Safety and Efficacy of Teneligliptin in Patients with Type 2 Diabetes Mellitus and Impaired Renal Function: Interim Report from Post-marketing Surveillance

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ABSTRACT

Introduction: Teneligliptin is a novel oral dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM). Safety and efficacy of teneligliptin have been demonstrated in clinical studies; however, data

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supporting its use in patients with moderate or severe renal impairment are limited. This interim analysis of a post-marketing surveillance of teneligliptin, exploRing the long-term efficacy and safety included cardiovascUlar events in patients with type 2 diaBetes treated bY teneligliptin in the real-world (RUBY), aims to verify the long-term safety and efficacy of teneligliptin in Japanese patients with T2DM and impaired renal function.

Methods: For this analysis, we used the data from case report forms of the RUBY surveillance between May 2013 and June 2017. The patients were classified into G1–G5 stages of chronic kidney disease according to estimated glomerular filtration rate (eGFR) at initiation of teneligliptin treatment. Safety and efficacy were evaluated in these subgroups. Patients on dialysis were also assessed. Safety was assessed from adverse drug reactions (ADRs). Glycemic control was evaluated up to 2 years after teneligliptin initiation.

Results: A total of 11,677 patients were enrolled in the surveillance and 11,425 patient case-report forms were collected for the interim analysis. The incidence of ADRs in each subgroup was 2.98–6.98% of patients, with no differences in the ADR profile (including hypoglycemia and renal function ADRs) between subgroups. At 1 and 2 years after starting teneligliptin, the least-squares mean change in HbA1c adjusted to the baseline was − 0.68 to − 0.85% and − 0.71 to − 0.85% across

the eGFR groups, respectively. Treatment with teneligliptin in patients on dialysis reduced or tended to reduce glycated albumin levels [− 2.29%, ($p < 0.001$) after 1 year; − 1.64%, ($p = 0.064$) after 2 years].

Conclusions: During long-term treatment, teneligliptin was generally well tolerated in patients with any stage of renal impairment from normal to end-stage renal disease, including those on dialysis, and improved glycemic control.

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Keywords: Dialysis; Dipeptidyl peptidase-4 inhibitor; Post-marketing surveillance; Renal impairment; Teneligliptin; Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is predicted to be a large increasing global health problem in the coming decades [1]. A recent report from the National Health and Nutrition survey estimated that in Japan in 2016, there were 10 million adults who were highly suspected to have diabetes, and a further 10 million who would possibly develop diabetes [2].

In order to reduce the risk of diabetic complications, guidelines for the management of diabetes set goals for glycemic control [3–5]. People with diabetes are at high risk of developing chronic kidney disease (CKD) as a result of microvascular damage caused by poor glycemic control and/or other comorbidities including hypertension and age-related nephron loss [6, 7]. Diabetic nephropathy is the most frequent primary reason that patients require dialysis in Japan [8]. Patients with T2DM and renal impairment have a high risk of developing hypoglycemia due to reduced insulin clearance and impaired renal gluconeogenesis, amongst other reasons [9]. In addition, the reduction in glomerular filtration rate (GFR) that occurs with the progression of CKD limits the therapeutic options available for achieving

optimal glycemic control, because the exposure of some antidiabetic agents that are eliminated via the renal route may be increased in these patients due to reduced urinary excretion [10]. Consequently, some antidiabetic agents are contraindicated or require significant dose reductions in advanced CKD [11].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of antidiabetic agents. These agents enhance glucose-dependent insulin secretion from pancreatic β-cells by inhibiting DPP-4-mediated degradation of endogenously released incretin hormones such as glucagon-like peptide-1 (GLP-1) [12]. Importantly, they present a low risk for hypoglycemia [12]. Emerging evidence suggests that DPP-4 inhibitors may have pleiotropic effects beyond improving glycemic control, including renal and cardiovascular protection [13–15].

Teneligliptin, a DPP-4 inhibitor, has been prescribed in Japan for the treatment of T2DM at a standard dose of 20 mg once daily since 2012 [16]. Twice the standard dose (40 mg once daily) can be used if 20 mg/day is insufficient to achieve glycemic control [17]. Teneligliptin can be administered to T2DM patients with renal impairment, including patients on dialysis, without the need for dose reduction [18, 19]. In South Korea, teneligliptin has been prescribed since 2014 [20].

The safety and efficacy of teneligliptin in Japanese patients with T2DM has been demonstrated when used as either a monotherapy [21–23] or in combination with pioglitazone, metformin, glimepiride, insulin, canagliflozin, glinide, or an alpha-glucosidase inhibitor in clinical trials for up to 52 weeks [23–27].

To date, however, clinical trials of teneligliptin in Japanese patients have only included a limited number of patients with moderate or severe renal impairment [23]. Consequently, there is insufficient information concerning the safety and efficacy of teneligliptin in this patient population. To help address this, a post-marketing surveillance (PMS) of teneligliptin, exploRing the long-term efficacy and safety included cardiovascUlar events in patients with type 2 diaBetes treated bY teneligliptin in the real-world (RUBY), has been ongoing under

clinical practice settings in $> 10,000$ Japanese patients with T2DM since May 2013 [28].

In this interim analysis, we evaluated the long-term safety and efficacy of teneligliptin in a subgroup of T2DM patients with renal impairment using case report forms (CRFs) collected from the RUBY surveillance during the period of May 2013 to June 2017.

METHODS

RUBY Post-marketing Surveillance Design: Patients and Procedures

Japanese patients with T2DM who were starting treatment with teneligliptin and could be observed long term were included in the ongoing RUBY surveillance (JapicCTI-153047) [28]. The decision to start treatment with teneligliptin was made by physicians in line with the approved label. Teneligliptin was administered once daily; the dose administered and any dose adjustments were decided by the prescribing physician according to the prescribing information.

Surveillance began in May 2013. Patients were enrolled between May 2013 and February 2015 via a central registration system, and will be observed for up to 3 years.

An online electronic data capture system was used to gather the patient data. Participating physicians recorded patient demography and baseline characteristics before teneligliptin was initiated, and completed follow-up CRFs for all enrolled patients taking teneligliptin for up to 3 years. Data in CRFs included information on pretreatment and concurrent drugs, response to teneligliptin treatment in terms of glycemic control, and adverse events (AEs).

The protocol for RUBY surveillance was approved by the Ministry of Health, Labour and Welfare of the Japanese Government. The RUBY surveillance was performed by Mitsubishi Tanabe Pharma Corporation, in accordance with the Japanese ministry directive on good post-marketing study practice (GPSP).

Interim Analysis of the Subgroup of Patients with T2DM and Renal Impairment

For this analysis, the data from CRFs collected between May 2013 and June 2017 were used. Estimated GFR (eGFR) was calculated from age, gender, and serum creatinine values recorded in the CRFs. eGFRs were not calculated for patients with missing serum creatinine values.

Patients with baseline renal function data were divided into those receiving and those not receiving dialysis at the initiation of teneligliptin treatment. Non-dialysis patients with measurable eGFR at the initiation of teneligliptin treatment were classified as follows according to renal function using CKD staging [29]: (i) normal or high (G1: eGFR ≥ 90 mL/min/1.73 m^2), (ii) mild impairment (G2: eGFR ≥ 60 to < 90 mL/min/1.73 m^2), (iii) mild-to-moderate impairment (G3a: eGFR ≥ 45 to < 60 mL/min/1.73 m^2); (iv) moderate-to-severe impairment (G3b: ≥ 30 to < 45 mL/min/1.73 m^2), (v) severe impairment (G4: eGFR ≥ 15 to < 30 mL/min/1.73 m^2), and (vi) kidney failure (G5: eGFR < 15 mL/min/1.73 m^2).

The safety and efficacy of teneligliptin was investigated in each subgroup of patients. Safety was assessed from adverse drug reactions (ADRs) reported throughout the surveillance period. ADRs were defined as AEs for which a causal relationship with teneligliptin could not be ruled out or was unknown. The type and severity of each ADR and its relationship to teneligliptin was reported by the physician at each site. Serious hypoglycemia was defined as a blood glucose level of ≤ 50 mg/dL or as judged by the physician.

Efficacy was assessed in terms of glycemic control as measured by the change over time in glycated hemoglobin (HbA1c; for non-dialysis patients), and glycated albumin (GA; for dialysis patients). Measurements of HbA1c and GA were made at 0, 3, 6, 12, 18, and 24 months after the initiation of teneligliptin treatment. The laboratory analyses were conducted using routine clinical assays in the institution participating in the surveillance.

Data Analysis

Continuous data were summarized based on the number of patients (*n*), mean, and standard deviation (SD), and discrete data were summarized based on the *n* and percentage values for each category. Least squares (LS) means and standard errors were calculated, with the baseline as a covariate, to measure the change in HbA1c over time; one-sample *t*-tests were used to determine if the difference between the HbA1c values before and after teneligliptin administration was statistically significant. Laboratory data were counted only for patients who had data both at baseline and after the administration of teneligliptin. Chi-square tests were performed to assess differences in ADR frequency between the eGFR categories. In addition, in order to assess the difference between the G2–G5 subgroups and G1, the 95% confidence interval (CI) of the risk ratio for ADRs in the eGFR subgroups was used. Statistical tests were two-sided with a 5% significance level, and two-sided 95% CIs were calculated. Statistical analysis was performed using SAS version 9.1.3 and above (SAS Institute Inc., Cary, NC, USA).

ADRs were categorized according to the Medical Dictionary for Regulatory Activities, Japanese version 20.0 (Pharmaceutical and Medical Device Regulatory Science Society of Japan, Tokyo, Japan). ADRs of special interest (previously associated with diabetes, antihyperglycemic agents, or DPP-4 inhibitors) were defined as those related to hypoglycemia, skin and subcutaneous tissue disorders, gastrointestinal disorders, hepatic disorders, renal disorders, cardiovascular events, and tumor.

RESULTS

Patients

In total, 11,677 patients were enrolled into the RUBY surveillance from 1755 institutions, and 11,425 patient case report forms were collected for the interim analysis. As of June 28, 2017, the proportion of patients who had withdrawn from the surveillance was 26.9%; similar proportions of patients had withdrawn across the subgroups (G1–G5 and dialysis). Of the 10,532 patients included in the safety analysis set, evaluable CRFs collected by June 28, 2017 were available for 9234 non-dialysis patients with calculable eGFR and 152 patients receiving dialysis at the start of teneligliptin treatment (see S1 in the Electronic supplementary material, ESM).

Of the 9234 patients with calculable eGFR, most had mild impairment (G2: 53.4%); 21.5% had normal/high renal function (G1), 16.2% had mild to moderate impairment (G3a), 6.0% had moderate to severe impairment (G3b), 2.3% had severe impairment (G4), and 0.6% had kidney failure (G5).

Patient background characteristics and concurrent medications for T2DM, hypertension, and dyslipidemia in each subgroup are shown in Table 1. Patients with severe renal impairment and those on dialysis had a longer duration of T2DM; a greater proportion of those patients also had diabetic complications (G4: 74.9%; G5: 70.0%; dialysis patients: 92.8%) compared with those with normal/high renal function or mild renal impairment (G1: 19.4%; G2: 21.5%). A greater proportion of those with severe renal impairment and those on dialysis had heart disease, including myocardial infarction, angina pectoris, or heart failure (G4: 40.5%; G5: 33.3%; dialysis patients: 46.1%) and hypertension (G4: 91.2%; G5: 88.3%; dialysis patients: 89.5%) as an underlying complication compared with patients with normal/high renal function and mild renal impairment (G1: 7.8% and 50.9%; G2: 15.4% and 61.5%, respectively).

Teneligliptin was prescribed as monotherapy for T2DM in 40.0–53.3% of patients across the subgroups with measurable eGFR and 53.9% of dialysis patients during the surveillance period. The remaining 46.1–60.0% of patients were prescribed teneligliptin therapy in combination with other antidiabetic drugs (Table 1). The mean starting daily doses of teneligliptin were 20.1–20.2 mg in all eGFR subgroups and 20.3 mg in dialysis patients (Table 1). Mean daily dosages during the surveillance period were 20.3–20.7 mg/day in eGFR subgroups and 21.3 mg/day in dialysis patients (Table 1).

Table 1 Patient baseline characteristics

Characteristic	Non-dialysis patients, eGFR at initiation of treatment (mL/min/1.73 m^2)						Dialysis patients (n = 152)
	G1 ≥ 90 (n = 1982)	G2 ≥ 60 to < 90 (n = 4929)	G3a ≥ 45 to < 60 (n = 1496)	G3b ≥ 30 to < 45 (n = 552)	G4 ≥ 15 to < 30 (n = 215)	G5 < 15 (n = 60)	
Male sex, n (%)	1179 (59.5)	3057 (62.0)	879 (58.8)	303 (54.9)	118 (54.9)	32 (53.3)	110 (72.4)
Age (years)	n = 1982	n = 4929	n = 1496	n = 552	n = 215	n = 60	n = 152
	56.8 (12.9)	65.6 (10.9)	72.3 (9.7)	74.3 (9.9)	74.4 (10.8)	69.5 (11.6)	67.4 (10.2)
Duration of T2DM (years)	n = 1392	n = 3487	n = 1001	n = 384	n = 127	n = 36	n = 82
	5.60 (6.24)	7.00 (7.55)	8.97 (8.73)	10.54 (8.96)	13.78 (9.78)	13.00 (11.13)	16.65 (9.23)
HbA1c (%)	n = 1864	n = 4629	n = 1405	n = 528	n = 200	n = 57	n = 99
	8.51 (1.92)	7.64 (1.35)	7.38 (1.20)	7.28 (1.13)	7.35 (1.38)	6.94 (1.19)	6.72 (1.12)
Glycated albumin (%)	n = 85	n = 228	n = 66	n = 39	n = 26	n = 17	n = 91
	21.60 (6.94)	19.27 (7.17)	20.20 (5.53)	21.20 (6.44)	19.53 (5.83)	20.02 (5.57)	23.48 (5.00)
Fasting blood glucose (mg/dL)	n = 730	n = 1817	n = 529	n = 201	n = 67	n = 21	n = 32
	169.0 (64.0)	147.8 (47.5)	143.4 (46.6)	148.3 (45.3)	140.1 (39.4)	131.3 (53.7)	146.5 (48.1)
BMI (kg/m^2)	n = 1437	n = 3416	n = 991	n = 396	n = 137	n = 39	n = 96
	25.92 (5.09)	25.09 (4.15)	25.18 (4.16)	25.16 (4.39)	24.90 (4.35)	23.77 (3.56)	22.88 (3.19)
eGFR (mL/min/1.73 m^2)	n = 1982	n = 4929	n = 1496	n = 552	n = 215	n = 60	–
	106.28 (18.94)	74.29 (8.18)	53.55 (4.23)	38.54 (4.23)	23.95 (4.23)	8.76 (4.23)	–
Diabetic complications, n (%)							
Any	385 (19.4)	1060 (21.5)	502 (33.6)	283 (51.3)	161 (74.9)	42 (70.0)	141 (92.8)
Neuropathy	127 (6.4)	445 (9.0)	196 (13.1)	107 (19.4)	48 (22.3)	13 (21.7)	47 (30.9)
Nephropathy	244 (12.3)	659 (13.4)	385 (25.7)	253 (45.8)	150 (69.8)	40 (66.7)	140 (92.1)
Retinopathy	145 (7.3)	412 (8.4)	174 (11.6)	105 (19.0)	54 (25.1)	21 (35.0)	72 (47.4)
Other complications, n (%)							
Renal disease[a]	257 (13.0)	723 (14.7)	459 (30.7)	334 (60.5)	177 (82.3)	45 (75.0)	146 (96.1)
Liver disease	550 (27.7)	1173 (23.8)	310 (20.7)	93 (16.8)	24 (11.2)	8 (13.3)	15 (9.9)
Heart disease	155 (7.8)	759 (15.4)	396 (26.5)	201 (36.4)	87 (40.5)	20 (33.3)	70 (46.1)
Hypertension	1009 (50.9)	3031 (61.5)	1099 (73.5)	475 (86.1)	196 (91.2)	53 (88.3)	136 (89.5)
Dyslipidemia	1293 (65.2)	3342 (67.8)	1063 (71.1)	406 (73.6)	159 (74.0)	36 (60.0)	66 (43.4)
Teneligliptin monotherapy, n (%)	901 (45.5)	2328 (47.2)	666 (44.5)	232 (42.0)	86 (40.0)	32 (53.3)	82 (53.9)
Concurrent T2DM medication, n (%)							
Any	1081 (54.5)	2601 (52.8)	830 (55.5)	320 (58.0)	129 (60.0)	28 (46.7)	70 (46.1)
Sulfonylurea	476 (24.0)	1231 (25.0)	406 (27.1)	152 (27.5)	53 (24.7)	8 (13.3)	1 (0.7)
Thiazolidine	186 (9.4)	413 (8.4)	146 (9.8)	55 (10.0)	7 (3.3)	2 (3.3)	0 (0.0)
Biguanide	540 (27.2)	1061 (21.5)	264 (17.6)	56 (10.1)	15 (7.0)	3 (5.0)	0 (0.0)
α- GI	195 (9.8)	539 (10.9)	210 (14.0)	90 (16.3)	38 (17.7)	8 (13.3)	21 (13.8)
Glinide	84 (4.2)	256 (5.2)	75 (5.0)	39 (7.1)	18 (8.4)	5 (8.3)	19 (12.5)
Insulin	141 (7.1)	332 (6.7)	117 (7.8)	68 (12.3)	39 (18.1)	11 (18.3)	35 (23.0)
SGLT2 inhibitor	91 (4.6)	151 (3.1)	24 (1.6)	5 (0.9)	1 (0.5)	1 (1.7)	0 (0.0)

Table 1 continued

Characteristic	Non-dialysis patients, eGFR at initiation of treatment (mL/min/1.73 m^2)						Dialysis patients (n = 152)
	G1 ≥ 90 (n = 1982)	G2 ≥ 60 to < 90 (n = 4929)	G3a ≥ 45 to < 60 (n = 1496)	G3b ≥ 30 to < 45 (n = 552)	G4 ≥ 15 to < 30 (n = 215)	G5 < 15 (n = 60)	
Non-T2DM medication, n (%)							
Hypertension drug	750 (37.8)	2438 (49.5)	912 (61.0)	413 (74.8)	165 (76.7)	43 (71.7)	117 (77.0)
Dyslipidemia drug	671 (33.9)	2143 (43.5)	736 (49.2)	265 (48.0)	110 (51.2)	28 (46.7)	40 (26.3)
Teneligliptin starting dose (mg/day)	n = 1979	n = 4929	n = 1494	n = 551	n = 214	n = 60	n = 152
	20.2 (2.0)	20.2 (2.0)	20.1 (2.0)	20.2 (2.6)	20.1 (2.1)	20.2 (2.9)	20.3 (2.9)
Teneligliptin dose during surveillance period (mg/day)	n = 1914	n = 4778	n = 1447	n = 537	n = 212	n = 58	n = 146
	20.3 (2.6)	20.4 (2.6)	20.4 (2.7)	20.5 (3.2)	20.7 (3.6)	20.7 (3.3)	21.3 (4.6)

Data are mean (SD) unless otherwise stated

α-GI α-Glucosidase inhibitor, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *SD* standard deviation, *SGLT2* sodium-glucose cotransporter-2, *T2DM* type 2 diabetes mellitus

[a] Includes diabetic nephropathy

Safety

In the safety analysis set, the mean duration of teneligliptin administration ranged from 534 days to 617 days across the subgroups (mean ± SD: G1: 581.45 ± 340.90 days; G2: 610.56 ± 340.87 days; G3a: 616.80 ± 336.73 days; G3b: 594.93 ± 341.58 days; G4: 561.54 ± 341.68 days; G5: 533.62 ± 345.22 days; and dialysis: 580.91 ± 371.74 days).

The incidences of all ADRs and special interest ADRs are shown in Table 2. Greater ADR incidence were observed in the G4 and G5 groups (15 of 215 patients (6.98%) and 4 of 60 patients (6.67%) respectively), compared with 59 of 1982 patients in the G1 group (2.98%). Of the ADRs reported in the 19 patients in the G4 and G5 subgroups, those occurring in 6 patients were considered to be possibly related to teneligliptin, while the causal relationship between teneligliptin and the ADRs in 13 patients was assessed as unknown, and 15 of 30 events in the 19 patients were also attributed to other causes (e.g., comorbidity or concomitant agent) by the prescribing physician. A higher incidence of serious ADRs occurred in the G4 and G5 groups [10 of 215 patients (4.65%) and 3 of 60 patients (5.00%), respectively] compared with patients with normal/high renal function [G1: 11 of 1982 (0.55%)]. ADRs and serious ADRs were observed in 5 and 1 of 152 dialysis patients (3.29% and 0.66%), respectively.

There were no significant differences in the incidence of each special interest ADR across the groups, including hypoglycemia, skin and subcutaneous tissue disorders, gastrointestinal disorders, hepatic disorders, renal-impairment-related ADRs, cardiovascular events, and tumor (Table 2). Five patients presenting the more advanced stages of renal impairment (G4/G5/dialysis groups) experienced a hypoglycemic episode: 1 patient each experienced non-serious and serious hypoglycemia in the G4 group, 1 patient had a non-serious hypoglycemic episode in the G5 group, and 2 patients had a non-serious hypoglycemic episode in the dialysis group. All of these patients were administered concomitant medication for T2DM (4 patients were using insulin and/or sulfonylureas and 1 was administered a glinide). Renal-impairment-related ADRs in the G4 group included hematuria (n = 1), renal impairment (n = 1), and increased blood creatinine (n = 1); the physician reported that the causal relationship of each of these events with teneligliptin was unknown, and 2 of those ADRs were also attributed to other causes (diabetic nephropathy comorbidity

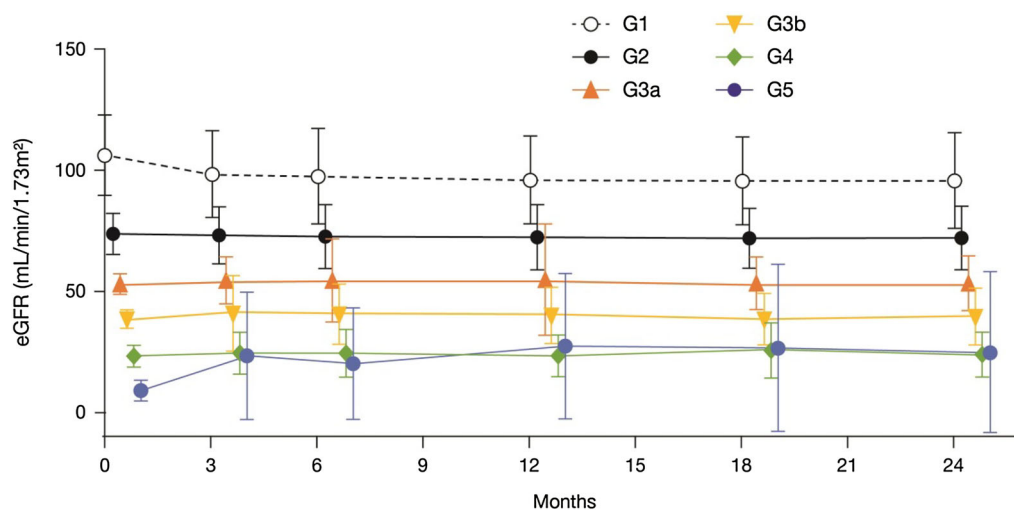**Table 2** Incidences of ADRs and special interest ADRs

	Non-dialysis patients, eGFR at initiation of treatment (mL/min/1.73 m^2)						Dialysis patients (n =152)
	G1 ≥ 90 (n = 1982)	G2 ≥ 60 to < 90 (n = 4929)	G3a ≥ 45 to < 60 (n = 1496)	G3b ≥ 30 to < 45 (n = 552)	G4 ≥ 15 to < 30 (n = 215)	G5 < 15 (n = 60)	
Any ADR	59 (2.98)	186 (3.77)	53 (3.54)	16 (2.90)	15 (6.98)[a]	4 (6.67)	5 (3.29)
Serious ADR	11 (0.55)	42 (0.85)	12 (0.80)	7 (1.27)	10 (4.65)[a]	3 (5.00)[a]	1 (0.66)
Special interest ADRs							
Hypoglycemia	6 (0.30)	13 (0.26)	7 (0.47)	1 (0.18)	2 (0.93)	1 (1.67)	2 (1.32)
Serious	2 (0.10)	3 (0.06)	2 (0.13)	1 (0.18)	1 (0.47)	0 (0.00)	0 (0.00)
SST disorders	10 (0.50)	16 (0.32)	4 (0.27)	3 (0.54)	1 (0.47)	0 (0.00)	0 (0.00)
Serious	0 (0.00)	1 (0.02)	0 (0.00)	1 (0.18)	1 (0.47)	0 (0.00)	0 (0.00)
GI disorders	8 (0.40)	37 (0.75)	13 (0.87)	2 (0.36)	1 (0.47)	0 (0.00)	1 (0.66)
Serious	1 (0.05)	5 (0.10)	1 (0.07)	2 (0.36)	0 (0.00)	0 (0.00)	0 (0.00)
Pancreatitis	1 (0.05)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Intestinal obstruction	0 (0.00)	3 (0.06)	0 (0.00)	1 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)
Hepatic impairment	3 (0.15)	29 (0.59)	4 (0.27)	3 (0.54)	1 (0.47)	0 (0.00)	0 (0.00)
Serious	1 (0.05)	1 (0.02)	1 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Renal impairment[b]	4 (0.20)	15 (0.30)	4 (0.27)	1 (0.18)	3 (1.40)	0 (0.00)	–
Serious	1 (0.05)	1 (0.02)	0 (0.00)	0 (0.00)	2 (0.93)	0 (0.00)	–
Cardiovascular event	2 (0.10)	8 (0.16)	1 (0.07)	2 (0.36)	0 (0.00)	0 (0.00)	0 (0.00)
Serious	1 (0.05)	7 (0.14)	1 (0.07)	1 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)
Tumor	4 (0.20)	11 (0.22)	4 (0.27)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Serious	4 (0.20)	11 (0.22)	4 (0.27)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Data are numbers of patients (%)

[a] Difference between eGFR subgroups is statistically significant according to chi-square test, and the lower end of the 95% CI for the incidence rate for the subgroup is 1 or more

[b] Renal impairment cannot be evaluated in patients on dialysis

ADR adverse drug reaction, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *GI* gastrointestinal, *SST* Skin and subcutaneous tissue

Fig. 1 Mean eGFR over time in patients with type 2 diabetes and varying levels of renal impairment (eGFR G1–G5), excluding dialysis patients. Data are presented as the mean ± SD. Datapoints are offset to aid clarity. *eGFR* estimated glomerular filtration rate, *SD* standard deviation

and dehydration). Cardiovascular-related ADRs were reported in 13 patients (10 were serious); no cardiovascular-related ADRs were reported in the G4, G5, and dialysis groups (Table 2). Cardiovascular AEs, including those not related to teneligliptin, were reported in 68 patients (G1, $n = 4$; G2, $n = 31$; G3a, $n = 12$; G3b, $n = 11$; G4, $n = 4$; G5, $n = 2$; and dialysis, $n = 4$). Tumor ADRs were reported in 19 patients; the relationship between all tumor ADRs and teneligliptin was unknown according to physician reports. Tumor AEs, including those with no relationship to teneligliptin, were reported in 87 patients (G1: $n = 11$; G2: $n = 38$; G3a: $n = 20$; G3b: $n = 6$; G4: $n = 6$; G5: $n = 1$; and dialysis: $n = 5$).

ADRs that were reported in at least five patients and serious ADRs reported in at least two patients across all subgroups are listed by preferred term in S2 of the ESM. The safety profile did not differ markedly among the subgroups. In the G4 and G5 subgroups, 2 and 9 patients, respectively, started dialysis during the period of evaluation; this was reported as an ADR in one patient in the G5 group, although the causal relationship with teneligliptin was unknown according to the reporting physician.

The eGFR profiles over time for the eGFR subgroups are shown in Fig. 1. Renal function remained relatively stable over 2 years in all subgroups.

Efficacy

Levels of HbA1c in the eGFR subgroups of non-dialysis patients and the change over 2 years after starting treatment with teneligliptin are shown in Fig. 2. At baseline, HbA1c levels were highest in patients with normal/high renal function (G1: 8.50%) and lowest in patients with kidney failure (G5: 7.04%) (Fig. 2a). There was a significant reduction in HbA1c levels observed over 2 years in G1, G2, G3a, G3b, and G4 patients ($p < 0.01$) (Fig. 2a); G1: $- 1.25 \pm 1.7\%$; G2: $- 0.67 \pm 1.25\%$; G3a: $- 0.51 \pm 1.17\%$; G3b: $- 0.37 \pm 1.12\%$; G4:
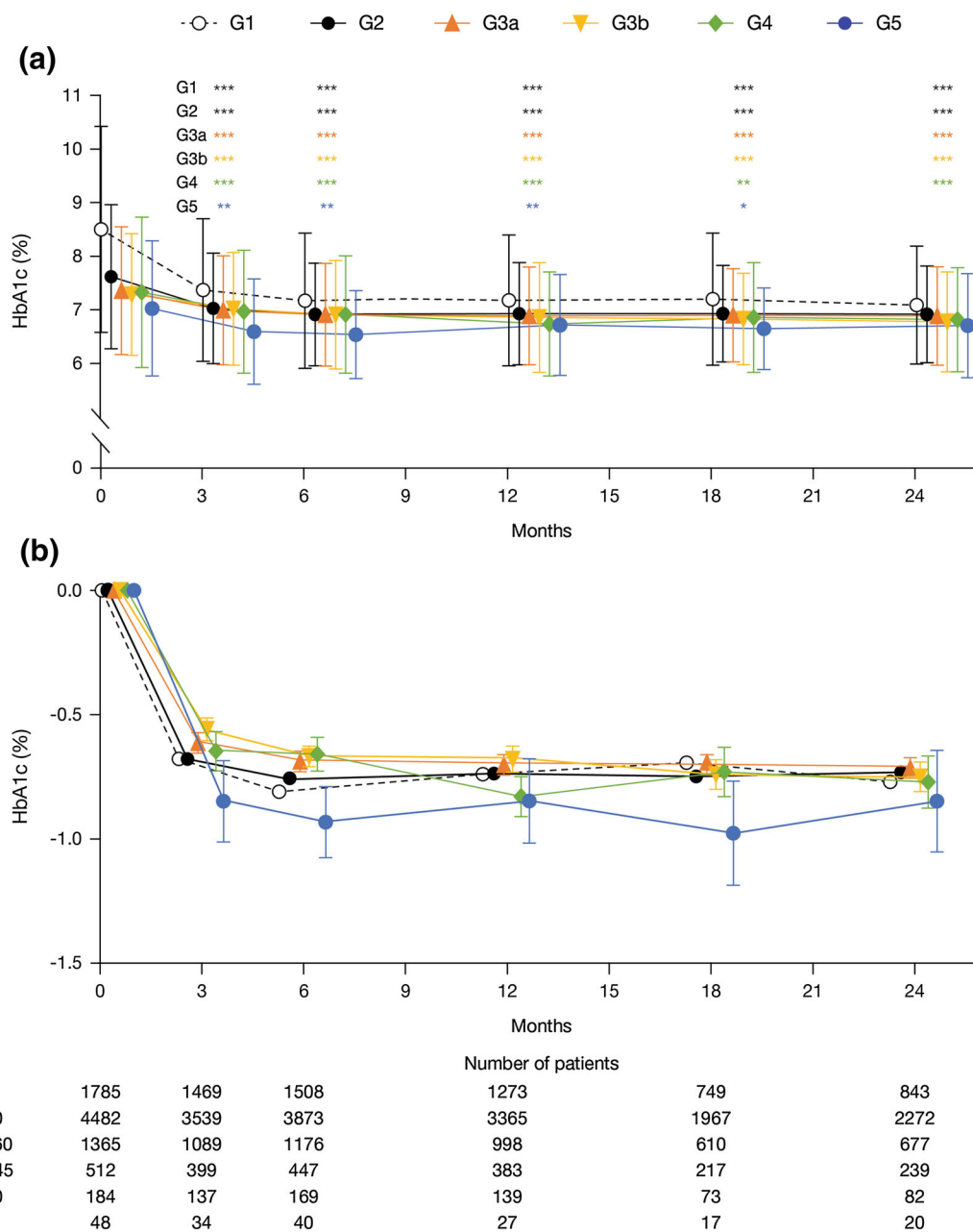
Fig. 2 Mean HbA1c over time (**a**) and LS mean change in HbA1c over time (**b**, adjusted for baseline HbA1c) in patients with type 2 diabetes and varying levels of renal impairment (eGFR G1–G5). Data are presented as the mean ± SD in **a** and the LS mean ± SE in **b**. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ versus baseline (month 0). Datapoints are offset to aid clarity. *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *LS* least squares, *SD* standard deviation, *SE* standard error

$-0.54 \pm 1.13\%$ at 2 years (all $p < 0.001$). HbA1c levels decreased or tended to decrease in G5 patients, although the reduction in HbA1c levels was not significant at 2 years of treatment

$(-0.53 \pm 1.25\%, p = 0.074)$, which may be due to the low baseline score and the limited number of patients. In order to adjust for differences in baseline HbA1c, the least squares mean of
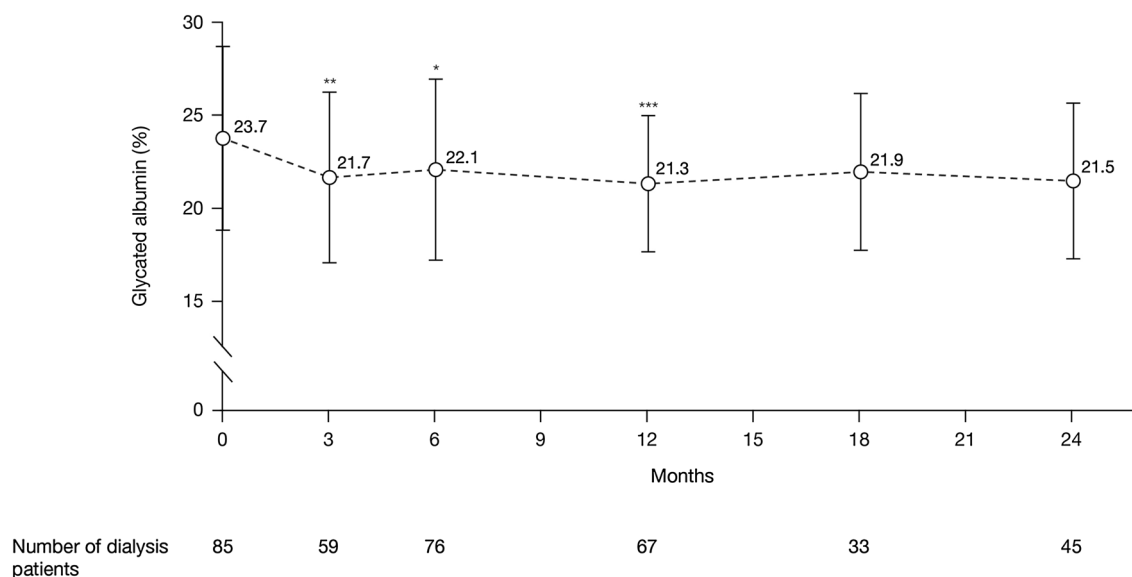
Fig. 3 Mean glycated albumin levels over time in patients with type 2 diabetes on hemodialysis. Data are presented as the mean ± standard deviation. $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ versus baseline (month 0)

HbA1c change was calculated for each eGFR subgroup (Fig. 2b). Following adjustment, HbA1c levels declined in all groups after the initiation of teneligliptin. There were no significant differences between eGFR subgroups in the reduction of HbA1c levels at 1 and 2 years after starting teneligliptin; HbA1c levels were reduced by 0.68–0.85% and 0.71–0.85%, respectively.

The mean GA level in patients receiving dialysis is illustrated in Fig. 3; the mean change in GA level after the initiation of teneligliptin was − 2.29% ($p < 0.001$) at 1 year and − 1.64% at 2 years ($p = 0.064$); this finding is limited by the number of patients available for analysis after 2 years of teneligliptin treatment ($n = 45$).

DISCUSSION

The aim of this interim analysis was to evaluate the long-term safety and efficacy of teneligliptin in patients with T2DM and reduced renal function. In this analysis, we documented ADR incidences ranging from 2.98% to 6.98% across patients with each stage of renal impairment, and no clear differences in the ADR profiles at the different stages of impairment were observed. The well-tolerated profile highlighted

by this post-marketing surveillance is supported by a previous study exploring teneligliptin in patients with end-stage renal disease [30]. Additionally, we showed that during 2 years of treatment with teneligliptin, glycemic control improved in all subgroups of patients, from those with normal or high levels of renal function to those with end-stage renal disease, including patients on dialysis.

Although all DPP-4 inhibitors have a common mechanism of action, these agents show significant structural heterogeneity, which dictate their differing pharmacokinetic and pharmacological properties [31]. One of the key differentiators is the route of elimination; some DPP-4 inhibitors are largely eliminated via the renal route (ranging from 75% to 87%) [32]. The renal clearance of teneligliptin is approximately 36% [31]. Consequently, dose adjustments are required for patients with moderate or severe renal impairment with most DPP-4 inhibitors, except for linagliptin and teneligliptin [31, 32]. In this interim analysis, the majority of patients received 20 mg/day of teneligliptin for an average duration ranging from 534 days to 617 days across the subgroups.

Generally, patients with renal impairment are at greater risk of AEs [33]. The onset of AEs or renal-related AEs has been shown to increase

with the reduction in eGFR in placebo-treated patients with T2DM [34, 35]. In the present surveillance, there was generally a higher prevalence of comorbidities other than diabetes (e.g., cardiovascular-related comorbidities such as hypertension) in patients with greater impairment of renal function compared to those with less impaired renal function at baseline. This could, in part, explain the higher incidence of ADRs and serious ADRs reported in G4 and G5 patients in our study. Indeed, a causal relationship with teneligliptin for most ADRs could not be determined by the prescribing physicians. Additionally, there were limitations of this interim analysis, including the different numbers of patients in the subgroups, the limited number of patients in the G5 group in particular, and no matched control group for each stage of renal impairment. For these reasons, we cannot confidently confirm a greater ADR risk for teneligliptin in the G4 and G5 patients based on results from this interim analysis. Instead, this analysis supports the need for further investigation of the ADR risk among patients with advanced renal impairment.

In this surveillance, there was no clear variation in the profile of ADRs, including hypoglycemia, according to the stage of renal impairment. Patients with diabetes who have impaired renal function are susceptible to developing hypoglycemia due to multiple factors, including reduced insulin clearance and impaired renal gluconeogenesis [9]. In this interim analysis, hypoglycemic episodes were reported in 5 patients presenting the more advanced stages of renal impairment (G4/G5/dialysis groups). The majority of these patients were utilizing insulin and sulfonylurea concomitantly—a treatment regimen associated with increased hypoglycemic risk [36]. Therefore, careful management is required to avoid hypoglycemic episodes when combining teneligliptin with the aforementioned regimen in T2DM patients with renal impairment.

In our study, the reduction in HbA1c levels ranged between 0.71% and 0.85% (baseline-HbA1c-adjusted least-squares mean) after 2 years of treatment in all eGFR subgroups. Improvements in HbA1c observed across the subgroups in our surveillance were similar to those seen in other studies investigating the efficacy of DPP-4 inhibitors in T2DM patients with renal impairment (reduction in HbA1c 0.4–0.7%) [37, 38]. Teneligliptin significantly improved glycemic control in patients with T2DM on dialysis [30, 39]. Furthermore, teneligliptin was found to reduce insulin dose requirements in dialysis patients [40]. Patients on dialysis often show lower values for HbA1c that do not reflect actual blood glucose control [41]. In this study, we used GA as an indicator of blood glucose control for patients on dialysis. According to the Best Practice for Diabetic Patients on Hemodialysis 2012 by the Japanese Society for Dialysis Therapy [41], tentative glucose control targets in patients with diabetes on dialysis are GA levels of < 20% in patients without a cardiovascular event history and < 24% in patients with a cardiovascular event history. In this interim analysis, GA levels in dialysis patients decreased from 23.74% to 21.34% after 1 year and 21.45% after 2 years of teneligliptin treatment. However, further analysis is required, as fewer CRF forms were collected from patients on dialysis than from those in other groups.

Although the data reported here were not generated in a controlled setting as part of a clinical trial, the post-marketing surveillance data provide important insights into teneligliptin use in routine practice and the type of ADRs that might occur among Japanese patients with renal impairment. A potential limitation of the present analysis is that the data collected after the administration of teneligliptin include that relating to cases in which other concurrent drugs may have been added or altered. This is in addition to some of the typical limitations of a post-marketing surveillance design, which include having incomplete data, possible reporting biases, no matched control group, and limitations in the generalizability of the findings.

CONCLUSION

In summary, the present interim analysis of teneligliptin after long-term treatment showed that the ADR profiles of patients with different

stages of renal impairment were similar. Teneligliptin was also associated with improvements in glycemic control in T2DM patients with renal impairment.

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