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BRIEF REPORT

Efficacy and safety of sitagliptin as compared with glimepiride in Japanese patients with type 2 diabetes mellitus aged ≥ 60 years (START-J trial)

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The aim of this study was to evaluate the efficacy and safety of sitagliptin administered to elderly patients with type 2 diabetes mellitus (T2DM) for 1 year as compared with glimepiride. Patients aged ≥60 years with T2DM and inadequately controlled blood glucose were randomly assigned to sitagliptin 50 mg once daily or glimepiride 0.5 mg once daily for 52 weeks. The primary efficacy endpoint was the change in glycated haemoglobin (HbA1c) from baseline to week 52. Secondary efficacy endpoints included self-monitored blood glucose and weight. Safety endpoints were adverse events including hypoglycaemia. Administration of sitagliptin or glimepiride to elderly patients with T2DM resulted in a significant decrease in HbA1c change from baseline. At 52 weeks, the least squares mean difference between the treatments was 0.11% (95% confidence interval [CI] −0.02 to 0.24; P = .087) (1.2 mmol/mol [−0.2 to 2.6]). The upper limit of the CI was below the predefined non-inferiority margin (0.3% [3.3 mmol/mol]), demonstrating non-inferiority of sitagliptin to glimepiride for the primary endpoint. Sitagliptin resulted in a significantly lower incidence rate of non-serious hypoglycaemia than glimepiride during the 52 weeks (4.7% vs 16.1%; P = .002); thus, sitagliptin is a useful therapeutic option for elderly patients with T2DM.

KEYWORDS

clinical trial, DPP-4 inhibitor, randomized trial, sitagliptin, sulphonylureas

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1 | INTRODUCTION

Elderly patients (aged ≥65 years) comprise 65.7% of all patients with diabetes in Japan.[1] In Japan, such patients are most commonly treated with sulphonylureas (SUs),[2] with a treatment goal proposed by the Japan Diabetes Society of glycated haemoglobin (HbA1c) <6.9% (51.9 mmol/mol). This goal is achieved in only 30% to 35% of patients taking SUs.[3,4] A post-marketing surveillance study of glimepiride,[5] the most commonly used SU, showed a significantly higher incidence of hypoglycaemia in elderly patients than in non-elderly patients (3.26% vs 1.89%), although the overall incidence of adverse events (AEs) was not significantly different (7.44% vs 7.86%). Hypoglycaemia is associated with serious medical problems, such as disturbed consciousness, cardiovascular disease and fall-related fractures.[6,7] For diabetes treatment to be safe, therefore, it is critical to minimize the risk of hypoglycaemic episodes.

Sitagliptin is the first drug of the incretin-based therapies in Japan and was made commercially available in December 2009. In a clinical study conducted outside Japan,[8] sitagliptin was shown to be effective for patients aged ≥65 years with type 2 diabetes mellitus (T2DM). In that study, the overall incidence of AEs did not differ from that observed in the placebo group, and no hypoglycaemia was reported. Thus, it seemed justified and worthwhile to compare the efficacy and safety of sitagliptin in Japanese patients aged ≥60 years with those of glimepiride to establish guiding principles for the treatment of elderly patients with T2DM.

2 | MATERIALS AND METHODS

The present two-arm, randomized, open-label study (START-J, SiTAgliptin in eldeRly Trial in Japan) was conducted at 104 centres in Japan. The study consisted of a 6-week screening period, followed by a 52-week treatment period. Participants completing the treatment period who were willing to continue their treatment were enrolled in a 52-week extension study. More information on methods is provided in File S1.

The trial was registered at ClinicalTrials.gov (NCT01183104) and with the University Hospital Medical Information Network (UMIN), Japan (UMIN000004047).

3 | RESULTS

3.1 | Participants and treatments

Participant disposition is presented in Table S1. Of the 305 participants, 148 received at least 1 dose of sitagliptin, while 143 received at least 1 dose of glimepiride. Of these, 119 participants receiving sitagliptin and 111 receiving glimepiride completed the 52-week treatment period. Baseline demographic and disease characteristics of the participants receiving sitagliptin were similar to those of participants receiving glimepiride (Table S2, Per Protocol Set).

A total of 10 participants (6.8%) in the sitagliptin group needed rescue treatment with glimepiride by week 52, while 2 participants (1.4%) in the glimepiride group needed rescue treatment with sitagliptin by week 52. A total of 80 participants who had received sitagliptin and 61 who had received glimepiride were enrolled in the extension study; 76 and 60 of these, respectively, completed the 104-week treatment.

3.2 | Efficacy

Significant reductions in HbA1c from baseline were observed in both of the treatment groups at weeks 24 and 52 (Figure 1, all $P < .001$ vs baseline, Per Protocol Set). The least squares (LS) mean reductions in

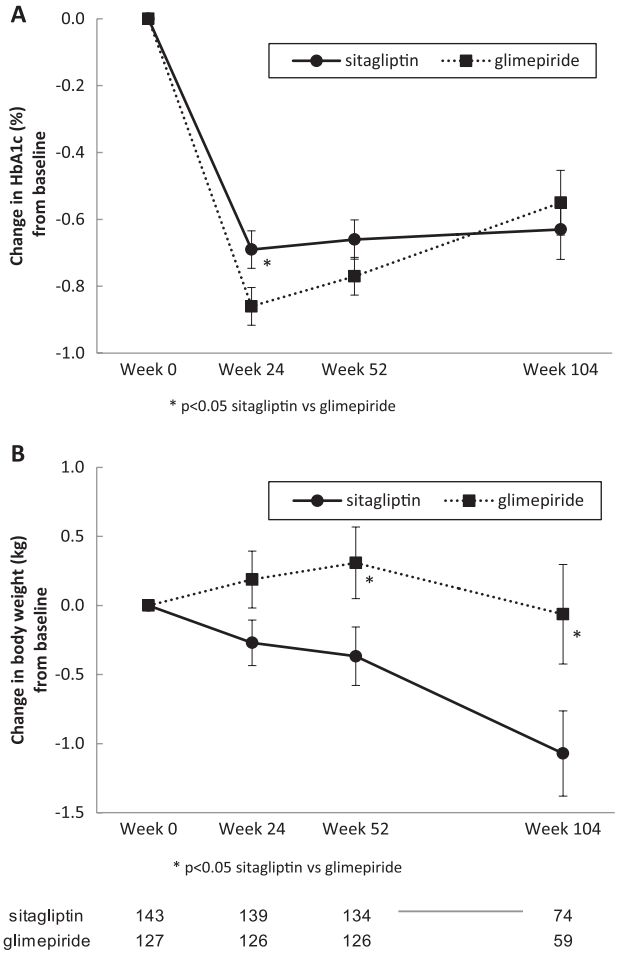

FIGURE 1 LS mean changes in HbA1c (A) and body weight (B; LOCF) from baseline. The bars indicate standard errors. Numbers below the panels are number of patients [Correction added on 22 June, after first online publication: Figure 1 and its caption were previously incorrect and have been amended in this version]

HbA1c (LOCF) from baseline in the sitagliptin and glimepiride groups were −0.69% and −0.86% (−7.5 and −9.4 mmol/mol) at week 24, and −0.66% and −0.77% (−7.2 and -8.4 mmol/mol) at week 52, respectively.

The difference in the changes in HbA1c (LOCF) between the treatments (sitagliptin − glimepiride) at week 52 was not significant (0.11%; $P = .087$), with the 95% confidence interval (CI) of the LS mean difference being −0.02%, 0.24% (1.2mmol/mol [−0.2, 2.6]). The upper limit of the CI fell below the predefined non-inferiority margin (0.3% [3.3 mmol/mol]), showing the non-inferiority of sitagliptin. The non-inferiority was also confirmed in the full analysis set population. At week 24, the difference in the changes in HbA1c between the treatments was significant (0.17 [95% CI 0.04, 0.29] %; $P = .01$) (1.9 [0.4, 3.2] mmol/mol).

In the participants in the extension study, the LS mean reduction in HbA1c (LOCF) from baseline at week 104 was −0.63% (−6.9 mmol/mol) in the sitagliptin group and −0.55% (−6.0 mmol/mol) in the glimepiride group. The difference between the treatment groups was not significant at week 104.

With respect to the means of 6-point self-monitored blood glucose at baseline and week 52, similar decreases in blood glucose levels from baseline were observed in the sitagliptin and glimepiride groups at week 52 (Figure S1).

Mean body weight increased until week 52, but returned to the baseline level at week 104 in the glimepiride group, while it progressively decreased in the sitagliptin group over the 104 weeks of treatment. The mean changes in body weight from baseline (LOCF) were −0.270 kg at week 24, −0.367 kg at week 52, and −1.071 kg at week 104 in the sitagliptin group, while they were 0.188, 0.309 and −0.063 kg, respectively, in the glimepiride group. The difference in body weight changes between the treatment groups was significant at week 52 ($P = .043$) and at week 104 ($P = .035$).

Proinsulin/insulin ratios (LOCF) were not notably changed in the glimepiride group (Figure S2; changes from baseline, −0.003 at week 24, −0.002 at week 52), while they decreased in the sitagliptin group (−0.040 at week 24, −0.049 at week 52). The differences between the treatments at weeks 24 and 52 were significant ($P = .004$, $P < .001$).

3.3 | Safety

No serious hypoglycaemia requiring assistance was reported in either group. The incidence rate of non-serious hypoglycaemia during the 52 weeks of treatment was significantly lower in the sitagliptin group (4.7%, 7/148 patients) than that in the glimepiride group (16.1%, 23/143 patients; $P = .002$, Fisher's exact test). The incidence rate of non-serious hypoglycaemia was lower in the sitagliptin group throughout the study period (Figure 2). Age, renal function and diabetes duration were not associated with non-serious hypoglycaemia (data not shown).

Overall, AEs were reported before rescue treatment in 46 participants (31.1%) in the sitagliptin group and 34 participants (23.8%) in the glimepiride group during the 104 weeks of treatment. Infections and neoplasms were more frequently reported in the sitagliptin group (infections, 10.8%; neoplasms, 5.4%) than in the glimepiride group (5.6%, 0%); however, most of them were considered unrelated to the treatment. Most of the AEs were mild or moderate. Table S3 summarizes the AEs that were reported during the 104 weeks of treatment and for which a causal relationship to the study drug could not be excluded. The overall incidence rate of these AEs during the 104 weeks of treatment, excluding those occurring after rescue therapy, was similar in the two treatment groups. The incidence of AEs leading to discontinuation did not differ between the treatment groups (sitagliptin, 6 patients; glimepiride, 6 patients). One patient had died in the glimepiride group by week 52.

Serious AEs were reported in more participants in the sitagliptin group (13 patients, 8.8%) than in the glimepiride group (3 patients, 2.1%); however, only 2 of the serious AEs reported in the sitagliptin group could not be ruled out as having a causal relationship to the study drug, and none were reported in >1 participant (Table S3).

4 | DISCUSSION

The present study shows that, while both sitagliptin and glimepiride similarly reduce HbA1c in elderly Japanese people with T2DM, the incidence of hypoglycaemia in the sitagliptin group was as low as one-third of that in the glimepiride group.

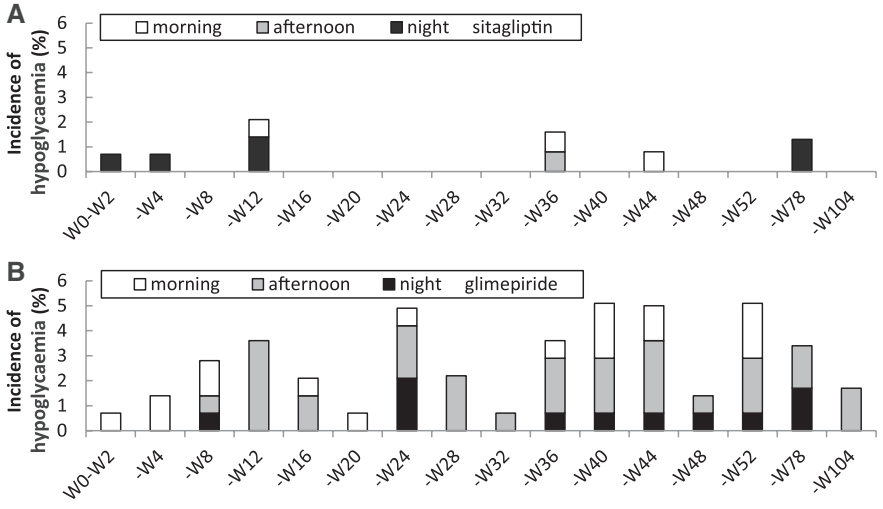

FIGURE 2 Incidence rates (%) of hypoglycaemia during 4-week observation periods up to week 52, between weeks 52 and 78, and between weeks 78 and 104. Panel A shows the rates for sitagliptin and Panel B shows rates for glimepiride. Denominators are the number of patients who received at least 1 dose of study drug during each observation period. Morning, from breakfast to lunch; afternoon, from lunch to evening meal; night, evening meal to breakfast; W, week

Consistent with the present results, dipeptidyl peptidase 4 (DPP-4) inhibitors are generally associated with fewer side effects than SUs;[9] they do not inherently cause hypoglycaemia, they are weight-neutral and they have been shown not to increase cardiovascular risk.[10–13] Although a higher rate of hypoglycaemia has been observed in people treated with SUs, it should be noted that glimepiride treatment in the present study did not induce severe hypoglycaemia for a 2-year trial period, which might be attributed to the use of low-dose glimepiride.

Regarding pancreatic β-cell function, the proinsulin/insulin ratio was significantly improved in the sitagliptin-treated group compared with that in the glimepiride-treated group. Recently, Kondo et al.[14] showed that sitagliptin treatment for 52 weeks significantly improved the glucose-induced early phase of insulin secretion, as evaluated by the insulinogenic index. Many elderly patients show impairment of pancreatic function, but the results obtained in these clinical trials suggest that long-term treatment with DPP-4 inhibitors may help to preserve residual pancreatic function.

In the present study, body weight in the sitagliptin group decreased by 1 kg, while it was unchanged in the glimepiride group. DPP-4 inhibitors are generally thought to be weight-neutral. The reason that weight was found to be decreased by sitagliptin treatment in the present study is not clear at present.

The AE profiles for which a causal relationship to the study drug could not be excluded were similar between the sitagliptin group and the glimepiride group during the 104 weeks. The results for AEs and serious AEs in this trial were essentially consistent with the safety profile of sitagliptin reported in pooled analyses of 25 sitagliptin studies in elderly patients with T2DM[15] and a 2-year observational study of the efficacy and safety of sitagliptin in elderly Japanese patients with T2DM.[16]

The present study has several limitations. First, when the study was started in 2010, the target patient number was 540, a number that should allow proof of the study hypothesis with a probability of 93%; however, the study was terminated in 2015 after enrolling 305 patients because of difficulty in patient recruitment. The paucity of participants may be explained by the fact that sitagliptin and other DPP-4 inhibitors rapidly became first-line therapy for T2DM in Japan during that period.[17] Second, because the median disease duration among the patients was 45 months, it seems likely that many of the elderly patients included in the present trial were in relatively good health. The findings of the present study should therefore be interpreted with caution when treating frail elderly patients with T2DM.

In conclusion, sitagliptin had slightly lower efficacy at week 24, but was non-inferior to glimepiride at week 52, and had generally better safety results with regard to hypoglycaemia.

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Conflict of interest

Y. Terauchi received consulting and/or speaker fees from MSD K.K., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Company and Limited, Mitsubishi Tanabe Pharma Corporation, Sanwa Kagaku Kenkyusho Co., Ltd., Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Sanofi K.K., Bayer Yakuhin, Ltd., Sumitomo Dainippon Pharma Co. Ltd., Shionogi & Co., Ltd., AstraZeneca K.K., Astellas Pharma Inc. and Taisho Toyama Pharmaceutical Co., Ltd. Y. Terauchi also received clinical commissioned/joint research grants from MSD K.K., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Company and Limited, Mitsubishi Tanabe Pharma Corporation, Sanwa Kagaku Kenkyusho Co., Ltd., Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Sanofi K.K., Bayer Yakuhin, Ltd., Sumitomo Dainippon Pharma Co. Ltd., Shionogi & Co., Ltd., AstraZeneca K.K., Astellas Pharma Inc. and Taisho Toyama Pharmaceutical Co., Ltd.

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N. Shihara reported no conflict of interest relevant to this study.

Author contributions

Y. T. and Y. S. contributed to conception, design of the research, analysis and interpretation of data and writing the manuscript. Y. Y. contributed to collection of data, analysis and interpretation of data and writing the manuscript. H. I., M. K., and J. S. contributed to analysis and interpretation of data. M. O. contributed to design of the research. D. Y. contributed to design of the research, collection of data, analysis and interpretation of data and writing the manuscript. N. S. contributed to analysis and interpretation of data and writing the manuscript. All the authors approved the version to be published. Y. T. is the guarantor of this work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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