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BRIEF REPORT

Efficacy and safety of trelagliptin in combination with insulin therapy in Japanese patients with type 2 diabetes: Results from a randomized, Phase IV study

Kohei Kaku MD[1] | Shingo Kuroda[2] | Kazuyuki Ishida[2] | Yuusuke Umeda[2]

[1]Department of Medicine, Kawasaki Medical School, Okayama, Japan

[2]Takeda Development Center Japan, Takeda Pharmaceutical Company Limited, Osaka, Japan

Correspondence
Kohei Kaku MD, Department of Medicine, Kawasaki Medical School, Okayama, Japan.
Email: kka@med.kawasaki-m.ac.jp

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We aimed to explore the efficacy and safety of once-weekly trelagliptin 100 mg as an add-on therapy to insulin in Japanese patients with type 2 diabetes mellitus with inadequate glycaemic control. Patients with haemoglobin A1c (HbA1c) 7.5% to 10.0% who were receiving 8 to 40 units of insulin per day were randomized to receive, with insulin, trelagliptin 100 mg (A/A, n = 116) or placebo (P/A, n = 124) for a 12-week double-blind (DB) phase, after which all received trelagliptin for a 40-week open-label phase. Primary endpoints were HbA1c change from baseline to the end of the DB phase and adverse events (AEs).

HbA1c significantly decreased in the A/A group vs the P/A group at the end of the DB phase (least square mean difference, −0.63% [95% CI, −0.83 to −0.44]: $P < .0001$). The frequency of treatment-emergent AEs during the DB phase was 44.0% in the A/A group and 47.6% in the P/A group. No patient experienced severe hypoglycaemia during trelagliptin treatment. Once-weekly trelagliptin 100 mg therapy with insulin demonstrated a significant reduction in HbA1c. Long-term treatment was well-tolerated, with no clinically significant hypoglycaemia, suggesting that trelagliptin with insulin is a meaningful treatment option in this patient population.

KEYWORDS

anti-diabetic drug, clinical trial, insulin therapy, phase IV study, randomized trial, type 2 diabetes

1 | INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in Japan has risen in recent decades from 6.6% in 1990 to 7.9% in 2010 and is expected to increase further, reaching 9.8% by 2030.[1] This has been attributed to an aging population[2] and to lifestyle factors associated with westernization, such as sedentary behaviour and obesity.[3,4] Despite a comprehensive armamentarium of anti-diabetic medications,[5] the increasing prevalence of T2DM suggests that new treatments and regimens are still required.

Trelagliptin succinate (trelagliptin; Zafatek®, Takeda Pharmaceutical Company Ltd) is a once-weekly (QW) dipeptidyl peptidase-4 (DPP-4) inhibitor, approved in Japan in 2015 for the treatment of T2DM patients, including those with moderate renal impairment.[6] In Phase II and III studies, trelagliptin has demonstrated clinically and statistically significant improvements in glycaemic control,[7] non-inferiority to once-daily alogliptin,[8] long-term safety and a good tolerability profile, both as a monotherapy treatment option and in combination with an existing oral anti-diabetic drug (OAD).[9] Moreover, in a Phase III open-label exploratory study, switching from a once-daily DPP-4 inhibitor (sitagliptin) to trelagliptin treatment had no major impact on glycaemic control or safety in T2DM patients.[10]

To improve glycaemic control, insulin can be used as an alternative or add-on therapy in patients with inadequate glycaemic control who are undergoing treatment with an OAD, diet and exercise.[11,12] Thus, this 2-phase multicentre study assessed the efficacy and safety of trelagliptin as an add-on therapy to insulin in patients with T2DM who are unable to achieve sufficient glycaemic control with insulin alone.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a Phase IV, multicentre, 12-week, randomized, double-blind, placebo-controlled study, followed by a 40-week open-label extended treatment period, to evaluate the efficacy and safety of trelagliptin 100 mg QW as an add-on therapy to insulin in Japanese T2DM patients with inadequate glycaemic control. The study (ClinicalTrials.gov NCT02324569; JAPIC JapicCTI-142734) was conducted from December 2014 to December 2016 at 43 sites in Japan. The study was designed in accordance with the Guideline for Clinical Evaluation of Hypoglycemic Agents in Japan,[13] and its revised draft; it was reviewed and approved by the appropriate institutional review board, and was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for human use, the Harmonized Tripartite Guideline for Good Clinical Practice, and all applicable regulations. Written informed consent was obtained from patients before study commencement.

2.2 | Participants

Japanese T2DM patients aged ≥20 years with inadequate glycaemic control despite treatment with insulin were recruited. Patient eligibility criteria included haemoglobin A1c (HbA1c) level ≥7.5 and <10.0% (≤10% variation from Week −6 to Week −2); fasting C-peptide value of ≥0.6 ng/mL (Week −6 and Week −2); daily insulin dose ≥8 and ≤40 units per day at a fixed dose and regimen; and fixed diet and exercise therapy. Please see Supporting Information (Materials and Methods) online for further details.

2.3 | Randomisation and study treatments

For the double-blind phase, eligible patients were randomized 1:1, using a permuted block schedule allocated to each site, to trelagliptin 100 mg QW with insulin (A/A group) or a placebo QW with insulin (P/A group) to be taken before breakfast. During the open-label phase, both groups received trelagliptin 100 mg QW with insulin, irrespective of their randomized treatment. Assessments were made at baseline, at Weeks 2 and 4, at 4-week intervals thereafter until Week 52 and at follow-up (Week 53). Safety and adherence were monitored throughout. In accordance with the Japanese Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (revised draft), the dose and regimen of insulin preparations were not changed during the double-blind phase, but were allowed to be altered at the physician's discretion during the open-label phase. Any anti-diabetic drugs other than insulin were prohibited throughout the study period. Please see Supporting Information (Materials and Methods) online for additional details.

2.4 | Study endpoints and assessments

The primary efficacy endpoint was change in HbA1c from baseline to the end of the double-blind phase. Additional efficacy measures included change from baseline at each visit for HbA1c, and the proportion of patients who reached target HbA1c levels of <6%, <7% or <8% at the end of the double-blind phase.

The primary safety endpoint was frequency and nature of treatment-emergent adverse events (TEAEs).

Other endpoints are discussed online in Supporting Information (Materials and Methods). Patients were assessed by the same investigator at each study visit.

2.5 | Statistical analyses

The total number of randomized patients was determined to be 125 per group in order to collect data from approximately 100 patients under treatment with the combination of trelagliptin and insulin preparations for 52 weeks, as required by the Japanese Guideline for Clinical Evaluation of Hypoglycemic Agents (revised draft), assuming a dropout rate of 20% during treatment. This also provided more than 90% power for the primary efficacy endpoint to detect the between-group difference of −0.4%, assuming the common standard deviation (SD) of 0.8% with a two-sided 5% significance level in a two-sample t-test.

All efficacy analyses were conducted on the full analysis set (FAS) unless otherwise stated and the safety analysis was conducted on the safety analysis set. Additional details can be found online in Supporting Information (Materials and Methods).

3 | RESULTS

Of the 539 patients who signed informed consent, 240 were randomized to receive treatment in the double-blind phase (A/A group, n = 116; P/A group, n = 124) (Figure S1 in File S1) and 231 received trelagliptin in the open-label phase (A/A group, n = 112; P/A group, n = 119). In total, 203 patients (A/A group, n = 100; P/A group, n = 103) completed both the double-blind phase and the open-label phase. All randomized patients were included in the FAS and safety analysis set.

The demographics and baseline patient characteristics were generally similar between groups (Table 1). More than 90% of patients fully complied with adherence to insulin during the screening period and the treatment period in both treatment groups. Further details can be found online in Supporting Information (Results).

3.1 | Efficacy

Based on an ANCOVA model with treatment group as a fixed effect and baseline HbA1c as a covariate, the least square (LS) mean (95% CI) change in HbA1c from baseline to the end of the double-blind phase was −0.56% (−0.701 to −0.425) for the A/A group and 0.07% (−0.061 to 0.205) for the P/A group. The LS mean difference (95% CI) was −0.63% (−0.826 to −0.443), demonstrating a significant decrease in HbA1c at the end of the double-blind phase in the A/A group compared to the P/A group ($P < .0001$) (Figure 1).

At the end of the double-blind phase, more patients in the A/A group vs the P/A group achieved HbA1c levels <7.0% (15.7% [n = 18/115] vs 2.4% [n = 3/124]) (Table S3 in File S1). The proportion difference (95% CI) was 13.2% (6.06 to 20.40). Other

TABLE 1 Baseline characteristics of the randomized population

Characteristic	A/A group (N = 116)	P/A group (N = 124)
Age, years (SD)	57.9 (10.9)	58.5 (11.1)
Weight, kg (SD)	69.5 (12.3)	68.1 (11.2)
Male, n (%)	90 (77.6)	82 (66.1)
BMI, kg/m^2 (SD)	25.39 (3.59)	25.16 (3.40)
Duration of diabetes, months (SD)	125.9 (92.8)	143.6 (90.2)
HbA1c, % (SD)	8.42 (0.68)	8.50 (0.68)
Fasting plasma glucose, mg/dL (SD)	160.6 (32.9)	167.3 (34.0)
Blood glucose in meal tolerance test (SD)[a]		
Pre-meal	164.0 (31.8)	167.0 (36.4)
Post-meal (0.5 h)	214.8 (35.7)	211.5 (39.3)
Post-meal (1 h)	272.6 (42.3)	269.6 (44.3)
Post-meal (2 h)	290.0 (52.1)	286.1 (54.0)
Daily dose of insulin preparation,[b] unit (SD)	19.8 (9.3)	18.8 (8.9)
Type of insulin preparation, n (%)		
Pre-mixed	48 (41.4)	47 (37.9)
Intermediate-acting	3 (2.6)	9 (7.3)
Long-acting	65 (56.0)	68 (54.8)
Creatinine clearance, mL/min (SD)	109.3 (36.1)	107.4 (40.3)
Fasting C-peptide, ng/mL (SD)	1.07 (0.53)	1.16 (0.65)
Fasting glucagon, pg/mL (SD)	97.5 (25.2)	93.8 (27.3)
Glycoalbumin, % (SD)	23.53 (3.34)	23.70 (3.29)
1,5-Anhydroglucitol, μg/mL (SD)	3.39 (2.35)	3.28 (2.98)
Insulinogenic index (SD)[c]	0.29 (0.28)	0.38 (0.69)

Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; SD, standard deviation. Results are presented as mean (standard deviation) unless otherwise indicated.

[a] N = 82 for the A/A group and N = 87 for the P/A group.

[b] At start of screening (Week −6).

[c] N = 80 each for the A/A and the P/A groups.

endpoints are discussed online in Supporting Information (Results). The mean change in glycaemic parameters from baseline to the end of the double-blind phase and end of trelagliptin treatment are detailed in Table S1 in File S1. The mean change in HbA1c from baseline to the end of the double-blind phase by sub-group is detailed in Table S2 in File S1. Mean change in HbA1c from baseline to Week 52 is depicted in Figure S2 in File S1.

3.2 | Safety

The incidence of TEAEs during the double-blind phase was comparable between the A/A and P/A groups (n = 51, 44.0%; n = 59, 47.6%, respectively) (Table S4 in File S1). TEAEs with an incidence of ≥2% in either treatment group (A/A vs P/A) were nasopharyngitis (7.8% vs 8.9%), hypoglycaemia (10.3% vs 8.9%) and upper respiratory tract inflammation (2.6% vs 4.0%) (Table S5 in File S1). There were no deaths reported. A total of 4 patients (3.4%) in the A/A group and 3 patients (2.4%) in the P/A group experienced serious TEAEs that were considered unrelated to the study drug. Severe hypoglycaemia was reported by 1 patient in the P/A group during the double-blind phase.

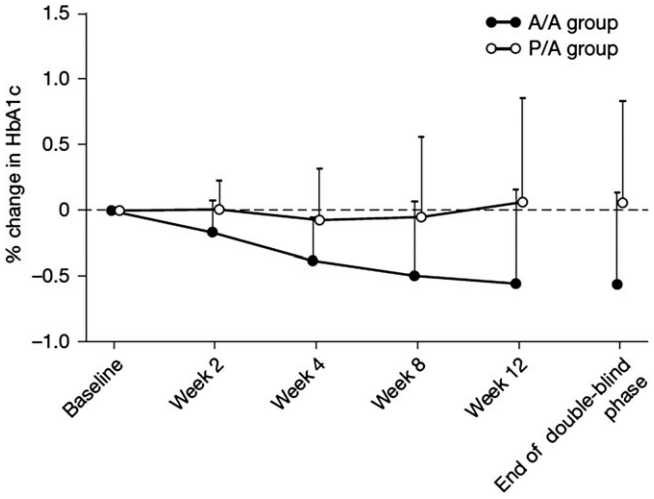

FIGURE 1 Mean change in HbA1c from baseline in the double-blind phase. The error bars represent standard deviation (SD). Abbreviations: A/A group, trelagliptin 100 mg with insulin; P/A group, placebo tablet with insulin; HbA1c, haemoglobin A1c; SD, standard deviation

The overall incidence of TEAEs after initiation of trelagliptin was 87.9% (n = 102) in the A/A group and 78.2% (n = 93) in the P/A group (Table S4 in File S1). The incidence of serious TEAEs was 13.8% (n = 16) and 7.6% (n = 9) in the A/A and P/A groups, respectively. In the A/A group, 1 patient died by suicide, which was assessed to be unrelated to the study drug. In the P/A group, 1 patient had a serious TEAE of chronic myeloid leukaemia, observed during the open-label phase, which was assessed to be related to the study drug. No severe hypoglycaemia was reported after initiation of trelagliptin. The incidence of TEAEs occurring ≥2% in either the A/A or the P/A group after initiation of trelagliptin is reported in Table S6 in File S1.

A total of 12 patients (10.3%) in the A/A group and 11 patients (8.9%) in the P/A group experienced hypoglycaemia-related TEAEs during the double-blind phase, while 22 patients (19.0%) in the A/A group and 18 patients (15.1%) in the P/A group experienced hypoglycaemia-related TEAEs after the first dose of trelagliptin. The drug-related TEAE with ≥2.0% incidence in any treatment group during the double-blind phase and after the initiation of trelagliptin was hypoglycaemia only (A/A group, 7.8% [n = 9]; P/A group, 6.5% [n = 8] and A/A group, 12.9% [n = 15]; P/A group, 10.9% [n = 13], respectively).

4 | DISCUSSION

This is the first report to demonstrate the efficacy and safety of once-weekly trelagliptin, a DPP-4 inhibitor, in combination with insulin therapy. Trelagliptin 100 mg QW plus concomitant insulin led to a significant reduction in HbA1c at the end of the double-blind phase in patients with inadequate glycaemic control despite treatment with insulin preparations as well as diet and exercise therapy ($P < .0001$ vs P/A group). This is further supported by the higher proportion of patients who achieved target HbA1c < 7.0% at the end of the double-blind phase in the A/A group compared with the P/A group (15.7% vs 2.4%).

The addition of trelagliptin 100 mg QW to ongoing insulin therapy was generally well tolerated throughout 52 weeks of treatment. During the double-blind phase, there were no significant differences in the incidence of TEAEs compared with the insulin monotherapy group. No clinically significant hypoglycaemic events were observed during administration of trelagliptin with insulin. A serious TEAE (chronic myeloid leukaemia), observed during the trelagliptin treatment phase in 1 patient originally randomized to the P/A group, was assessed by the investigator to be related to the study drug; however, this event could have been explained by a genetic predisposition or some other undetermined factor.

There were some limitations concerning generalization of the results of the present study. The main limitation is that it was conducted only in Japanese patients. In addition, Japanese patients aged <20 years, or those with evident liver or renal impairment, were excluded and, therefore, the effectiveness of the combination therapy was not confirmed in these sub-populations. Furthermore, natural variations in patients or the influence of changes in insulin dose were not taken into consideration for the evaluation of long-term efficacy and safety; thus, further studies are warranted.

Current evidence indicates that trelagliptin QW is efficacious[6,8] and well-tolerated as both a long-term mono- and combination therapy treatment option.[9] The efficacy and safety data from the present study support the notion that trelagliptin 100 mg QW in combination with insulin could be a potential therapeutic option, with careful consideration for hypoglycaemia, in Japanese T2DM patients.

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Conflict of interest

K. K. has received research funding, consultancy fees or lecture fees from Astellas Pharma, AstraZeneca, Novo Nordisk Pharma, Eli Lilly, Sanwakagaku Kenkyusho, Takeda Pharmaceutical, Taisho Pharmaceutical, MSD, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Boehringer-Ingelheim, and Ono Pharmaceutical; he has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. S. K., K. I. and Y. U. are employees of Takeda Pharmaceutical Company Limited.

Author contributions

K. K. contributed to the study design, the conduct of the study, data collection and manuscript preparation. S. K. contributed to the study design, data analysis and manuscript preparation. K. I. and Y. U. contributed to the conduct of the study, data collection and manuscript preparation.

ORCID

Kohei Kaku http://orcid.org/0000-0003-1574-0565

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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