety analysis set, which included all patients who received at least one dose of the study medication, and no statistical inference was made for safety analyses. A treatment-emergent AE (TEAE) was defined as an AE that occurred on or after the start of study medication. TEAEs were summarized and displayed using the MedDRA preferred terms and system organ classes. Other safety data were summarized using descriptive statistics (number of individuals; mean; standard deviation; maximum, minimum and quartile values) as well as using a shift table. Efficacy evaluation was carried out for the full analysis set, and comprised all patients who received at least one dose of the study medication. Secondary and other efficacy variables were summarized using descriptive statistics and two-sided 95% confidence intervals (CI) for the mean values. No between-group comparison was made, as this was a non-randomized study that did not aim at a between-group comparison, such as trelagliptin monotherapy vs combination therapy. All statistical analyses were carried out with SAS, version 9.2 (SAS Institute, Cary, NC, USA). The study was registered with ClinicalTrials.gov number NCT01431807.

RESULTS

On the basis of the results of interim analysis that included data from the first 301 patients who received the study drug, the Independent Safety Data Monitoring Committee concluded that the sponsor had to continue the study without protocol amendment, and the study was thus continued as planned. Therefore, the efficacy and safety results of the final analysis (analyses carried out when all tests/observations were completed and the database was locked) are described below.

The present study was carried out between 20 September 2011 and 27 June 2013. Of the 930 patients who provided informed consent, 680 patients received the following antidiabetic therapies along with diet/exercise therapies: trelagliptin monotherapy ($n = 248$), and trelagliptin combination therapy with a sulfonylurea ($n = 158$), a glinide ($n = 67$), an α-glucosidase inhibitor ($n = 65$), a biguanide ($n = 70$) or a thiazolidinedione ($n = 72$). Of the 680 patients, 601 patients completed the study. The most common reason for withdrawal was AEs in all treatment arms except for the glinide combination arm (lack of efficacy). In each therapy arm, the mean age was 55.3–62.0 years, the proportion of male patients was 65.7–79.2%, the mean body mass index was 24.19–26.23 kg/m^2 and the mean HbA_{1c} was 7.82–8.09% at baseline (Table 1). The mean treatment compliance rate with trelagliptin was very high: 99.37–99.76% in all treatment groups. Basal oral antidiabetic drug compliance was also very high: 97.05–98.79% in all combination therapy groups.

Regarding safety, during the 52-week treatment period, 80.4% (547/680) of the patients experienced at least one TEAE, including 79.8% (198/248) with trelagliptin monotherapy, and for combination treatment, 87.3% (138/158) with a sulfonylurea, 77.6% (52/67) with a glinide, 81.5% (53/65) with an α-glucosidase inhibitor, 64.3% (45/70) with a biguanide and 84.7% (61/72) with a thiazolidinedione (Table 2). The most frequently reported TEAE in each group was nasopharyngitis. The percentage of patients with mild, moderate, and severe TEAEs was 69.6% (473/680), 9.3% (63/680) and 1.6% (11/680), respectively (Table 2). Most TEAEs were mild and moderate in severity.

No death was reported during the entire study period.

Serious TEAEs occurred in 4.9% (33/680) of all patients, including 3.6% (9/248) with trelagliptin monotherapy, and for combination treatment, 7.0% (11/158) with a sulfonylurea, 7.5% (5/67) with a glinide, 4.6% (3/65) with an α-glucosidase inhibitor, 1.4% (1/70) with a biguanide and 5.6% (4/72) with a thiazolidinedione. Among the serious TEAEs, only cerebral infarction was reported in more than one patient (0.8% [2/248] in the monotherapy group) in each treatment group, and the events were considered to be unrelated to the study drug. Drug-related serious TEAEs were reported in 0.4% (3/680) of patients, including ileus (1.5%) for combination therapy with a glinide, cholecystitis (1.4%) for with a biguanide and bladder cancer (1.4%) for with a thiazolidinedione (1 patient each); all of the events led to study drug discontinuation, but were mild or moderate in severity and resolved.

TEAEs leading to discontinuation of the study medication were reported in 5.6% (38/680) of all patients, including 3.6% (9/248) with trelagliptin monotherapy, and for combination treatment, 5.7% (9/158) with a sulfonylurea, 7.5% (5/67) with a glinide, 7.7% (5/65) with an α-glucosidase inhibitor, 7.1% (5/70) with a biguanide and 6.9% (5/72) with a thiazolidinedione. However, none of these TEAEs were reported in more than

Table 1 | Demographic and baseline characteristics

Characteristic/category	Trelagliptin monotherapy n = 248	Combination with SU n = 158	Combination with Glinide n = 67	Combination with α-GI n = 65	Combination with BG n = 70	Combination with TZD n = 72	Overall n = 680
Age (years)	59.7 (9.64)	59.4 (9.91)	61.3 (9.86)	61.1 (9.42)	55.3 (10.77)	62.0 (9.68)	59.7 (9.95)
Age categories (years)							
<65	170 (68.5)	108 (68.4)	43 (64.2)	40 (61.5)	55 (78.6)	43 (59.7)	459 (67.5)
≥65	78 (31.5)	50 (31.6)	24 (35.8)	25 (38.5)	15 (21.4)	29 (40.3)	221 (32.5)
Sex							
Male	175 (70.6)	113 (71.5)	44 (65.7)	48 (73.8)	51 (72.9)	57 (79.2)	488 (71.8)
Female	73 (29.4)	45 (28.5)	23 (34.3)	17 (26.2)	19 (27.1)	15 (20.8)	192 (28.2)
Weight (kg)	68.03 (13.33)	67.36 (14.44)	65.80 (12.53)	65.13 (11.50)	73.10 (15.78)	70.69 (11.49)	68.18 (13.58)
BMI (kg/m²)	25.35 (4.14)	24.71 (3.69)	24.62 (3.68)	24.19 (3.04)	26.23 (4.42)	26.10 (4.17)	25.19 (3.97)
Duration of T2DM (months)	70.6 (61.37)	102.3 (69.62)	109.8 (74.84)	96.9 (71.82)	104.3 (65.68)	109.9 (80.86)	91.9 (70.13)
HbA$_{1c}$ (%)	7.87 (0.87)	8.09 (0.84)	7.87 (0.78)	8.07 (0.98)	7.82 (0.94)	7.91 (0.96)	7.94 (0.89)
FPG (mg/dL)	160.5 (35.56)	168.5 (33.07)	173.1 (33.64)	170.4 (37.74)	157.8 (36.13)	157.8 (34.92)	164.0 (35.30)
Fasting insulin (μU/mL)	8.79 (6.79)	8.04 (5.26)	8.00 (5.03)	8.67 (6.06)	9.38 (8.04)	5.84 (3.33)	8.28 (6.14)
Fasting glucagon (pg/mL)	72.8 (20.54)	71.9 (20.06)	69.9 (20.30)	69.8 (18.61)	74.9 (19.26)	67.3 (14.97)	71.7 (19.62)
Glycoalbumin (%)	22.10 (4.09)	22.45 (3.85)	21.93 (3.15)	23.05 (4.34)	20.72 (3.73)	23.15 (4.51)	22.22 (4.03)
HOMA-IR	3.54 (2.94)	3.44 (2.48)	3.56 (2.63)	3.72 (2.85)	3.95 (4.53)	2.33 (1.65)	3.45 (2.92)
HOMA-β (%)	35.48 (29.87)	29.13 (21.37)	26.60 (15.36)	31.92 (24.55)	36.25 (23.85)	23.90 (14.10)	31.67 (24.67)

Values represent the mean (standard deviation), except for age categories and sex, for which the number of patients (%) is presented. α-GI, α-glucosidase inhibitor; BG, biguanide; BMI, body mass index; Glinide, rapid-acting insulin secretagogue; HOMA-β, homeostasis model assessments of β-cell function; HOMA-IR, homeostasis model assessments of insulin resistance; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

Table 2 | Treatment-emergent adverse events occurring in 5% or more patients in any treatment groups

	Trelagliptin monotherapy n = 248	Combination with SU n = 158	Combination with Glinide n = 67	Combination with α-GI n = 65	Combination with BG n = 70	Combination with TZD n = 72	Overall n = 680
Any TEAEs	198 (79.8)	138 (87.3)	52 (77.6)	53 (81.5)	45 (64.3)	61 (84.7)	547 (80.4)
No. TEAEs	669	436	217	165	99	214	1800
TEAE leading to discontinuation of study medication	9 (3.6)	9 (5.7)	5 (7.5)	5 (7.7)	5 (7.1)	5 (6.9)	38 (5.6)
Drug-related TEAEs	39 (15.7)	17 (10.8)	8 (11.9)	4 (6.2)	8 (11.4)	10 (13.9)	86 (12.6)
No. drug-related TEAEs	69	23	9	5	9	15	130
Mild TEAEs	179 (72.2)	115 (72.8)	41 (61.2)	46 (70.8)	40 (57.1)	52 (72.2)	473 (69.6)
Moderate TEAEs	17 (6.9)	19 (12.0)	9 (13.4)	6 (9.2)	4 (5.7)	8 (11.1)	63 (9.3)
Severe TEAEs	2 (0.8)	4 (2.5)	2 (3.0)	1 (1.5)	1 (1.4)	1 (1.4)	11 (1.6)
Serious TEAEs	9 (3.6)	11 (7.0)	5 (7.5)	3 (4.6)	1 (1.4)	4 (5.6)	33 (4.9)
Serious drug-related TEAEs	0	0	1 (1.5)	0	1 (1.4)	1 (1.4)	3 (0.4)
Constipation	8 (3.2)	4 (2.5)	8 (11.9)	3 (4.6)	0	1 (1.4)	24 (3.5)
Nasopharyngitis	70 (28.2)	44 (27.8)	16 (23.9)	29 (44.6)	16 (22.9)	22 (30.6)	197 (29.0)
Bronchitis	14 (5.6)	9 (5.7)	2 (3.0)	2 (3.1)	1 (1.4)	0	28 (4.1)
Pharyngitis	8 (3.2)	5 (3.2)	7 (10.4)	2 (3.1)	1 (1.4)	2 (2.8)	25 (3.7)
Contusion	15 (6.0)	8 (5.1)	6 (9.0)	2 (3.1)	1 (1.4)	2 (2.8)	34 (5.0)
Fall	13 (5.2)	8 (5.1)	6 (9.0)	0	1 (1.4)	5 (6.9)	33 (4.9)
Blood creatine phosphokinase increased	9 (3.6)	10 (6.3)	5 (7.5)	5 (7.7)	0	9 (12.5)	38 (5.6)
Lipase increased	7 (2.8)	4 (2.5)	2 (3.0)	1 (1.5)	4 (5.7)	2 (2.8)	20 (2.9)
Back pain	17 (6.9)	6 (3.8)	4 (6.0)	2 (3.1)	4 (5.7)	4 (5.6)	37 (5.4)
Arthralgia	7 (2.8)	8 (5.1)	3 (4.5)	0	0	3 (4.2)	21 (3.1)
Myalgia	6 (2.4)	5 (3.2)	1 (1.5)	4 (6.2)	0	4 (5.6)	20 (2.9)
Upper respiratory tract inflammation	22 (8.9)	23 (14.6)	3 (4.5)	4 (6.2)	3 (4.3)	6 (8.3)	61 (9.0)
Eczema	8 (3.2)	8 (5.1)	5 (7.5)	0	2 (2.9)	2 (2.8)	25 (3.7)
Hypertension	8 (3.2)	3 (1.9)	2 (3.0)	2 (3.1)	1 (1.4)	5 (6.9)	21 (3.1)

Values represent the number (%) of patients. α-GI, α-glucosidase inhibitor; BG, biguanide; Glinide, rapid-acting insulin secretagogue; SU, sulfonylurea; TEAE, treatment-emergent adverse event; TZD, thiazolidinedione.

one patient in any treatment arm. Drug-related TEAEs leading to discontinuation of the study medication occurred in 2.6% (18/680) of overall patients, including 2.8% (7/248) with trelagliptin monotherapy, and for combination treatment, 0.6% (1/158) with a sulfonylurea, 4.5% (3/67) with a glinide, 1.5% (1/65) with an α-glucosidase inhibitor, 5.7% (4/70) with a biguanide and 2.8% (2/72) with a thiazolidinedione. No drug-related TEAEs leading to study drug discontinuation were reported in more than one participant in any treatment arms.

Hypoglycemia was reported in 1.8% (12/680) of all patients who received either long-term monotherapy or combination therapy: 0.4% (1/248) for trelagliptin monotherapy, and 4.4% (7/158), 1.5% (1/67), 1.5% (1/65), 1.4% (1/70), and 1.4% (1/72) for combination therapy with a sulfonylurea, a glinide, an α-glucosidase inhibitor, a biguanide and a thiazolidinedione, respectively. All of these were mild in severity. In addition, self-measured blood glucose never decreased to 55 mg/dL or less in any patients who received combination therapy with a sulfonylurea. The incidence of skin-related TEAEs was 7.1–14.9%, and their severity was mild or moderate. Pancreatitis was reported in one patient in combination with a thiazolidinedione, but was not considered to be related to the study drug. No clinically relevant changes in ECG results, vital signs or laboratory tests were noted in any treatment group (data not shown).

Regarding efficacy, the mean HbA_{1c} at each assessment point in the treatment period gradually decreased from week 2 until weeks 12–32 of the treatment period, and the decrease was maintained until week 52 of the treatment period in all treatment arms (Figure 1). The mean change in HbA_{1c} from baseline at the end of the treatment was −0.57% for trelagliptin monotherapy, and −0.37%, −0.25%, −0.67%, −0.31%, and −0.74% for combination therapy with a sulfonylurea, a glinide, an α-glucosidase inhibitor, a biguanide and a thiazolidinedione, respectively (Table 3).

The proportions of patients who achieved HbA_{1c} levels of <7.0% at the end of treatment (post-hoc analysis) were 36.0% for trelagliptin monotherapy, and 22.7%, 34.4%, 35.0%, 46.9%, and 44.6% for combination therapy with a sulfonylurea, a glinide, an α-glucosidase inhibitor, a biguanide and a thiazolidinedione, respectively (Table 3).

Mean FPG at each assessment point in the treatment period rapidly decreased from week 2 of the treatment period in all treatment arms (Figure S1). The mean change in FPG from baseline at the end of treatment were −10.0 mg/dL for trelagliptin monotherapy, and −0.8 mg/dL, −4.8 mg/dL, −13.5 mg/dL, −2.4 mg/dL, and −10.6 mg/dL for combination with a sulfonylurea, a glinide, an α-glucosidase inhibitor, a biguanide and a thiazolidinedione, respectively (Table 3).

The mean inhibition rate of DPP-4 activity, which was planned to be measured at 7 days after dosing, was sustained throughout 52 weeks and was 76.48–79.60% at the end of treatment (Figure 2). As other variables of glycemic control, the mean change from baseline in glycoalbumin at the end of the treatment period was also decreased (−1.43 to −3.09%) in all treatment groups. The mean change in fasting insulin and fasting glucagon from baseline at the end of treatment was 0.15 to 0.52 μU/mL and 4.8 to 8.2 pg/mL, respectively, in all treatment groups. The mean change in HOMA-IR and the mean change in HOMA-β from baseline in each treatment group were −0.30 to 0.12 and 2.47 to 6.43%, respectively. No treatment arms showed notable changes in bodyweight at the end of the treatment period (−0.57 to 1.31 kg; Table 3).
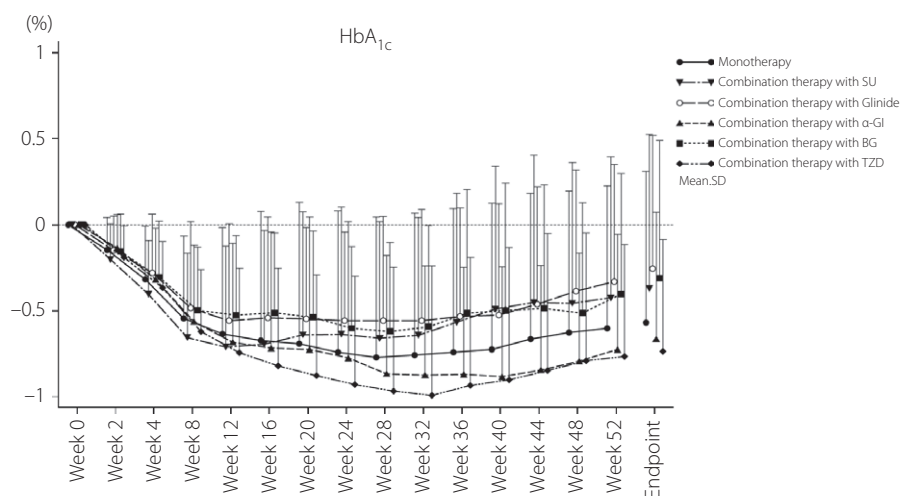

Figure 1 | Changes in glycosylated hemoglobin (HbA_{1c}) levels from baseline at each assessment point (full analysis set). Data represent the mean ± standard deviation. In all therapy arms, mean HbA_{1c} at each assessment point in the treatment period gradually decreased until weeks 12–32 of the treatment period, and the decrease was maintained until week 52 of the treatment period. α-GI, α-glucosidase inhibitor; BG, biguanide; Glinide, rapid-acting insulin secretagogue; SU, sulfonylurea; TZD, thiazolidinedione.

Table 3 | Summary of efficacy variables at the end of treatment and compliance rate

Variable	Trelagliptin monotherapy n = 248	Combination with SU n = 158	Combination with Glinide n = 67	Combination with α-GI n = 65	Combination with BG n = 70	Combination with TZD n = 72
Change from baseline in HbA$_{1c}$ (%)						
Mean (SD)	−0.57 (0.88)	−0.37 (0.90)	−0.25 (0.78)[†]	−0.67 (0.74)	−0.31 (0.82)	−0.74 (0.65)
95% CI	−0.68, −0.46	−0.51, −0.23	−0.45, −0.06	−0.85, −0.48	−0.50, −0.11	−0.89, −0.58
Response rate (%)						
HbA$_{1c}$ <7.0%	36.0 (81/225)	22.7 (35/154)	34.4 (22/64)	35.0 (21/60)	46.9 (30/64)	44.6 (29/65)
95% CI	29.73, 42.65	16.37, 30.16	22.95, 47.30	23.13, 48.40	34.28, 59.77	32.27, 57.47
Change from baseline in FPG (mg/dL)						
Mean (SD)	−10.0 (31.17)	−0.8 (35.53)	−4.8 (33.38)[†]	−13.5 (31.39)	−2.4 (29.32)	−10.6 (22.65)
95% CI	−13.88, −6.09	−6.42, 4.75	−13.01, 3.40	−21.27, −5.71	−9.39, 4.59	−15.91, −5.26
Change from baseline in fasting insulin (μU/mL)						
Mean (SD)	0.18 (5.61)	0.51 (4.12)	0.24 (4.02)[‡]	0.15 (3.30)	0.47 (5.95)[§]	0.52 (2.05)
95% CI	−0.52, 0.88	−0.14, 1.15	−0.78, 1.26	−0.67, 0.97	−0.96, 1.90	0.04, 1.00
Change from baseline in fasting glucagon (pg/mL)						
Mean (SD)	5.1 (13.91)	6.3 (16.03)	6.0 (16.16)[†]	4.8 (16.74)	8.2 (13.53)[§]	5.5 (13.29)[¶]
95% CI	3.36, 6.85	3.73, 8.77	2.01, 9.96	0.70, 8.99	4.92, 11.42	2.35, 8.64
Change from baseline in glycoalbumin (%)						
Mean (SD)	−2.59 (3.34)	−1.60 (3.22)	−1.52 (2.60)[†]	−2.83 (2.97)	−1.43 (2.82)	−3.09 (2.33)
95% CI	−3.01, −2.17	−2.10, −1.09	−2.16, −0.88	−3.56, −2.09	−2.10, −0.76	−3.63, −2.54
Change from baseline in weight (kg)						
Mean (SD)	−0.25 (2.44)	0.52 (1.77)	−0.03 (1.71)[†]	0.05 (1.12)	−0.57 (2.60)	1.31 (3.02)
95% CI	−0.55, 0.06	0.25, 0.80	−0.45, 0.39	−0.23, 0.33	−1.19, 0.05	0.60, 2.02
Change from baseline in HOMA-IR						
Mean (SD)	−0.15 (2.98)	0.12 (2.05)	0.06 (2.54)[‡]	−0.30 (1.97)	0.04 (2.93)[§]	0.02 (1.07)
95% CI	−0.52, 0.23	−0.20, 0.44	−0.59, 0.71	−0.79, 0.19	−0.66, 0.75	−0.23, 0.27
Change from baseline in HOMA-β (%)						
Mean (SD)	4.95 (19.34)	2.47 (13.94)	2.65 (11.27)[‡]	6.43 (17.99)	4.94 (19.00)[§]	5.53 (10.72)[§]
95% CI	2.53, 7.37	0.28, 4.66	−0.21, 5.51	1.97, 10.89	0.38, 9.51	3.01, 8.05
DPP-4 inhibition rate (%)						
Mean (SD)	78.97 (15.65)	76.48 (18.74)	78.93 (15.83) [††]	78.33 (18.35)	76.64 (19.61)	79.60 (14.69)
95% CI	77.01, 80.93	73.54, 79.43	75.01, 82.85	73.79, 82.88	71.96, 81.31	76.15, 83.05
Study drug compliance rate (%)[‡‡]						
Mean (SD)	99.49 (1.39)	99.50 (1.51)	99.41 (1.55)	99.37 (1.56)	99.76 (0.81)	99.63 (1.14)
Basal antidiabetic drug compliance rate (%)						
Mean (SD)	–	98.64 (3.63)	97.05 (4.16)	98.60 (2.00)	97.48 (5.51)	98.79 (2.07)

[†]n = 66, [‡]n = 62, [§]n = 69, [¶]n = 71, [††]n = 65. [‡‡]Compliance rate with trelagliptin. 95% CI, two-sided 95% confidence interval; α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4, dipeptidyl peptidase-4; Glinide, rapid-acting insulin secretagogue; HOMA-β, homeostasis model assessments of β-cell function; HOMA-IR, homeostasis model assessments of insulin resistance; SD, standard deviation; SU, sulfonylurea; TZD, thiazolidinedione.
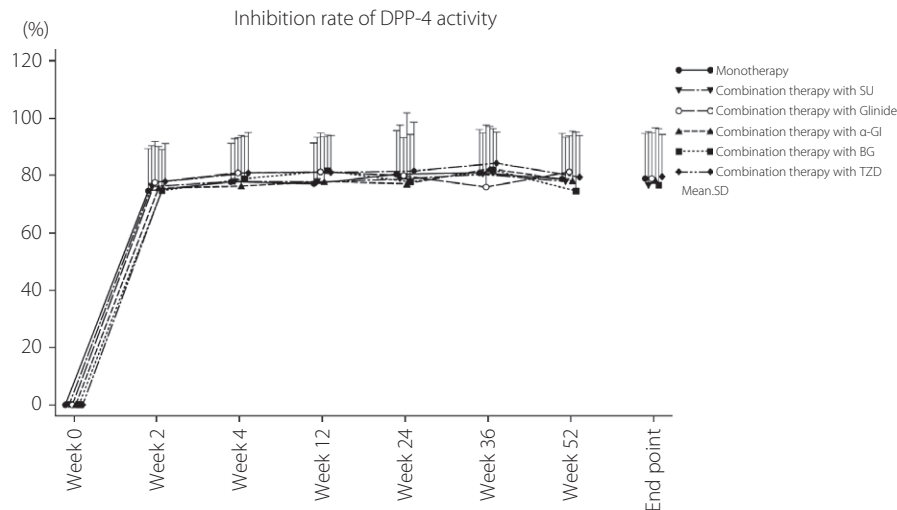
Figure 2 | Changes in inhibition rate of dipeptidyl peptidase-4 activity (full analysis set). Data represent the mean ± standard deviation. The mean inhibition rate of dipeptidyl peptidase-4 (DPP-4) activity was maintained at approximately 75–80% at all assessment points from week 2 to the end of the treatment period in all therapy arms. α-GI, α-glucosidase inhibitor; BG, biguanide; Glinide, rapid-acting insulin secretagogue; SU, sulfonylurea; TZD, thiazolidinedione.

DISCUSSION

This is the first report evaluating the long-term safety and efficacy of once-weekly oral trelagliptin at a dose of 100 mg as monotherapy or in combination with an existing antidiabetic drug in patients with type 2 diabetes mellitus, who were inadequately controlled despite diet and exercise therapy or treatment with an existing oral antidiabetic drug along with diet and exercise therapy. In the present study, once-weekly oral trelagliptin showed well-tolerated safety and efficacy for 52 weeks both as monotherapy and in combination therapy in Japanese patients with type 2 diabetes mellitus.

The available evidence of trelagliptin to date suggests that it is effective with once-weekly dosing. In the phase 1 study, trelagliptin showed sustained inhibition of DPP-4 activity for 7 days[10]. In the phase 2 study, 12 weeks treatment with trelagliptin produced a dose-dependent improvement in glycemic control, with significant reductions in HbA_{1c} seen at doses of up to 200 mg trelagliptin vs placebo[11]. At dose of 100 mg, the mean rate of DPP-4 inhibition was also sustained at approximately 80% at 7 days after dosing. In the phase 3 study, trelagliptin showed similar efficacy and safety to alogliptin, and the DPP-4 inhibition rate in the trelagliptin 100 mg group at 7 days after dosing showed no notable difference with that in the alogliptin group at 1 day after dosing[12]. In the present study, DPP-4 inhibition in each treatment group was maintained at approximately 75–80% throughout the 52-week treatment period, and efficacy was shown in all treatment groups. These results support the potential of trelagliptin as an antidiabetic therapy that can be given once a week. It is notable that in the present study, rates of compliance with trelagliptin and the basal antidiabetic drug during the study were very high (more than 97%) for all treatment groups, but the interpreta-

tion of these results should be made carefully, because the situation in the clinical study in which drugs are managed rather strictly might be different from real-world settings.

At present, once-weekly injectable therapies with several long-acting GLP-1 receptor agonists are available for the treatment of type 2 diabetes mellitus, but current oral antidiabetic therapies require administration at least once daily. The availability of a once-weekly oral medication for type 2 diabetes mellitus might provide a potentially useful therapeutic option to patients and physicians while improving adherence to therapy medication.

The main limitation of the present study was that it was carried out as an open-label study and a controlled group was not set, and natural variations in patients or influences by participating in this clinical trial was not taken into consideration. Therefore, safety and efficacy in combination therapy is expected to be further confirmed. Furthermore, the number of patients in each combination group was relatively too small to adequately assess less common TEAEs. Furthermore, the present study only involved the Japanese patient population, and therefore a further study investigating the therapeutic safety and efficacy in a larger number of patients and in non-Japanese patients is necessary.

In conclusion, long-term treatment with once-weekly oral trelagliptin at a dose of 100 mg as monotherapy or in combination therapy with an existing oral antidiabetic drug for 52 weeks showed a decrease in change in HbA_{1c} and FPG, and was well tolerated showing no major safety issues in patients with type 2 diabetes mellitus that had been inadequately controlled despite diet and exercise or treatment with an existing oral antidiabetic drug along with diet and exercise. As no other long-acting oral antidiabetic drug are available, once-weekly oral trelagliptin could provide clinicians and patients with a promising therapeutic option for the treatment of type 2 diabetes mellitus.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1| Changes in fasting plasma glucose from baseline at each assessment point (full analysis set).