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ORIGINAL ARTICLE

Gastrointestinal symptoms in patients receiving imeglimin in combination with metformin: A post-hoc analysis of imeglimin clinical trial data

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ABSTRACT

Introduction: An increased rate of gastrointestinal (GI) symptoms is reported in patients with type 2 diabetes receiving imeglimin plus metformin vs monotherapy or in combination with other antidiabetic drugs. This post-hoc analysis explored GI symptom incidence, risk factors for their occurrence, and the impact on therapeutic efficacy during imeglimin and metformin combination therapy.

Materials and Methods: Data were derived from the 52-week, open-label, phase 3 TIMES-2 trial in Japanese type 2 diabetes patients. Patients in the imeglimin plus metformin group were divided into two subgroups based on the presence of GI symptoms and diarrhea, with efficacy and safety assessed. Factors associated with their occurrence were explored using multivariate logistic regression analysis.

Results: Of 64 patients analyzed, GI symptoms and diarrhea occurred in 40.6% (n = 26) and 17.2% (n = 11) of patients, respectively. Metformin dose and patient age did not significantly affect their incidence. Events occurred more frequently within the first 4 months of treatment. Approximately half resolved within 1 week, and most were mild. Type 2 diabetes duration <5 years was significantly associated with diarrhea (odds ratio = 5.979; P = 0.039). Significant hypoglycemic effects were observed from baseline, irrespective of GI symptoms or diarrhea. However, the degree of HbA1c improvement tended to be greater in patients with GI symptoms and diarrhea.

Conclusions: Increased awareness regarding the potential for GI symptoms, including diarrhea, during imeglimin plus metformin combination therapy is warranted. This data will provide clinicians with useful information regarding symptomatic treatment when it occurs and help determine whether to continue treatment administration and is expected to improve patient adherence.

INTRODUCTION

Imeglimin, launched in 2021, is an oral hypoglycemic drug[1] with both insulin secretagogue and insulin resistance-improving properties[2]. Its efficacy has been established as both monotherapy and when used in combination with oral antihyperglycemic agents, GLP-1RA, and insulin preparations[3–5]. Effectiveness has been observed when imeglimin and metformin are used in combination[6], and an additive synergistic effect is suspected. In a recent mouse study, the combined use of imeglimin and metformin increased β-cell mass and enhanced protection of pancreatic β-cells[7]. However, gastrointestinal (GI) symptoms have frequently been reported when imeglimin and metformin are used in combination. Although metformin monotherapy is generally well tolerated, GI symptoms, particularly diarrhea, are also common[8], and may lead to treatment discontinuation[9]. Factors such as gender, age, and BMI are associated with the development of diarrhea in patients undergoing metformin monotherapy[10,11]. Given that imeglimin is structurally similar

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to metformin[12], it is important to examine the GI effects of imeglimin and metformin combination therapy in detail and the management of these symptoms.

In Japan, metformin is the second most prescribed medication for type 2 diabetes, following DPP4-i, and is widely used as a first-line treatment[13]. Considering the progressive nature of type 2 diabetes and the likely requirement for combination therapy in many events, it is anticipated that opportunities for imeglimin and metformin co-administration will increase in the future. Using data derived from the 52-week, open-label, multicenter phase 3 TIMES-2 study, we conducted a post-hoc analysis to explore the incidence of GI symptoms, risk factors for their occurrence, and their potential impact on therapeutic efficacy during imeglimin and metformin combination therapy.

MATERIALS AND METHODS

Data sources

Data were derived from the phase 3 TIMES-2 study of imeglimin in type 2 diabetes (protocol PXL008-019, JRCT number: 2080223726).

Study design

Detailed information regarding study design and eligibility has been published previously[4]. Briefly, the phase 3 TIMES-2 study was a long-term, open-label, multicenter study designed to assess the safety and tolerability of imeglimin 1,000 mg twice daily (BID) orally as monotherapy or in combination with other hypoglycemic agents for 52 weeks.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was provided prior to study participation.

Patients

Japanese adults aged ≥20 years with type 2 diabetes treated with diet/exercise alone or together with a single antidiabetic monotherapy were enrolled in the 52-week, long-term study. Patients treated with diet and exercise plus treatment with α-glucosidase inhibitors, BIG, DPP4-i, GLIN, injectable GLP1-RA, SGLT2-i, SU, or TZD were included in the long-term combination groups.

Type, dose, and regimen of background antidiabetic therapy were required to be unchanged for ≥12 weeks prior to screening. Other inclusion criteria for combination therapy included a HbA1c of 7.5–10.5% and an eGFR ≥60 mL/min/1.73 m^2. Key exclusion criteria for all groups included insulin therapy within 30 days prior to screening, heart failure (New York Heart Association class III or IV), or any acute coronary or cerebrovascular events in the 24 weeks before screening.

Statistical analysis

The safety population included all patients in the imeglimin plus metformin combination group who received ≥1 dose of the study drug and was used for all safety and efficacy analyses ($N = 64$).

Incidence of GI symptoms and diarrhea was analyzed in the imeglimin plus metformin combination group, including their severity, onset date, duration, and implementation of symptomatic treatment. Additionally, the incidence of GI events and diarrhea was analyzed based on age categories (<65 years/≥65 years) and metformin dosage categories (≤1,000 mg/>1,000 mg).

To explore factors associated with the development of GI symptoms and diarrhea, multivariate logistic regression analysis was performed. The independent variables used included age (<65 years/≥65 years), gender (male/female), BMI (<25/≥25), diabetes duration (<5 years/≥5 years), and baseline HbA1c (<8%/≥8%). Exploratory analyses were performed to examine the incidence of GI symptoms and diarrhea resulting from the overlapping risk factors identified in the results. Subgroup analyses were conducted for factors identified as significantly associated with the occurrence of GI symptoms and diarrhea in multivariate logistic regression analysis.

Post-hoc analyses for efficacy and safety were also performed in patient subgroups according to the incidence of GI symptoms and diarrhea during the study period.

Efficacy assessments included changes in HbA1c and fasting blood glucose from baseline with a mixed effects model for repeated measures and treatment response rate (HbA1c reduction of ≥1.0% from baseline) with a logistic regression model. Safety assessments included incidence of adverse events (AEs), changes in body weight from baseline, and imeglimin blood levels. The incidence of AEs in each treatment group was analyzed descriptively by System Organ Class using the Medical Dictionary for Regulatory Activities (MedRA), version 20.1. P-values <0.05 were considered statistically significant. All statistical analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Sixty-four patients received ≥1 dose of imeglimin plus metformin during the TIMES-2 study and were included in the safety population.

The frequency of GI symptoms reported across treatment groups in the TIMES-2 study is presented in Table S1, with the highest incidence observed in the imeglimin plus metformin group (40.6% [26/64 patients, 59 events]). Diarrhea was the most common GI symptom in the imeglimin plus metformin group (17.2% [11/64 patients, 16 events]). Baseline clinical characteristics and pharmacokinetics of patients stratified by subgroups according to the occurrence of GI symptoms and diarrhea are also summarized in Table 1 and Table S2, respectively.

Safety analysis of digestive symptoms and diarrhea

Gastrointestinal symptoms and diarrhea occurred in 38.3% (18/47 patients) and 14.9% (7/47 patients) of patients aged <65 years, and in 47.1% (8/17 patients) and 23.5% (4/17 patients) of patients aged ≥65 years, respectively (Figure S1A).

Table 1 | Baseline clinical characteristics according to the presence/absence of gastrointestinal symptoms and diarrhea (safety population)

	Presence/absence of GI symptoms (*N* = 64)		Presence/absence of diarrhea (*N* = 64)	
	With GI symptoms (*N* = 26)	Without GI symptoms (*N* = 38)	With diarrhea (*N* = 11)	Without diarrhea (*N* = 53)
Age (years), mean (SD)	57.9 (12.9)	57.5 (9.4)	58.2 (12.6)	57.5 (10.6)
Sex, male, *n* (%)	16 (61.5)	30 (78.9)	6 (54.5)	40 (75.5)
BMI (kg/m^2), mean (SD)	26.0 (3.8)	26.3 (3.6)	26.3 (4.2)	26.2 (3.6)
HbA1c (%), mean (SD)	8.3 (0.6)	8.1 (0.6)	8.3 (0.6)	8.1 (0.6)
eGFR (mL/min/1.73 m^2)	81.6 (21.7)	83.4 (15.8)	80.3 (26.7)	83.2 (16.3)
Duration of diabetes, years, mean (SD)	8.2 (5.8)	9.5 (6.6)	7.6 (6.3)	9.2 (6.3)
HOMA-IR	2.7 (2.1)	2.2 (1.4)	2.8 (2.2)	2.3 (1.6)
HOMA-β (%), mean (SD)	20.5 (18.3)	17.9 (10.7)	22.3 (20.5)	18.2 (12.7)
Metformin dose (mg), mean (SD)	1,134.6 (454.0)	1,322.4 (601.0)	1,090.9 (358.3)	1,278.3 (579.4)
Metformin dose, *n* (%)				
500 mg	3 (11.5)	5 (13.2)	1 (9.1)	7 (13.2)
750 mg	5 (19.2)	4 (10.5)	2 (18.2)	7 (13.2)
1,000 mg	8 (30.8)	10 (26.3)	4 (36.4)	14 (26.4)
1,250 mg	0	1 (2.6)	0	1 (1.9)
1,500 mg	8 (30.8)	9 (23.7)	4 (36.4)	13 (24.5)
2,000 mg	1 (3.8)	1 (2.6)	0	2 (3.8)
2,250 mg	1 (3.8)	8 (21.1)	0	9 (17.0)

BMI, body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA1c, glycated hemoglobin A1C; HOMA, homeostatic model assessment; IR, insulin resistance. [Correction statement added on March 12, 2025, after first online publication: In Table 1, Metformin dose, n (%) values have been updated.]

Gastrointestinal symptoms and diarrhea occurred in 45.7% (16/35 patients) and 20.0% (7/35 patients) of patients receiving a metformin dose of ≤1,000 mg and in 34.5% (10/29 patients) and 13.8% (4/29 patients) of patients receiving a metformin dose >1,000 mg, respectively (Figure S1B). There were no significant differences in the frequency of GI symptoms and diarrhea by age group and metformin dose (Figure S1).

The severity of GI symptoms was mild in 88.5% (23/26 patients), moderate in 7.7% (2/26 patients), and severe in 3.8% (1/26 patients) (Table S3). The severity of diarrhea was mild in all patients (11/11 patients). Treatment discontinuation due to GI symptoms and diarrhea occurred in 5 patients and 1 patient, respectively (Table S4).

The onset of GI symptoms and diarrhea is presented in Figure 1, with the highest incidence observed within the first week of imeglimin treatment. The duration of GI symptoms and diarrhea is presented in Figure 2, with 45.8% (27/59 events) and 56.3% (9/16 events) resolving within 1 week, respectively. A total of 37.3% (22/59 events) and 25.0% (4/16 events) received pharmacological treatment for GI symptoms and diarrhea (Table S5). When the duration of GI symptoms and diarrhea was less than 1 week, 11.1% (3/27 events) and 11.1% (1/9 events) of patients received symptomatic treatment, respectively. This increased to 59.4% (19/32 events) and 42.9% (3/7 events) of patients, respectively, when the duration of GI symptoms and diarrhea was more than 1 week (Table S6).

Multivariate logistic regression analysis found no factors that were significantly associated with the occurrence of GI symptoms (Figure S2A). Diabetes duration of <5 years was significantly associated with the occurrence of diarrhea (odds ratio [OR] 5.979, $P = 0.039$) in patients receiving imeglimin plus metformin (Figure S2B).

Items with an OR greater than 1 were considered potential risk factors for diarrhea (female, OR = 3.77; age ≥65 years, OR = 4.48; baseline BMI <25 kg/m^2, OR = 2.43; baseline HbA1c ≥8.0%, OR = 7.79). The rate of GI symptoms and diarrhea for patients with the combined presence of these factors is shown in Figure S3A,B respectively.

The rate of GI symptoms was 33.3% (2/6 patients) for patients with 0 risk factors, 12.5% (2/16 patients) for patients with 1 risk factor, 40.7% (11/27 patients) for patients with 2 risk factors, 76.9% (10/13 patients) for patients with 3 risk factors, and 50% (1/2 patients) for patients with 4 risk factors (Figure S3A).The rate of diarrhea events was 0% (0/6 patients) each for patients with 0 and 1 risk factor, 18.5% (5/27 patients) for patients with 2 risk factors, 38.5% (5/13 patients) for patients with 3 risk factors, and 50% (1/2 patients) for patients with 4 risk factors (Figure S3B).

In patients who experienced GI symptoms and diarrhea, a trend towards a higher incidence of non-GI-related AEs was observed (Table S7).

Effect of onset of gastrointestinal symptoms and diarrhea on efficacy

Significant reductions in HbA1c from baseline were observed at all assessment time points, regardless of the presence of GI symptoms (Figure 3A) and diarrhea (Figure 3B).

Least squares means (LSM) (95% confidence interval [CI]) of HbA1c (%) changes from baseline at 52 weeks were −0.89 (−1.20, −0.57) in patients with GI symptoms vs −0.53 (−0.77, −0.28) in patients without GI symptoms, and −0.91 (−1.40, −0.42) in patients with diarrhea vs −0.63 (−0.84, −0.42) in patients without diarrhea ($P < 0.001$ vs baseline, each).

Differences in HbA1c change from baseline between patients with GI symptoms and those without GI symptoms were not

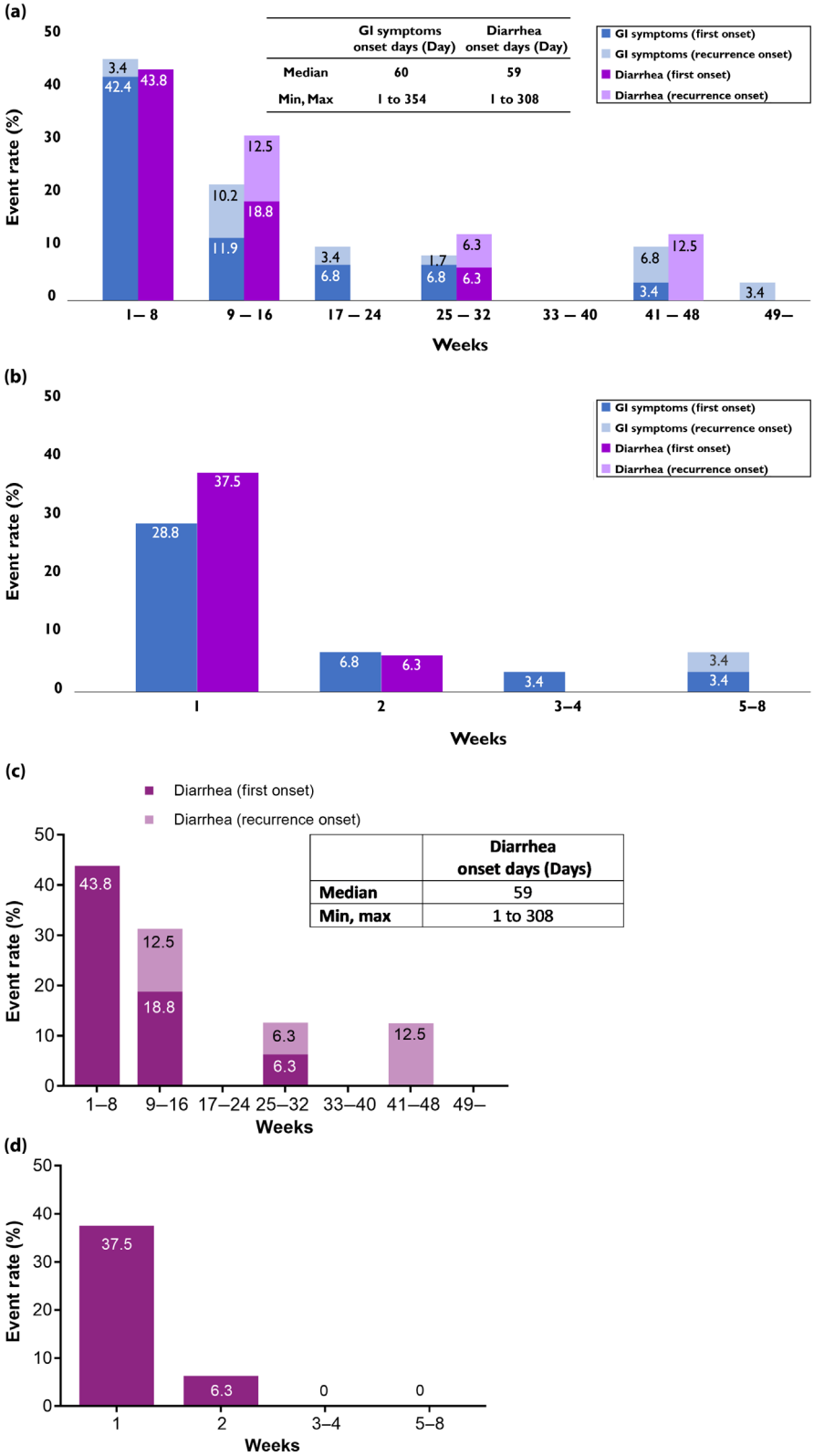

Figure 1 | Onset of a–b) gastrointestinal symptoms (59 events) and c–d) diarrhea (16 events). (a) and (c): event throughout the study. (b) and (d): event in Weeks 1–8.

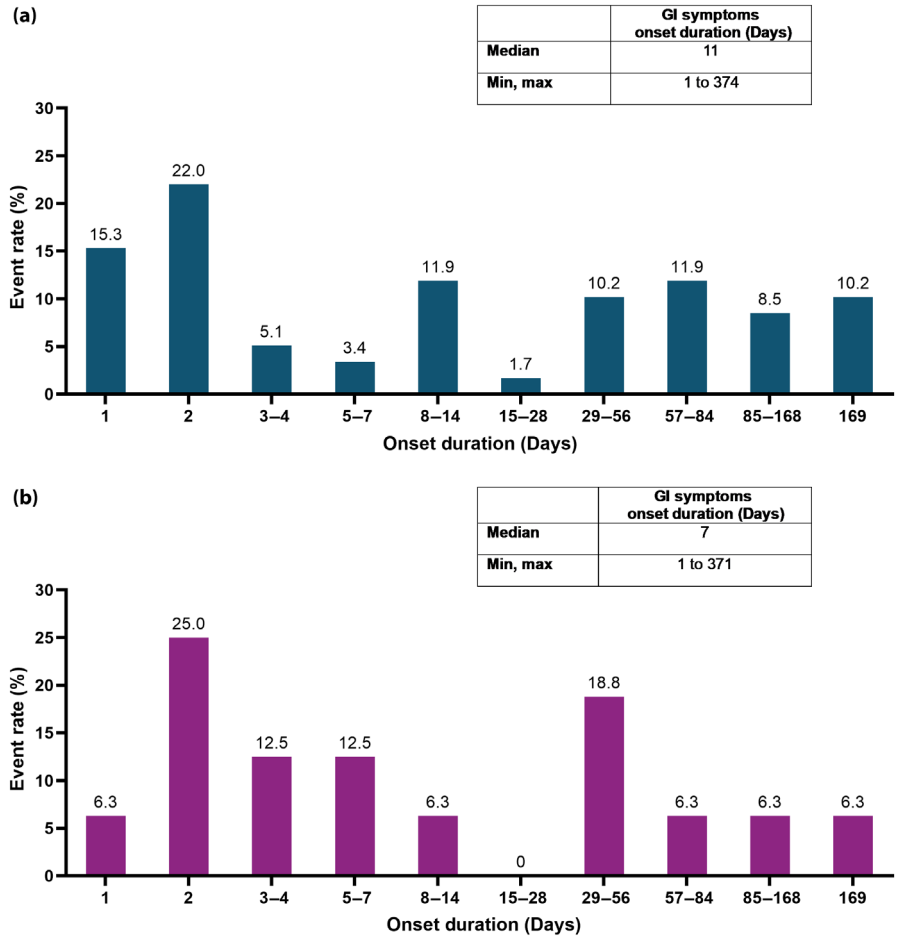

Figure 2 | Duration of onset of (a) gastrointestinal symptoms and (b) diarrhea.

significant at 52 weeks (−0.36 [95% CI: −0.760, 0.036], $P = 0.074$), but significant differences were observed from 8 to 48 weeks (Figure 3A).

The difference in HbA1c change from baseline between patients with and without diarrhea was not significant at any time point (Figure 3B).

LSM (95% CI) of fasting blood glucose (mg/dL) changes from baseline was −31.24 (95% CI: −42.39, −20.08) in patients with GI symptoms vs −20.12 (95% CI: −28.57, −11.66) in patients without GI symptoms, and −33.00 (95% CI: −49.89, −16.11) in patients with diarrhea vs −22.75 (95% CI: −30.19, −15.32) in patients without diarrhea ($P < 0.001$ vs baseline, each) (Figure S4). Differences in fasting blood glucose change were not significant at 52 weeks (−11.12 [95% CI: −25.15, 2.91], $P = 0.117$ vs baseline) between patients with and without GI symptoms but were significant at several assessment points (Figure S4A). The difference in fasting plasma glucose change from baseline between patients with and without diarrhea was not significant at any time point (Figure S4B).

For the analysis of treatment response, 46.2% of patients with GI symptoms vs 15.8% of patients without GI symptoms and 45.5% of patients with diarrhea vs 24.5% of patients without diarrhea had a treatment response (LOCF), defined as an HbA1c reduction of ≥1% (Figure S5). A significantly higher proportion of patients with GI symptoms had a treatment response (LOCF) compared with those without GI symptoms (OR: 4.13, $P < 0.05$) (Figure S5).

Weight (kg) change from baseline at 52 weeks was −0.10 (95% CI: −0.90, 0.70) in patients with GI symptoms vs −0.00 (95% CI: −0.64, 0.64) in patients without GI symptoms, and 0.00 (95% CI: −1.16, 1.17) in patients with diarrhea vs −0.05 (95% CI: −0.60, 0.51) in patients without diarrhea (Figure 4).

No meaningful differences were observed in the plasma concentration of imeglimin based on the presence or absence of GI symptoms and diarrhea (Table S2).

Subgroup analysis by type 2 diabetes duration was performed, as a duration of <5 years was identified as significantly associated with the occurrence of diarrhea in multivariate logistic regression analysis. LSM (95% CI) of

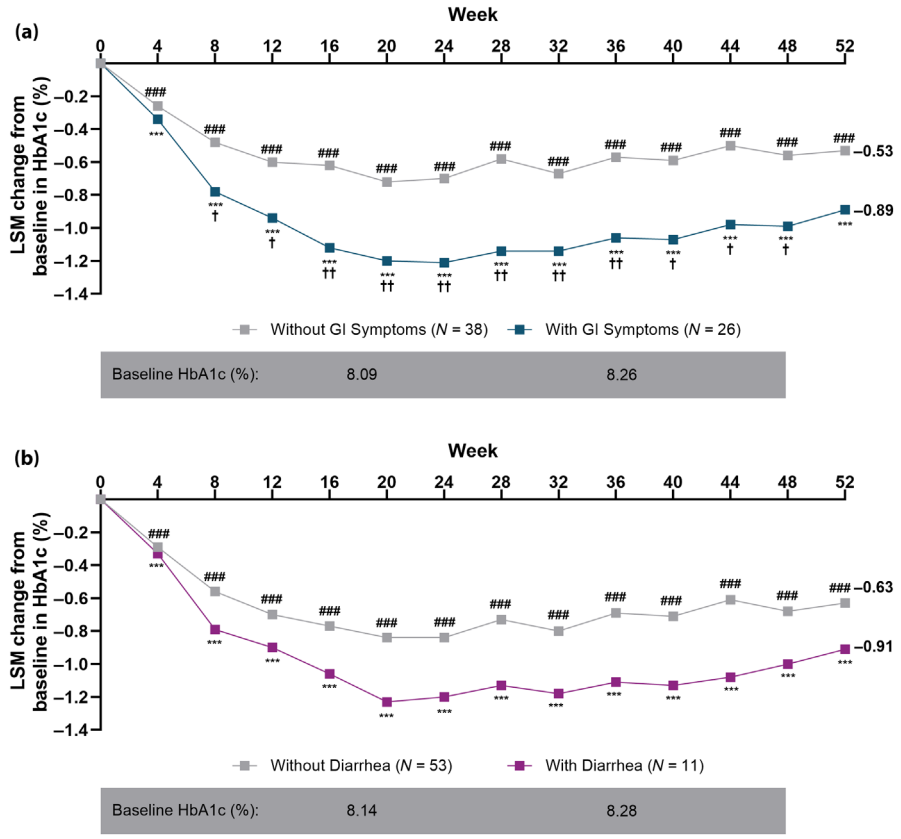

Figure 3 | Change in HbA1c from baseline by onset of (a) gastrointestinal symptoms and (b) diarrhea.

HbA1c (%) from baseline at 52 weeks was −0.89 (95% CI: −1.23, −0.55) in patients with a type 2 diabetes duration <5 years vs −0.56 (95% CI: −0.80, −0.33) in patients with a type 2 diabetes duration ≥5 years at 52 weeks. Baseline demographic data and change in HbA1c from baseline by disease duration (<5 years vs ≥5 years) are shown in Table S8 and Figure S6, respectively.

DISCUSSION

In this post-hoc analysis of data from 64 patients undergoing combination treatment with imeglimin plus metformin in the TIMES-2 study, there was an increased incidence of GI symptoms in patients receiving imeglimin plus metformin compared with monotherapy or when used in conjunction with other antihyperglycemic agents, but most events of GI symptoms and diarrhea associated with combination treatment were mild, and no significant tolerability issues were observed. Age and metformin dose had no significant impact on the development of GI symptoms and diarrhea. Onset of GI symptoms and diarrhea was observed early after initiating imeglimin treatment, and subsequent events were less frequent after 16 weeks, suggesting the need for early monitoring when starting combination therapy.

Similar results have been reported regarding the onset of GI symptoms with metformin monotherapy, which often occurs at the start of treatment initiation or dose escalation[6]. The duration of GI symptoms and diarrhea varied, with approximately half of patients experiencing resolution within 1 week. However, a minority of patients experienced prolonged symptoms. Development of chronic diarrhea has been reported with metformin monotherapy[14], which points to the need for caution when employing imeglimin plus metformin therapy, particularly during treatment initiation and in patients at increased risk of symptom development.

We also performed a subgroup analysis examining the effect of GI symptoms and diarrhea on treatment efficacy. Regardless of the presence or absence of GI symptoms and diarrhea, imeglimin plus metformin combination therapy resulted in significant the blood glucose-lowering effects compared with baseline. Interestingly, the magnitude of blood glucose-lowering effect was greater in the group who developed GI symptoms and diarrhea.

There was no significant difference in weight change between patients with and without GI symptoms and diarrhea, and it is strongly suggested that imeglimin plus metformin does not cause severe gastrointestinal symptoms or diarrhea resulting in

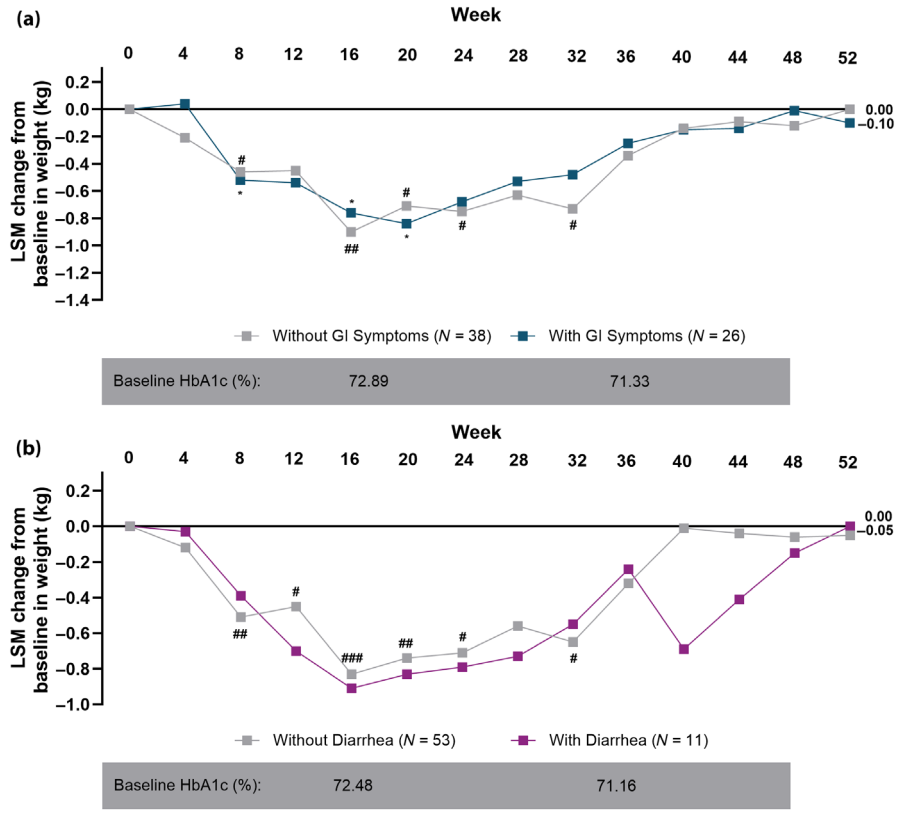

Figure 4 | Change in weight from baseline by presence of (a) gastrointestinal symptoms and (b) diarrhea.

weight loss. The presence of GI symptoms and diarrhea may impact the blood glucose-lowering effect of the combination therapy in as yet unknown ways. Despite considering the potential effect of imeglimin blood plasma concentration on blood glucose reduction, no significant differences were observed between the groups with and without GI symptoms and diarrhea.

The high efficacy observed with the combination therapy may be attributed to its impact on the gut microbiota[15]. Disruptions in the gut microbiota have been demonstrated in individuals with type 2 diabetes compared with those who do not have type 2 diabetes[16–18]. Metformin has been shown to alter the gut microbiota, with a particular increase in *Akkermansia*[19–23]. Similarly, imeglimin is also associated with alterations in intestinal bacteria, and an increase in *Akkermansia* in particular has been observed[15]. A lower abundance of *Akkermansia* has also been observed in the gut of obese individuals and patients with type 2 diabetes compared with healthy individuals[24]. Improvements in obesity and type 2 diabetes have also been shown following administration of *Akkermansia* in mice and human studies[25]. Although there are currently no studies examining the effect of imeglimin plus metformin on the gut microbiota, it is possible that there are additional effects on the gut microbiota, which may lead to the development of GI symptoms and higher efficacy. Furthermore, metformin is associated with several effects on the GI tract beyond modulation of the gut microbiota, such as suppression of intestinal bile acid resorption, reduction in the rate of glucose absorption, enhancement of GLP-1 secretion and action, and slowing of gastric emptying[26]. Imeglimin has been recently launched, and thus sufficient information regarding its effects on the GI tract is lacking. Due to its structural similarity to metformin and partial overlap in action, it is plausible that it possesses similar effects on the GI tract. However, the lack of data currently hinders our ability to explicitly deduce the effects of imeglimin monotherapy or in combination with metformin on the gut microbiota and the GI tract.

Multivariate logistic regression analysis was also conducted to exploratively examine the risk factors associated with the development of diarrhea with imeglimin plus metformin combination therapy. Disease duration of <5 years was significantly associated with diarrhea development. Previous studies have found that longer disease the duration is associated with the development of GI symptoms in type 2 diabetes, suggesting that progression of autonomic neuropathy is largely responsible for the development of diarrhea[27]. As such, we included

duration of type 2 diabetes as an explanatory variable. Unexpectedly, our results found an inverse relationship where disease duration of <5 years was associated with diarrhea development. It is possible that this discrepancy is because our study did not include individuals with a longer disease duration compared to previously reported studies, and the average disease duration in the imeglimin plus metformin group was approximately 9 years. Furthermore, the higher incidence of GI symptoms in patients with shorter disease duration may suggest that the combination regimen may have greater sensitivity in patients with shorter disease duration and thus may show greater efficacy and AEs. However, since the number of diarrhea cases in this study was small, further investigation with a larger sample size is required to examine patient background factors related to its development in more detail.

The results of our analysis should be examined in light of its limitations, most of which are inherent to its post hoc nature. First, although the data were collected prospectively, the analysis was conducted retrospectively and may therefore be susceptible to specific biases. Second, the sample size was relatively small, particularly for the patient subgroups, which may have introduced statistical variability that could impact the results. Third, the trial design was non-blinded, and it was not a placebo-controlled trial. Therefore, there is a possibility that the observed effects were influenced by placebo effects or observation bias. Fourth, investigations into GI symptoms caused by imeglimin monotherapy were insufficient. In this study, we investigated factors related to the onset of GI symptoms caused by the combination of imeglimin and metformin, but we were unable to investigate factors related to the onset of GI symptoms caused by imeglimin monotherapy due to the small number of events. Hence, a proper comparison and evaluation of the incidence of GI symptoms between imeglimin monotherapy and the combination of imeglimin with metformin cannot be made. Fifth, the study duration was short, and the study data was limited to 52 weeks, which is insufficient to thoroughly assess the long-term efficacy of imeglimin plus metformin combination therapy for over a year.

Imeglimin represents a novel mechanistic approach for the treatment of type 2 diabetes. GI symptoms and diarrhea observed with the combination of imeglimin plus metformin were often mild, and, although sometimes persistent in certain patients, most patients tolerated the treatment well. Type 2 diabetes duration <5 years was significantly associated with diarrhea. Significant hypoglycemic effects were observed from baseline, irrespective of GI symptoms or diarrhea. However, the degree of HbA1c improvement tended to be greater in patients with GI symptoms and diarrhea. The higher efficacy observed in this group suggests that a comprehensive evaluation of risk–benefit is necessary for individual patients when considering treatment continuation. It is anticipated that this data will help improve adherence to imeglimin plus metformin combination therapy and contribute to patient satisfaction with the treatment.

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ETHICS STATEMENT

This post hoc analysis was conducted using data from the phase 3 TIMES-2 study of imeglimin in type 2 diabetes (protocol PXL008-019, JAPIC number: 2080223726). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the appropriate institutional review boards and regulatory agencies. Patients provided written informed consent to participate in the study.

DISCLOSURE

KH and KKo are employees of Sumitomo Pharma Co., Ltd. HW has received honoraria for lectures for Mitsubishi Tanabe Pharma, Sumitomo Pharma, Sanwa Kagaku, Takeda Pharmaceuticals, Sanofi, Kowa, MSD, Nippon Boehringer Ingelheim, Eli Lilly, Novo Nordisk, AstraZeneca, Ono Pharmaceutical, Astellas, Kyowa Kirin, Terumo, Taisho Pharmaceutical, Abbott, and Kissei Pharmaceutical, and research activities for Takeda Pharmaceuticals, Nippon Boehringer Ingelheim, Kissei Pharmaceutical, Novo Nordisk, Mitsubishi Tanabe Pharma, Lifescan Japan, Kyowa Kirin, Sumitomo Pharma, Eli Lilly Japan, Teijin Pharma, Taisho Pharmaceutical, Abbott Japan, Daiichi Sankyo, Astellas, Ono Pharmaceutical Co. Ltd., Sanofi, MSD, Soiken Inc., Sanwa Kagaku, and Kowa. KKa has been an advisor to Sanwa Kagaku and received honoraria for lectures from Astellas, AstraZeneca, Daiichi Sankyo, Kowa, Sumitomo Pharma Co. Ltd., MSD, Ono Pharmaceutical, Co. Ltd., Sanwa Kagaku, Novo Nordisk, Nippon Boehringer Ingelheim, Eli Lilly Japan, Taisho Pharmaceutical, Takeda Pharmaceuticals, and Mitsubishi Tanabe Pharma, and received scholarship grants from Nippon Boehringer Ingelheim, Taisho Pharmaceutical and Kowa. KU has received honoraria for lectures from AstraZeneca, Taisho Pharmaceutical, Novo Nordisk, Sumitomo Pharma, Kowa, Mitsubishi Tanabe Pharma, and Ono Pharmaceutical; research grants from Sumitomo Pharma, Novo Nordisk, Eli Lilly Japan, Sanofi, Abbott Japan, MSD, and Nippon Boehringer Ingelheim; and scholarship grants from Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Sumitomo Pharma, Takeda Pharmaceuticals, and Sanofi. HW, KKa, and KU are editorial board members of the *Journal of Diabetes Investigation* and

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Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

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

Table S1 | Main gastrointestinal symptoms reported in the TIMES-2 study.

Table S2 | Pharmacokinetics over time by presence/absence of (a) GI symptoms and (b) diarrhea.

Table S3 | Severity of gastrointestinal symptoms and diarrhea overall and at each onset.

Table S4 | Patient disposition by (a) gastrointestinal symptoms and (b) diarrhea.

Table S5 | Treatment of gastrointestinal symptoms and diarrhea.

Table S6 | Frequency of treatment intervention by duration.

Table S7 | Incidence of adverse events by presence/absence of (a) gastrointestinal symptoms and (b) diarrhea.

Table S8 | Demographic data by duration of type 2 diabetes (<5 years/≥5 years).

Figure S1 | Incidence of gastrointestinal symptoms and diarrhea by (a) age category and (b) metformin dose category.

Figure S2 | Multivariate logistic regression analysis of factors associated with (a) gastrointestinal symptoms and (b) diarrhea occurrence.

Figure S3 | Incidence of (a) gastrointestinal symptoms and (b) diarrhea by number of risk factors.

Figure S4 | Change in fasting blood glucose from baseline by presence of (a) gastrointestinal symptoms and (b) diarrhea.

Figure S5 | Analysis of treatment response by presence of (a) gastrointestinal symptoms and (b) diarrhea.

Figure S6 | Change in HbA1c from baseline by disease duration (<5 years vs ≥5 years).