

# Efficacy and safety of trelagliptin in Japanese patients with type 2 diabetes with severe renal impairment or end-stage renal disease: Results from a randomized, phase 3 study

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## Keywords

Chronic kidney failure, Trelagliptin, Type 2 diabetes mellitus

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## ABSTRACT

**Introduction:** To investigate the efficacy and safety of trelagliptin 25 mg in patients with type 2 diabetes mellitus with severe renal impairment or end-stage renal disease.

**Materials and Methods:** This multicenter, randomized, phase 3 study comprised a 12-week double-blind phase followed by a 40-week open-label phase. Patients had type 2 diabetes mellitus with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (undergoing hemodialysis), and were receiving diet and/or exercise therapy with/without one antidiabetic drug.

**Results:** Patients were randomized to trelagliptin (A/A,  $n = 55$ ) or placebo (P/A,  $n = 52$ ; double-blind phase). Both groups received trelagliptin in the open-label phase. The least square mean change (95% confidence interval [CI]) from baseline in hemoglobin A1c at the end of the double-blind phase was  $-0.71\%$  (95% CI  $-0.885, -0.542$ ) and  $0.01\%$  (95% CI  $-0.170, 0.183$ ) in the A/A and P/A groups, respectively (intergroup least square means difference  $-0.72\%$ , 95% CI  $-0.966, -0.473$ ;  $P < 0.0001$ ). Mean hemoglobin A1c decreased after trelagliptin treatment in the P/A group to similar levels observed in the A/A group and remained comparable in both groups versus baseline up to week 52. In the double-blind phase, the incidence of treatment-emergent adverse events (TEAEs) was 72.7% and 61.5% in the A/A and P/A group, respectively; most TEAEs were mild-to-moderate, except in one patient (P/A group), who experienced two severe TEAEs. The incidence of serious TEAEs was 7.3% and 3.8% in the A/A and P/A group, respectively.

**Conclusions:** Once-weekly trelagliptin 25 mg was efficacious, with no major safety concerns, and represents a meaningful treatment option in this patient population.

## INTRODUCTION

Type 2 diabetes mellitus is a chronic, progressive, metabolic disorder caused by defects in insulin secretion, insulin action or a combination of both<sup>1</sup>. In 2017, the International Diabetes Federation estimated that 425 million people worldwide were living with diabetes, which is expected to increase to 629 million (183 million in the Western Pacific Region) by 2045<sup>2</sup>. The burden of diabetes is growing in Japan, likely driven by the Westernization of lifestyle and an aging population<sup>3</sup>.

Although the management of type 2 diabetes mellitus is complex, the primary goal of treatment is to achieve optimal glycemic control and delay the onset of diabetes-related complications<sup>4</sup>. Glycemic control in patients with chronic kidney disease (CKD) adds another layer of complexity. Diabetes is the leading cause of CKD and a major public health issue worldwide<sup>5,6</sup>. Approximately 25% of type 2 diabetes mellitus patients in Japan have renal impairment (RI) classified as moderate-to-severe CKD (glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup>)<sup>7</sup>. Diabetes and comorbid CKD is associated with increased mortality, mainly due to increased cardiovascular disease<sup>8</sup>.

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At the time of writing, several oral antidiabetes drugs (OADs; mitiglinide calcium hydrate, repaglinide, alpha glucosidase inhibitors and some dipeptidyl peptidase-4 [DPP-4] inhibitors) were approved for use in type 2 diabetes mellitus patients in Japan with severe RI or end-stage renal disease (ESRD). Of these, DPP-4 inhibitors pose a low potential risk of hypoglycemia, as their glucose-lowering effects are glucose-dependent, and are increasingly used to treat type 2 diabetes mellitus patients with severe RI or ESRD<sup>9</sup>.

Medication adherence is generally poor among type 2 diabetes mellitus patients, and is a common issue in clinical practice. As adherence declines as the dosage and number of prescribed medications increases, a once-weekly formulation of a DPP-4 inhibitor is considered useful for the treatment of type 2 diabetes mellitus patients with CKD<sup>10–13</sup>. Trelagliptin is a once-weekly DPP-4 inhibitor approved in Japan in 2015 for the treatment of type 2 diabetes mellitus<sup>14</sup>. A review of the clinical efficacy and safety of trelagliptin has been published<sup>13</sup>.

Trelagliptin is primarily excreted through the kidneys, and is administered at a dose of 100 mg once per week for patients with or without mild RI<sup>14</sup>. A pharmacokinetics (PK) study of a single dose of trelagliptin 50 mg in non-Japanese patients with CKD (Study No. SYR-472\_101) showed that the area under the curve of trelagliptin increased by 55.7% in patients with mild RI (creatinine clearance [Ccr] >50 to ≤80 mL/min), 105.7% in moderate RI (Ccr ≥30 to ≤50 mL/min), 201.4% in severe RI (Ccr <30 mL/min, but not undergoing hemodialysis) and 268.1% in patients with ESRD undergoing hemodialysis compared with healthy (Ccr >80 mL/min) adults, thus indicating increased exposure to trelagliptin<sup>14</sup>. Based on these data, dose adjustment of trelagliptin is not required for patients with mild RI, but reduction to half the standard dose (50 mg/week) is indicated in patients with moderate RI<sup>14</sup>. At the time of writing, trelagliptin was contraindicated for use in type 2 diabetes mellitus patients with severe RI or ESRD<sup>14</sup>, for whom one-quarter of the standard dose had been considered appropriate based on the aforementioned PK study.

Type 2 diabetes mellitus with comorbid CKD is a major public health issue, and therefore a once-weekly DPP-4 inhibitor would be a useful treatment option. We carried out the first phase 3, randomized, placebo-controlled study to examine the efficacy and safety of trelagliptin in Japanese type 2 diabetes mellitus patients with severe RI or ESRD (ClinicalTrials.gov: NCT02512068).

## METHODS

### Study design and patients

This multicenter, randomized, placebo-controlled, parallel-group phase 3 study consisted of a 12-week, double-blind phase followed by a 40-week, open-label phase. A 6-week screening period preceded the double-blind phase and a 2-week follow-up period followed the open-label phase (Figure S1).

A total of 18 patient visits took place: at the start (week -6), middle (week -2) and end (week 0) of the screening period; at

weeks 2 and 4 of the treatment period; then every 4 weeks until the end of treatment (week 52), and at the end of the follow-up period (week 54). The study was carried out from July 2015 to April 2018 at 51 sites in Japan. Based on the aforementioned PK study (SYR-472\_101), trelagliptin 25 mg/week was selected as a suitable investigative dose for patients with severe RI or ESRD.

Key eligibility criteria were age ≥20 years, and a diagnosis of type 2 diabetes mellitus and either severe RI (Ccr <30 mL/min without hemodialysis or peritoneal dialysis) or ESRD (undergoing hemodialysis). Patients were also required to be on a fixed diet and/or exercise therapy (if any) and had to meet one of the following treatment criteria from at least 6 weeks before the start of the screening period: (i) receiving no antidiabetic medication (including insulin preparations); (ii) be currently treated with one OAD (mitiglinide calcium hydrate, repaglinide, acarbose, miglitol or voglibose) at a fixed dose and regimen; or (iii) be currently treated with one long-acting, intermediate-acting or mixed (containing ≤30% of rapid-acting or ultrarapid-acting insulin in volume) soluble insulin preparation at a fixed dose and regimen (≤40 units/day). Further inclusion criteria were a fasting C-peptide concentration ≥0.6 ng/mL, a hemoglobin concentration ≥10.0 g/dL and a stable hemoglobin A1c (HbA1c) value ≥7.0%, but <10.0%. Eligibility criteria were amended to include patients on hemodialysis with HbA1c <7.0% if they had a stable glycoalbumin concentration of ≥20%<sup>15</sup> – this amendment was made to reflect the actual status of glycemic control in patients with ESRD.

Key exclusion criteria included hypoglycemia within 6 weeks before, or during, the screening period; severe ketosis, diabetic coma or pre-coma; hemoglobinopathy; treatment with excluded medications (including other DPP-4 inhibitors, and glucagon-like peptide-1 receptor agonists, sulfonylureas, biguanides, thiazolidinediones, nateglinide and sodium/glucose cotransporter-2 inhibitors); and inadequately controlled hypertension.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. Approval was obtained from a regional institutional review board before screening, and all patients provided written informed consent before study commencement.

### Treatments

Patients were randomized 1:1 to receive oral trelagliptin 25 mg (A/A group) or placebo (P/A group) once-weekly at the start of the double-blind phase. All patients received trelagliptin 25 mg in the open-label phase. For patients receiving an OAD (mitiglinide calcium hydrate, repaglinide, acarbose, miglitol or voglibose) at the start of the screening period, change to dose and/or regimen was only allowed during the open-label phase and the follow-up period. Patients who were not receiving any OAD during the double-blind phase were permitted to start treatment with one OAD (described above) after week 16, if necessary. For patients receiving an insulin preparation at the

start of the screening period, change to dose and/or regimen were permitted at the discretion of the investigator and sub-investigator after the screening period. Patients were encouraged to maintain their existing diet and exercise regimens throughout the study.

### End-points and assessments

Primary efficacy and safety end-points were measured as change from baseline (week 0) HbA1c at the end of the double-blind phase (week 12), and the incidence of adverse events (AEs) during the double-blind phase and after the initiation of trelagliptin 25 mg, respectively. Secondary efficacy end-points were time course of changes from baseline in HbA1c, fasting blood glucose and glycoalbumin levels. Additional end-points were: PK, incidence of hypoglycemia in patients using insulin preparations, fasting C-peptide, fasting glucagon, DPP-4 activity and weight. All clinical laboratory tests were carried out at an independent central laboratory (LSI Medience Corporation, Tokyo, Japan).

The intensity of each AE was classified as mild (transient and easily tolerated by the patient), moderate (causes patient discomfort and interrupts their usual activities) or severe (causes considerable interference with the patient's usual activities).

### Sample size

A sample size of 180 (90 per group) was initially planned to achieve >90% power in detecting an intergroup difference in the mean change in HbA1c of -0.40% (standard deviation in each group was assumed to be 0.8%) from baseline to the end of the double-blind phase using a two-sample *t*-test with a significance level of 5% (two-sided). This target effect size was determined on the assumption that efficacy would be similar to that of trelagliptin 100 mg in type 2 diabetes mellitus patients without CKD<sup>16</sup>. The sample size was amended to 106 (53 per group) providing at least 70% power in detecting an intergroup difference (significance level of 5%, two-sided), as it was difficult to achieve the original sample size due to a higher than expected rate of patients who did not meet the eligibility criteria or dropped out during screening.

### Randomization

The randomization schedule was generated by an independent randomization officer using a permuted block schedule. SAS (version 9.2; SAS Institute Japan Ltd., Tokyo, Japan) and Microsoft Excel 2007 (Microsoft Japan Co., Ltd., Tokyo, Japan) were used.

Tablets containing trelagliptin 25 mg or a placebo appeared identical, and batches of each tablet were assigned an identification number. The tablets were then allocated to each study site and assigned to eligible patients in consecutive order of the tablet's identification number. To facilitate maintenance of blinding, measured values of study drug concentration and DPP-4 activity were not reported to the investigators until after the study.

### Statistical analysis

For the primary efficacy end-point, the mean change from baseline HbA1c at the end of the double-blind phase was compared between groups based on an analysis of covariance (ANCOVA) model, with factors of treatment group and baseline HbA1c. The same ANCOVA model was used to calculate the least square (LS) mean and the two-sided 95% confidence interval (CI) for each treatment group, as well as the intergroup difference in the LS mean between the treatment groups and the two-sided 95% CI.

For secondary efficacy end-points of HbA1c, fasting blood glucose and glycoalbumin, summary statistics (including the number of patients, mean and standard deviation) of measurement values and change from baseline were calculated for each treatment group at weeks 0, 2 and 4, and at 4-week intervals thereafter until week 52. In addition, the intergroup difference in the mean change from baseline and two-sided 95% CI were calculated at each evaluation point within the double-blind phase. For the analysis of the proportion of patients achieving the guideline-recommended HbA1c targets (6.0%, 7.0% or 8.0%)<sup>17</sup> at the end of the double-blind phase and the open-label phase, patients who had not achieved the respective target HbA1c at baseline were included in the analysis.

For the additional efficacy end-points of fasting C-peptide, fasting glucagon, DPP-4 activity and weight, summary statistics of the measurement values were calculated for each treatment group at the end of the double-blind phase and open-label phase. In addition, summary statistics of the change from baseline in each group, a point estimate of the intergroup difference in the mean change from baseline, and the two-sided 95% CI of the intergroup difference were calculated for fasting C-peptide, fasting glucagon and weight. For DPP-4 activity, summary statistics of the inhibition rate from baseline in each group, a point estimate of the intergroup difference in the inhibition rate from baseline, and the two-sided 95% CI of the intergroup difference were calculated.

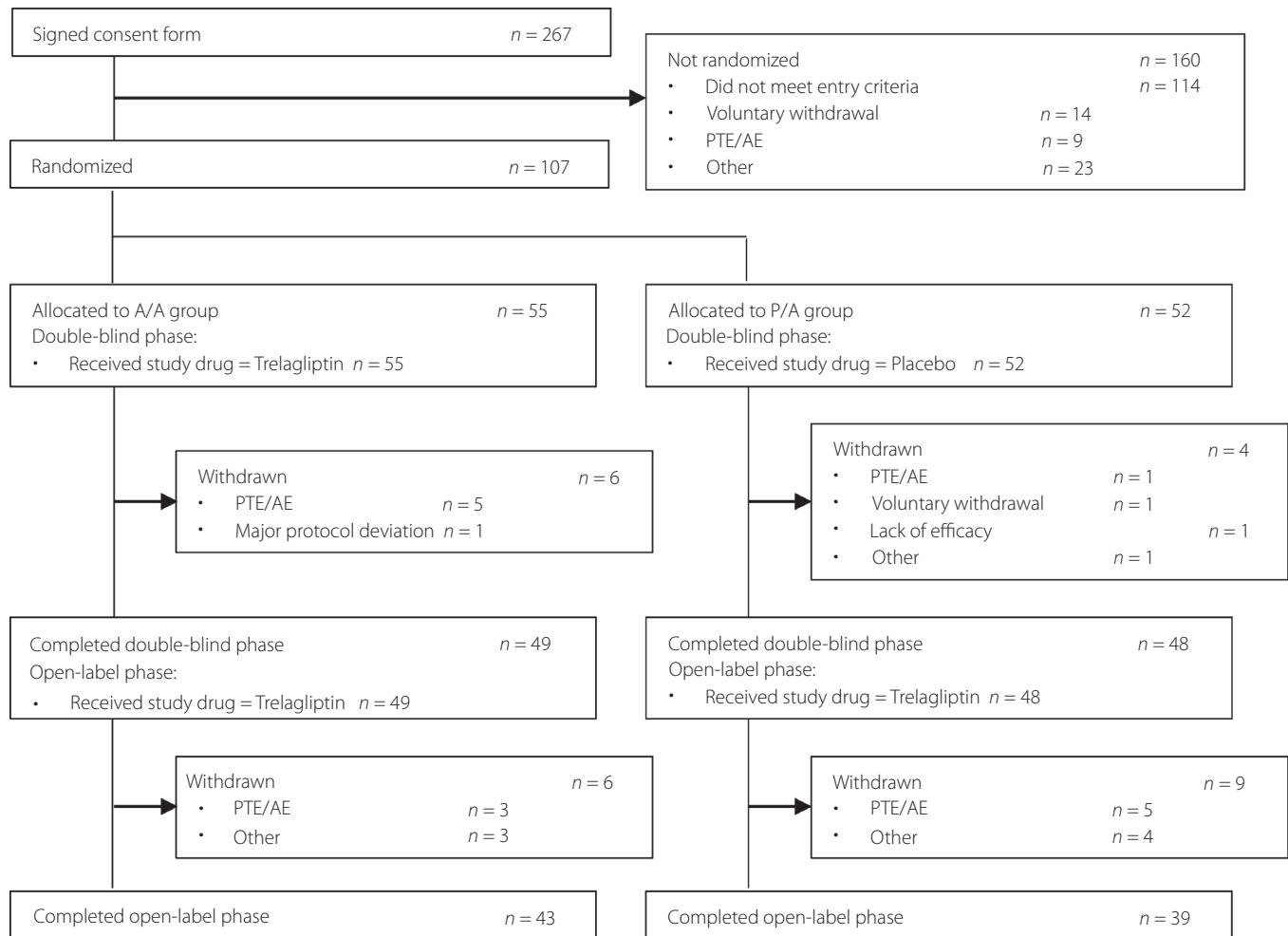
A treatment-emergent AE (TEAE) was defined as an AE with a date of onset on or after the start date of study drug administration. TEAEs were coded using MedDRA (version 21.0), and displayed using Preferred Terms for the double-blind phase and for the period after trelagliptin initiation.

The full analysis set was defined as all patients who were randomized and received at least one dose of the study drug, and was the main analysis set used for efficacy analyses. The safety analysis set was defined as all patients who received at least one dose of the study drug, and was used to analyze safety end-points. No interim analyses for efficacy or safety were carried out.

## RESULTS

### Patients

Of 267 patients screened, 107 were randomized to the A/A group ( $n = 55$ ) or the P/A group ( $n = 52$ ) in the double-blind phase (Figure 1). A total of 49 (89.1%) patients in the A/A group and 48 (92.3%) in the P/A group completed the double-



**Figure 1** | Patient disposition. Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase, and trelagliptin 25 mg/week (A/A group and P/A group) in the open-label phase. AE, adverse event; PTE, pretreatment event.

blind phase. During the open-label phase, 43 (78.2%) patients in the A/A group and 39 (75.0%) patients in the P/A group completed the study. All randomized patients ( $n = 107$ ) were included in the full analysis and safety analysis sets.

Baseline characteristics were generally similar between the A/A group and P/A group (Table 1). Approximately three-quarters of patients (72.7%, A/A group; 75.0%, P/A group) had ESRD (were on hemodialysis), and 27.3% (A/A group) and 25.0% (P/A group) of the patients had severe RI. The hematological profile was similar between patients in the A/A group and P/A group (Table S1) at baseline.

### Efficacy

At the end of the double-blind phase (week 12), the mean HbA1c decreased in patients treated with trelagliptin (A/A group), but not in those with placebo (P/A group, Figure 2). The LS mean (95% CI) change from baseline in HbA1c at the end of the double-blind phase was  $-0.71\%$  ( $-0.885$ ,  $-0.542$ ) in the A/A group and  $0.01\%$  ( $-0.170$ ,  $0.183$ ) in the P/A group.

The intergroup LS means difference in HbA1c change from baseline was  $-0.72\%$  (95% CI  $-0.966$  to  $-0.473$ ;  $P < 0.0001$ ), showing a significant decrease in HbA1c in the A/A group compared with the P/A group. After trelagliptin treatment initiated in the P/A group during the open-label phase, mean HbA1c decreased to a similar level as the A/A group (Figure 2). Mean HbA1c in both groups remained low compared with baseline at all evaluation points after the start of administration of trelagliptin 25 mg up to week 52 (Figure 2). At the end of the double-blind phase, more patients in the A/A group compared with the P/A group achieved an HbA1c value of  $<7.0\%$  (50.0% [ $n = 22/44$ ] vs 17.1% [ $n = 7/41$ ]; Table S2). The difference (95% CI) between proportions was 32.9% (14.194, 51.660). At the end of trelagliptin treatment, approximately half of all patients treated with trelagliptin had achieved an HbA1c value of  $<7.0\%$  (A/A group, 50.0% [ $n = 22/44$ ]; P/A group, 48.6% [ $n = 37/18$ ]; Table S2).

The mean change from baseline in fasting blood glucose, glycoalbumin and fasting glucagon at the end of the double-blind

**Table 1** | Baseline demographics and disease characteristics

Characteristics	A/A group (n = 55)	P/A group (n = 52)	Total (n = 107)
Age (years)	65.8 (10.28)	65.8 (10.46)	65.8 (10.32)
Male, n (%)	38 (69.1)	39 (75.0)	77 (72.0)
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	24.41 (3.525)	24.97 (4.017)	24.68 (3.765)
Duration of disease (months)	239.7 (116.8)	219.3 (106.35)	229.8 (111.79)
On hemodialysis, n (%)	40 (72.7)	39 (75.0)	79 (73.8)
Prescribed exercise as therapy, n (%)	13 (23.6)	12 (23.1)	25 (23.4)
Prescribed an antidiabetic drug, n (%) <sup>‡</sup>	35 (63.6)	33 (63.5)	68 (63.6)
Rapid-acting insulin secretagogues, n (%)	9 (16.4)	8 (15.4)	17 (15.9)
Mitiglinide calcium hydrate, n (%)	5 (9.1)	3 (5.8)	8 (7.5)
Repaglinide, n (%)	4 (7.3)	5 (9.6)	9 (8.4)
α-Glucosidase inhibitors, n (%)	8 (14.5)	12 (23.1)	20 (18.7)
Acarbose, n (%)	0 (0.0)	2 (3.8)	2 (1.9)
Miglitol, n (%)	3 (5.5)	2 (3.8)	5 (4.7)
Voglibose, n (%)	5 (9.1)	8 (15.4)	13 (12.1)
Insulin preparations, n (%) <sup>¶</sup>	18 (32.7)	13 (25.0)	31 (29.0)
Mixed, n (%)	8 (47.1)	5 (41.7)	13 (44.8)
Intermediate-acting, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Long-acting soluble, n (%)	9 (52.9)	7 (58.3)	16 (55.2)
Ccr (mL/min) <sup>†</sup>	10.7 (8.32)	11.3 (8.29)	11 (8.27)
eGFR (mL/min/1.73 m <sup>2</sup> ) <sup>†</sup>	8.3 (7.28)	8.7 (8.00)	8.5 (7.61)
HbA1c (%) <sup>†</sup>	7.57 (0.849)	7.74 (1.049)	7.65 (0.951)
Fasting blood glucose (mg/dL) <sup>†</sup>	143.1 (32.58)	151.1 (39.30)	147.0 (36.05)
Glycoalbumin (%) <sup>†</sup>	23.21 (4.091)	24.29 (4.565)	23.74 (4.341)
Fasting C-peptide (ng/mL) <sup>†</sup>	7.07 (5.481)	7.41 (4.580)	7.23 (5.042)
Fasting glucagon (pg/mL) <sup>†</sup>	177.4 (55.40)	165.7 (38.13)	171.7 (47.93)
DPP-4 activity (nmol/min/mL) <sup>†,§</sup>	8.4745 (1.98793)	8.4200 (2.04675)	8.4478 (2.00754)

Data are mean (standard deviation) unless otherwise stated. Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase. <sup>†</sup>At the end of screening period (week 0). <sup>‡</sup>At the start of the screening period (week -6). <sup>§</sup>A/A group: n = 54 (because of missing baseline value in one case), Total: n = 106. <sup>¶</sup>Type of insulin preparation was unknown for one patient in each group. BMI, body mass index; Ccr, creatinine clearance; DPP-4, dipeptidyl peptidase-4; eGFR, glomerular filtration rate; HbA1c, hemoglobin A1c; n, number of patients.

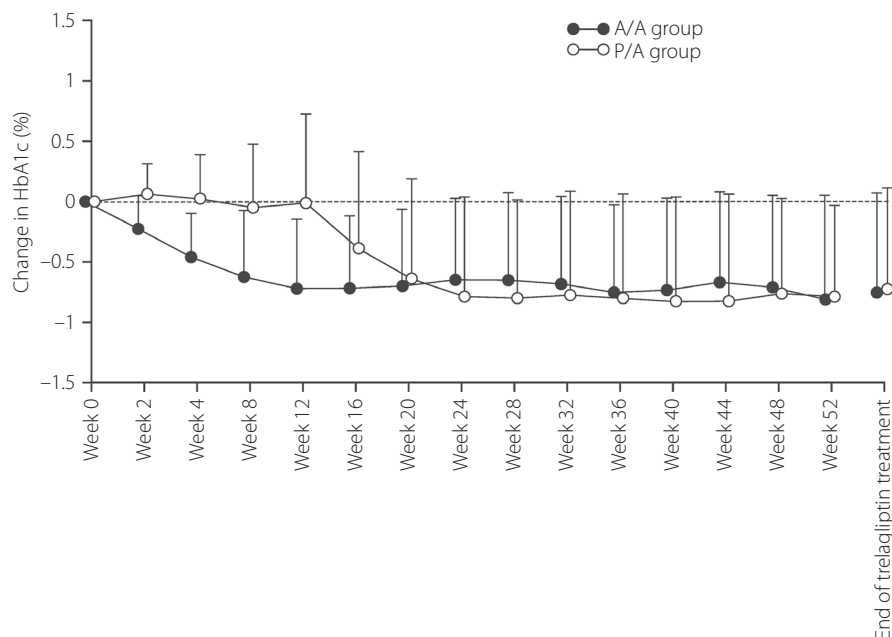
phase showed a greater reduction in the A/A group compared with the P/A group (Table 2). The mean difference (95% CI) between the A/A group and P/A group was -15.6 mg/dL (-26.67, -4.62) for fasting blood glucose, -2.66% (-3.608, -1.715) for glycoalbumin and -19.3 pg/mL (-32.21, -6.32) for fasting glucagon. At the end of trelagliptin treatment, the following decreases from baseline measurements were observed in the A/A group and P/A group: fasting blood glucose, -14.3 and -7.3 mg/dL; glycoalbumin, -3.12% and -3.06%; and fasting glucagon -16.3 and -14.6 pg/mL, respectively. The change over time in glycoalbumin and fasting blood glucose is presented in Figure S2a and b, respectively. There were no intergroup differences in changes in bodyweight and fasting C-peptide from baseline (Table 2).

DPP-4 inhibition by trelagliptin was sustained throughout the study (Table 2). The mean rates of DPP-4 inhibition were 93.06% (A/A group) and -0.04% (P/A group) at the end of the double-blind phase, and 90.91% (A/A group) and 94.08% (P/A group) at the end of the open-label phase, respectively.

The mean percentage of medication adherence in the double-blind phase was 99.47% (overall), 99.26% (A/A group) and 99.69% (P/A group), and in the open-label phase was 99.32% (overall), 99.26% (A/A group) and 99.39% (P/A group).

### Safety

During the double-blind phase, the incidence of TEAEs was 72.7% (n = 40/55) in the A/A group and 61.5% (n = 32/52) in the P/A group (Table 3). TEAEs with an incidence of ≥5% in either treatment group were nasopharyngitis, hypoglycemia, muscle spasms, contusion, fall, hyperkalemia and headache (Table S3). Most TEAEs were mild or moderate, except two incidents of severe TEAEs (ventricular tachycardia and unstable angina) that were seen in one patient in the P/A group. The incidence of serious TEAEs was 7.3% (n = 4/55) and 3.8% (n = 2/52) in the A/A group and P/A group, respectively (Table 3). Five patients discontinued treatment, due to a different TEAE (four patients in the A/A group experienced hypoglycemia, hypoesthesia, CKD or electrocardiogram QT prolongation; one patient in the P/A group experienced unstable angina).



**Figure 2** | Mean change in hemoglobin A1c (HbA1c) from baseline to week 52. Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase (week 0–12), and trelagliptin 25 mg/week (A/A group and P/A group) in the open-label phase (week 12–52). Data represent the mean and standard deviation.

**Table 2** | Mean change from baseline in glycemic parameters

	Change from baseline at the end of the double-blind phase			Change from baseline at the end of trelagliptin treatment	
	A/A group (n = 55)	P/A group (n = 52)	Point estimate of intergroup difference (95% CI)	A/A group (n = 55)	P/A group (n = 48)
HbA1c (%)	-0.70 (0.555)	0.00 (0.731)	-0.70 (-0.948, -0.452)	-0.76 (0.824)	-0.74 (0.843)
Fasting blood glucose (mg/dL)	-14.8 (31.51)	0.8 (25.50)	-15.6 (-26.67, -4.62)	-14.3 (37.48)	-7.3 (34.31)
Glycoalbumin (%)	-2.81 (2.401)	-0.15 (2.537)	-2.66 (-3.608, -1.715)	-3.12 (2.580)	-3.06 (2.604)
Fasting glucagon (pg/mL)	-18.1 (36.28)	1.2 (30.86)	-19.3 (-32.21, -6.32)	-16.3 (38.54)	-14.6 (30.96)
DPP-4 inhibition (%)	93.06 (8.623)	-0.04 (9.528)	93.10 (89.606, 96.601)	90.91 (24.378)	94.08 (2.436)
Fasting C-peptide (ng/mL)	-0.18 (3.037)	-0.01 (2.393)	-0.17 (-1.219, 0.885)	-0.10 (2.726)	0.34 (2.242)
Bodyweight (kg)	-0.07 (0.875)	-0.11 (0.812)	0.05 (-0.276, 0.372)	-0.34 (1.805)	-0.26 (2.227)

Data are mean (standard deviation) unless otherwise stated. Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase, and trelagliptin 25 mg/week (A/A group and P/A group) in the open-label phase. CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HbA1c, hemoglobin A1c; n, number of patients.

The incidence of TEAEs after the initiation of trelagliptin (week 0 in the A/A group and week 12 in the P/A group) was 98.2% ( $n = 54/55$ ) in the A/A group and 100.0% ( $n = 48/48$ ) in the P/A group (Table 3). TEAEs with an incidence of  $\geq 5\%$  in either treatment group are shown in Table S4. The incidence of severe TEAEs was 5.5% ( $n = 3/55$ ) and 6.3% ( $n = 3/48$ ) in the A/A group and P/A group, respectively (Table 3). The incidence of serious TEAEs was 41.8% ( $n = 23/55$ ) and 33.3% ( $n = 16/48$ ) in the A/A group and P/A group, respectively (Table 3). A total of 12 patients discontinued treatment, due to a different TEAE (A/A group,  $n = 7$ ; P/A group,  $n = 5$ ).

There were no deaths, and no serious drug-related TEAEs. Clinically important hypoglycemia was not observed, even when the study drug was administered concomitantly with insulin.

#### Pharmacokinetics

The mean plasma concentration of trelagliptin was 20.00 ng/mL at week 4 and 21.60 ng/mL at week 12. Analysis of patients receiving and not receiving hemodialysis showed mean trelagliptin plasma concentrations of 23.46 ng/mL and 10.12 ng/mL at week 4, and 25.09 ng/mL and 11.94 ng/mL at week 12, respectively.

**Table 3** | Overview of treatment-emergent adverse events occurring during this study

Patients, n (%)	Double-blind phase		After the first dose of trelagliptin	
	A/A group (n = 55)	P/A group (n = 52)	A/A group (n = 55)	P/A group (n = 48)
TEAEs	40 (72.7)	32 (61.5)	54 (98.2)	48 (100.0)
Related	10 (18.2)	4 (7.7)	13 (23.6)	6 (12.5)
Not related	30 (54.5)	28 (53.8)	41 (74.5)	42 (87.5)
Mild	33 (60.0)	24 (46.2)	28 (50.9)	28 (58.3)
Moderate	7 (12.7)	7 (13.5)	23 (41.8)	17 (35.4)
Severe	0 (0.0)	1 (1.9)	3 (5.5)	3 (6.3)
Leading to drug discontinuation	4 (7.3)	1 (1.9)	7 (12.7)	5 (10.4)
Serious TEAEs	4 (7.3)	2 (3.8)	23 (41.8)	16 (33.3)
Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Related	4 (7.3)	2 (3.8)	23 (41.8)	16 (33.3)
Leading to drug discontinuation	1 (1.8)	1 (1.9)	3 (5.5)	5 (10.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase, and trelagliptin 25 mg/week (A/A group and P/A group) in the open-label phase. TEAEs, treatment-emergent adverse events.

## DISCUSSION

The results of the present randomized phase 3 study show that once-weekly trelagliptin administered at one-quarter of the standard dose (25 mg) for 12 weeks significantly decreased HbA1c levels by 0.72% compared with placebo in Japanese type 2 diabetes mellitus patients with severe RI or ESRD, who had inadequate glycemic control despite diet and/or exercise therapy with/without treatment with one OAD or insulin preparation. At the time of writing, there was no reported phase 3 data for a DPP-4 inhibitor in the aforementioned patient population. Mean HbA1c values were decreased compared with baseline throughout the open-label phase, where all patients received trelagliptin, for up to 52 weeks. In the double-blind phase, the safety profile of trelagliptin was generally comparable with that of the placebo, and no clinically important hypoglycemic events were observed. During the open-label phase, trelagliptin was well-tolerated and showed no major safety concerns.

According to a previous clinical study, the area under the curve of trelagliptin was higher in patients with CKD compared with those with normal renal function<sup>14</sup>. In the present study, where the patients with CKD received trelagliptin 25 mg, no obvious difference was observed in mean trelagliptin plasma concentration (mostly collected between cycles at trough phases) between week 4 and week 12; however, these values were numerically higher than those in patients with normal renal function receiving trelagliptin 100 mg<sup>14</sup>. These findings are expected from the results of a previous PK study (SYR-472\_101)<sup>14</sup>. Furthermore, trelagliptin plasma concentrations in patients with severe RI or ESRD in the present study were generally predictable from a population PK model (unpubl.) developed using data from the SYR-472\_101 study; using this population PK model, the estimated mean values of apparent

trelagliptin clearance in patients with severe RI or ESRD were 5.3 and 3.2 L/h, respectively. These values were 35% and 21%, respectively, of the trelagliptin clearance rate in patients with normal renal function (15.1 L/h) with a mean Ccr of 104.6 mL/min (unpubl.). Taken together, these data suggest that trelagliptin at one-quarter of the standard dose (25 mg/week) might be a suitable dose for type 2 diabetes mellitus patients with severe RI or ESRD.

Any impact of hemodialysis on trelagliptin plasma concentration was considered negligible in the present study, as long-term sustained DPP-4 inhibition by trelagliptin was observed. In line with this, the results of our previous PK study (SYR-472\_101) showed that just 9.2% of trelagliptin was removed 4 h after starting hemodialysis<sup>14</sup>.

CKD is common in patients with type 2 diabetes mellitus, and is associated with an increased incidence of hypoglycemia<sup>18</sup>. Additional risk factors for hypoglycemia caused by CKD include altered drug metabolism and impaired renal glucose release. DPP-4 inhibitors are considered to have the potential to address several challenges associated with hypoglycemic agents in patients with CKD due to the lower risk of hypoglycemia given their mechanism of action<sup>19</sup>.

More than two-thirds of patients with diabetes have inadequate adherence to oral antidiabetic therapy<sup>20</sup>. Several factors that might interfere with the treatment regimen for type 2 diabetes mellitus have been suggested: depression, regimen complexity resulting from multiple daily doses, ESRD, and remembering to take and refill medication<sup>12,21,22</sup>. In the present study, the rates of compliance with the study drug were ≥90% in >85% of the patients for all treatment groups. The availability of trelagliptin to type 2 diabetes mellitus patients with severe RI or ESRD will provide an additional treatment option for the patients and their physicians.

The limitations of the present study include small sample size, especially for those with severe RI (18 in A/A group and 13 in P/A group). In addition, the influence of changes in antidiabetic drug dose and regimen or natural variations in patients were not taken into consideration for the evaluation of the efficacy and safety in the present study. Finally, the study was carried out in the Japanese population; thus, further investigations are warranted in a larger population including non-Japanese patients to assess the generalizability of the present study.

The present study reveals trelagliptin 25 mg as a promising therapeutic option for type 2 diabetes mellitus patients with severe RI or ESRD who have insufficient glycemic control with their current regimen. It is expected that good blood glucose control can be sustained for a long-term period, when trelagliptin is administered alone or as an add-on to another OAD, and with/without diet and/or exercise therapy.

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### DISCLOSURE

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## SUPPORTING INFORMATION

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

**Figure S1** | Study design.

**Figure S2** | Mean change in (a) glycoalbumin and (b) fasting blood glucose from baseline to week 52. Patients received trelagliptin 25 mg/week (A/A group) or placebo (P/A group) in the double-blind phase (Week 0–12), and trelagliptin 25 mg/week (A/A group and P/A group) in the open-label phase (Week 12–52). Data represent the mean and standard deviation.

**Table S1** | Baseline hematological parameters.

**Table S2** | Rate of patients achieving target hemoglobin A1c level.

**Table S3** | Treatment-emergent adverse events  $\geq 5.0\%$  during the double-blind phase in the safety analysis set.

**Table S4** | Treatment-emergent adverse events  $\geq 5.0\%$  after the first dose of trelagliptin in the safety analysis set.