Efficacy and safety of sitagliptin/metformin fixed-dose combination compared with glimepiride in patients with type 2 diabetes: A multicenter randomized double-blind study†

Highlights
• Compared with glimepiride, Sita/Met as an initial treatment showed a great improvements in glycemic control and FPG levels after 30 weeks. And Sita/Met led to slight reduction of body weight and less hypoglycemia than glimepiride.
• The present study is the first to evaluate the safety and efficacy of Sita/Met FDC compared with glimepiride in patients with T2D as initial management in Korea.

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Abstract
Background: Early initiation of combination therapy using antihyperglycemic agents is recommended for treating type 2 diabetes (T2D). The present multicenter double-blind randomized parallel-group study examined the efficacy and safety of a sitagliptin and metformin fixed-dose combination (Sita/Met) compared with glimepiride in T2D patients as initial treatment.

Methods: Type 2 diabetes patients (aged ≥18 years) were randomized to Sita/Met or glimepiride for 30 weeks after a wash-off run-in period. The primary endpoint was change from baseline (CFB) in HbA1c. Secondary endpoints included the proportion of patients achieving target goal (HbA1c < 7.0 % [53 mmol/mol]) and CFB in fasting plasma glucose (FPG). Safety assessments comprised weight gain from baseline and the incidence of adverse events (AEs).

Results: In total, 292 patients were randomized to Sita/Met (n = 147) or glimepiride (n = 145). After 30 weeks, Sita/Met demonstrated superior O diarrhea in reducing HbA1c (−1.49 % vs −0.71 %, respectively; between-group difference −0.78 %; P < 0.001). A significantly higher proportion of patients achieved the target goal with Sita/Met (81.2 %) than with glimepiride (40.1 %; P < 0.001). Greater reduction in FPG occurred with Sita/Met than with glimepiride (least-squares mean difference −23.5 mg/dL; P < 0.001). Both drugs were generally well tolerated. Hypoglycemia events and weight gain were significantly lower in patients with Sita/Met than with glimepiride (5.5 % vs 20.1 % and −0.83 vs +0.90 kg, respectively; both P < 0.001). No serious drug-related AEs or deaths were reported.

Conclusions: Compared with glimepiride, Sita/Met as an initial treatment led to significantly greater improvements in glycemic control and body weight changes, with a lower incidence of hypoglycemia, over 30 weeks.

Keywords: glimepiride, hypoglycemia, metformin, sitagliptin phosphate.
Introduction

The clinical and economic burden associated with diabete s and its management remains an enduring challenge to the healthcare community. The global prevalence of diabetes in 2014 was estimated to be 9 % among adults; type 2 diabetes (T2D) comprises 90 % of these cases. In Korea, according to the Korea National Health and Nutrition Examination Survey 2011, the estimated prevalence of diabetes in adults aged ≥30 years is 10.5 % based on fasting plasma glucose (FPG) only and 12.4 % based on both FPG and HbA1c.

Diabetes is strongly associated with both microvascular and macrovascular complications resulting in organ and tissue damage in 30 %-50 % of patients, and the risk of these complications is significantly associated with previous hyperglycemia. Because glycemic therapy primarily targets microvascular complications, the relationship between glycemic control and macrovascular complications is less strong. However, intensive glycemic control early in diabetes has a beneficial momentum that may persist for a decade or more, even when later treatment is less intensive. These recent data support the evolving treatment paradigm for targeting the early achievement of glycemic goals in T2D patients.

The American Association of Clinical Endocrinologists (AACE) treatment algorithm recommends the early use of combination therapy with metformin when initial HbA1c levels are >7.5 % (58 mmol/mol) because targeting HbA1c levels <7.0 % (53 mmol/mol) is known to be important in achieving a sustained reduction in microvascular, and possibly macrovascular, complications. The American Diabetes Association (ADA) 2015 Standards of Medical Care in Diabetes suggest initiating a combination of two non-insulin oral antihyperglycemic agents (AHAs) in patients with a high baseline HbA1c (≥9.0 % [75 mmol/mol]) because these patients are unlikely to achieve target HbA1c with metformin monotherapy. Therefore, early initiation of combination therapy using AHAs that act through distinctly different mechanisms may be especially valuable in treating patients with T2D.

In current practice, a sulfonylurea is often used as first-line therapy to stimulate insulin secretion in T2D patients. Because of its ability to improve insulin secretion, a well-established defect in T2D, glimepiride has been used as first-line monotherapy in many countries, including Korea. However, concerns have been raised regarding the safety of sulfonylureas because of higher rates of all-cause mortality compared with metformin. Moreover, glimepiride has been associated with hypoglycemia and weight gain. Sitagliptin, an orally administered, potent, and highly selective inhibitor of dipeptidyl peptidase (DPP) 4, was the first agent of its class to be approved for use in the management of adults with T2D. Sitagliptin enhances insulin secretion and suppresses glucagon concentrations through the incretin pathway and has a glucose-dependent mode of action. Clinical studies have demonstrated that the combination of sitagliptin and metformin (Sita/Met) is synergistic, highly efficacious, and well tolerated in patients with T2D. However, a Sita/Met fixed-dose combination (FDC) has not been analyzed previously in Korea.

The aim of the present study, conducted in Korea, was to examine the efficacy and safety of initial treatment with Sita/Met FDC compared with glimepiride in patients with T2D.

Methods

Study design

The present multicenter randomized double-blinded parallel-group study was conducted from 6 May 2010 to 29 October 2013 at 21 centers in South Korea over 39 weeks (Clinicaltrials.gov ID: NCT00993187; Merck protocol MK-0431 A-202). Patients were randomized in a 1:1 ratio for a treatment period of 30 weeks following an optional 6-week run-in/wash-off and mandatory 2-week single-blinded placebo run-in (Fig. 1a). The study was conducted in accordance with Good Clinical Practice standards, the Declaration of Helsinki, and applicable national and/or local statutes and regulations. Approval from the Independent Ethics Committee at each investigation site and written informed consent from each patient participating were obtained before commencing the study.

Participants

Adults (aged ≥18 years) with T2D were included in the initial run-in period if they were not pregnant or
breast-feeding and were highly unlikely to conceive during the study or the follow-up period. Eligibility requirements at screening visit included patients with HbA1c levels ranging from ≥7.0% (53 mmol/mol) to ≤9.5% (80 mmol/mol) for patients not on AHAs for at least 12 weeks or from ≥6.5% (48 mmol/mol) to ≤9.0% (75 mmol/mol) for patients taking AHAs. Patients initiated the placebo run-in period if their HbA1c ranged from ≥7.0% (53 mmol/mol) to <9.5% (80 mmol/mol).

Preliminary screening excluded patients with a history of type 1 diabetes or ketoacidosis and those who required insulin in the 12 weeks prior to Visit 1. Patients were ineligible if they were on or required specific treatments, such as a weight loss program (except maintenance phase) or medication (8 weeks prior); any glucagon-like peptide-1 (GLP-1) analog, DPP-4 inhibitor, or peroxisome proliferator-activated receptor (PPAR)-γ agonist (12 weeks prior); oral corticosteroids for ≥14 days; immunomodulating agents; surgery with general anesthesia (30 days prior or planned); or any investigational drug treatment (8 weeks prior). Other exclusion criteria included hypersensitivity or contraindication to any sulfonylurea, DPP-4 inhibitor, or biguanide medication; serum creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women; triglycerides >500 mg/dL; thyroid-stimulating hormone imbalance; active liver disease (other than fatty liver); cardiovascular (CV) diseases; human immunodeficiency virus

Figure 1  Study design and patient disposition. (a) Schematic of the study design. (b) Details of patient disposition. Sita/Met FDC, sitagliptin and metformin fixed-dose combination; AE, adverse event; SAE, serious AE. *A study site was closed because the investigator had resigned and it was not possible to transfer the patient to another site. The sponsor decided to close the site and exclude this patient during the screening period.
positivity; hematological disorders; history of malignancy; positive urine pregnancy test; body mass index (BMI) >35 kg/m²; or conditions that could result in non-compliance or may pose a risk to the patient as judged appropriate by the investigator or medical monitor. Patients were excluded at the placebo run-in period or at randomization if their FPG or site fasting fingerstick was <110 mg/dL or >300 mg/dL, respectively.

Intervention

Patients received diet and exercise recommendations and instructions on the use of glucose meters in the run-in/wash-off period. During the placebo period, Sita/Met FDC 50/500 mg-matching placebo tablets (one tablet with the morning and then evening meal) were administered along with a glimepiride 1 mg-matching placebo tablet to be taken once daily before the morning meal.

During the treatment period, the test group received Sita/Met FDC (Janumet; Merck & Co., Inc., West Point, PA, USA) 50/500 mg twice daily to be taken orally at meal times, up-titrated to 50/1000 mg twice daily over a period of 4 weeks. After the initial 4-week period, down-titratiob of Sita/Met FDC was allowed until Week 8 if intolerance occurred, with no change in dosing thereafter. Placebo tablets matching glimepiride (Merck & Co., Inc.; Manufacturer: InvaGen Pharmaceuticals, Hauppauge, NY, USA) were administered once a day. The control group received an initial dose of 1 mg/day glimepiride, titrated to 6 mg/day over the initial 8 weeks of treatment as judged appropriate by the investigator and based on ADA guidelines. Placebo tablets matching Sita/Met FDC were administered twice daily. To assure blinding, a “double-dummy” approach was used as follows: (i) patients in the Sita/Met FDC group received tablets of either Sita/Met FDC 50/500 mg and/or Sita/Met FDC 50/1000 mg and placebo tablets matching glimepiride; (ii) patients in the glimepiride group received two placebo tablets matching Sita/Met FDC (Sita/Met FDC 50/500 mg and/or Sita/Met FDC 50/1000 mg) and active glimepiride tablets (dose based on titration), each of which was 1 or 2 mg.

Compliance

A compliance of 85 % (as measured by tablet count) with single-blinded placebo tablets was required for meeting eligibility during the run-in period. During the treatment period, compliance was assessed using the following formula: % compliance = (no. days on therapy/no. days the patients should be on therapy) × 100.

Randomization, allocation, blinding

Randomization schedules were generated by a statistician not associated with the conduct of the study. At the end of the placebo run-in period (Visit 5), all eligible patients were assigned the next allocation number from the appropriate schedule supplied by DreamCIS (Seoul, Korea). Blinded supplies and sealed code envelopes were supplied by Merck Sharp & Dohme (West Point, PA, USA). The study was double blind wherein the investigator, study nurse, pharmacist and patient remained blinded to the study medications.

Assessments and outcome measures

Assessment of the glucose-lowering efficacy of the treatments was based on HbA1c, FPG, and tolerance of the study drug. The primary efficacy endpoint was change from baseline to Week 30 in HbA1c levels. Secondary endpoints included change from baseline to Week 30 in FPG levels and the proportion of patients achieving the goal of HbA1c <7.0 % (53 mmol/mol) at Week 30. Safety endpoints included incidence of hypoglycemia and change in body weight from baseline. Overall safety and tolerability were assessed through drug-related adverse events (AEs), blood chemistry (including alanine aminotransferase, aspartate transaminase, total bilirubin, and alkaline phosphatase), hematology (including complete blood count, differential, and absolute neutrophil count), vital signs, and urinalysis.

Statistical analysis

Approximately 139 patients per treatment group or 278 patients in total were needed to detect a true mean difference of 0.4 % in change from baseline to Week 30 in HbA1c between the Sita/Met FDC and glimepiride groups at two-sided α, with a 0.05 level of significance. This calculation was based on an SD estimate of 1 % for HbA1c change from baseline at Week 30, assuming 90 % power and a 5 % non-evaluable rate.

The primary endpoint analysis to compare superiority between treatment groups was conducted using analysis of covariance (ANCOVA) on the full analysis set (FAS), with \( P < 0.005 \) for a two-tailed \( t \)-test as the criteria for determining superiority. The FAS included patient data according to the treatment assigned at randomization, regardless of the treatment received during the course of the study; patient inclusion was dependent on the presence of a baseline measurement, consumption of at least one study dose, and a post-randomization measurement. The ANCOVA model included terms for treatment, stratum (AHA treatment used at screening or not), and baseline HbA1c value as covariates. Missing
data were handled based on the last observation carried forward (LOCF) method.

An ANCOVA was performed for continuous endpoints to compare change from baseline between treatments, with P values, corresponding 95 % confidence intervals (CIs), and treatment-effect least-squares (LS) means provided for each endpoint. Logistic regression was used to analyze the proportion of patients meeting the HbA1c goal at Week 30. Efficacy analyses were based on the FAS, whereas safety analyses were based on the all-patients-as-treated (APaT) population (all randomized patients who had received at least one dose of study medication, with each patient being counted in the treatment group of the drug they actually received).

Subgroup analyses were conducted for the primary endpoint to assess the consistency of the treatment effect with factors for treatment, stratum, subgroup, treatment-by-subgroup interaction, and baseline HbA1c.

**Results**

Of the 628 patients with T2D screened for the study, 336 were excluded, 292 were randomized (147 in the Sita/Met FDC group and 145 in the glimepiride group), and 229 patients completed the study (Fig. 1b). The study discontinuation rate was 17.7 % in the Sita/Met FDC group and 22.9 % in the glimepiride group.

The baseline characteristics were mostly comparable between the two groups (Table 1), except that the Sita/Met FDC group had a slightly longer duration of T2D (4.6 vs. 3.9 years). The mean age of patients was 54.8 and 53.1 years in the Sita/Met FDC and glimepiride groups, respectively. Previous medication use was reported by 80.3 % of patients in the Sita/Met FDC group and 84.8 % of patients in the glimepiride group, respectively. Previous medication was mostly on lipid-modifying agents, followed by antithrombotic agents and agents acting on the renin–angiotensin system.

### Table 1 Baseline patient demographic and clinical characteristics

| Parameter                          | Sita/Met FDC (n = 147) | Glimepiride (n = 145) | Total (n = 292) |
|------------------------------------|------------------------|-----------------------|----------------|
| Age (years)                        | 54.8 ± 8.5             | 53.1 ± 9.2            | 53.9 ± 8.9     |
| Gender                             |                         |                       |                |
| Male                               | 81 (55.1)              | 84 (57.9)             | 165 (56.5)     |
| Female                             | 66 (44.9)              | 61 (42.1)             | 127 (43.5)     |
| Weight (kg)                        | 67.9 ± 8.8             | 67.7 ± 10.4           | 67.5 ± 9.6     |
| BMI (kg/m²)                        | 25.2 ± 2.7             | 25.0 ± 2.8            | 25.1 ± 2.7     |
| Duration of type                   | 4.6 ± 4.6              | 3.9 ± 3.7             | 4.2 ± 4.2      |
| 2 diabetes (years)                 | 38.8 ± 9.0             | 81.0 ± 9.9            | 80.0 ± 8.0     |
| HbA1c                              | 8.0 ± 0.9              | 8.1 ± 0.9             | 8.0 ± 0.8      |
| FPG (mg/dL)                        | 171.5 ± 41.2           | 168.3 ± 39.4          | 169.9 ± 40.3   |
| GFR                                | 75.9 ± 11.7            | 76.7 ± 16.2           | 76.2 ± 13.3    |
| Total cholesterol (mg/dL)          | 176.1 ± 34.9           | 171.0 ± 32.4          | 173.5 ± 33.7   |
| LDL-C (mg/dL)                      | 97.3 ± 33.0            | 95.0 ± 28.1           | 96.2 ± 30.6    |
| HDL-C (mg/dL)                      | 48.2 ± 11.0            | 48.8 ± 10.1           | 48.5 ± 10.5    |
| Triglyceride (mg/dL)               | 150.5 ± 68.2           | 131.4 ± 72.1          | 142.3 ± 80.8   |
| SBP (mmHg)                         | 126.3 ± 11.2           | 126.3 ± 13.2          | 126.8 ± 12.2   |
| DBP (mmHg)                         | 76.7 ± 8.1             | 77.7 ± 8.5            | 77.2 ± 8.3     |
| Prior antihyperglycemic medication | Yes                    | No                    |                |
| Yes                                | 90 (61.2)              | 82 (56.6)             | 172 (58.9)     |
| No                                 | 57 (38.8)              | 63 (43.4)             | 120 (41.1)     |
| Previous medication                | 118 (80.3)             | 123 (84.8)            | 241 (82.5)     |
| Lipid-lowering agents              | 65 (44.2)              | 66 (45.5)             | 131 (44.9)     |
| RAS inhibitors                     | 43 (29.3)              | 43 (29.7)             | 86 (29.5)      |
| Anti-platelet agents               | 57 (38.8)              | 53 (36.6)             | 110 (37.7)     |

Unless indicated otherwise, data are given as the mean ± SD or n (%). SitaMet FDC, sitagliptin and metformin fixed-dose combination; DBP, diastolic blood pressure; FPG, fasting plasma glucose; RAS, renin–angiotensin system; SBP, systolic blood pressure; BMI, body mass index; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Patients had a high level (>90%) of treatment compliance in both groups. Most patients took the study medication for more than 24 weeks and the mean duration of exposure in any dose was generally similar in the two treatment groups (175.6 days in the Sita/Met FDC group and 166.6 days in glimepiride group).

Dose titrations in the glimepiride group

The mean dose of glimepiride used in the study was 2.0 mg (range 1.0–6.0 mg). A maximum dose of 1 mg was administered in 46.1% (65/141) of patients, with only 17.7% (25/141) of patients receiving a maximum dose of 6 mg (Table 2). The final dose of glimepiride was 1 mg in 49.6% (70/141) of patients and 6 mg in only 17.0% (24/141) of patients.

Efficacy analysis (FAS)

Primary endpoint

At Week 30, the mean HbA1c fell from 8% (64 mmol/mol) at baseline to 6.5% (48 mmol/mol) in the Sita/Met FDC group, and from 8.1% (65 mmol/mol) to 7.3% (56 mmol/mol) in the glimepiride group. The LS mean change in HbA1c from baseline was −1.49% and −0.71% in the Sita/Met FDC and glimepiride groups, respectively (Fig. 2a). The between-group difference of −0.78% (95% CI −0.96, −0.59) demonstrated superiority of Sita/Met over glimepiride (P < 0.001).

Secondary endpoints

At 30 weeks, a significantly higher proportion of patients in the Sita/Met FDC group met the target...
HbA1c goal of <7.0 % (53 mmol/mol) compared with the glimepiride group (81.2 % vs 40.1 %; P < 0.0011 relative risk 2.02; Fig. 2b). Treatment with Sita/Met FDC provided superior reduction (from baseline) in FPG compared with glimepiride (LS mean difference – 23.5 mg/dL; P < 0.001; Fig. 2c). In subgroup analysis, meaningful reductions in HbA1c level from baseline were observed in both treatment groups within all subgroups. A greater reduction from baseline with higher baseline HbA1c level was observed in both treatment groups. Subgroup analysis revealed a significant (P < 0.05) change from baseline HbA1c levels at Week 30 in all subgroups tested except those >65 years of age (Fig. 3).

Safety analysis

Of the 290 patients in the APaT population, 88 (60.3 %) and 101 (70.1 %) patients in the Sita/Met FDC and glimepiride groups, respectively, experienced an AE. Drug-related AEs were observed in 37 (25.3 %) and 39 (27.1 %) patients in the Sita/Met FDC and glimepiride groups, respectively. Serious AEs were reported in eight (5.5 %) and nine (6.3 %) patients in the Sita/Met FDC and glimepiride groups, respectively. No drug-related serious AEs or deaths were reported in either group. The most common AEs belonged to the system organ class of gastrointestinal disorders, infections, and infestations, as well as metabolism and nutrition disorders (Table 3). Frequently reported drug-related AEs were gastrointestinal disorders including dyspepsia, diarrhea, and nausea in the Sita/Met FDC group, and metabolism and nutrition disorders, including hypoglycemia, in the glimepiride group. Seven (4.8 %) and three (2.1 %) patients in the Sita/Met FDC and glimepiride groups, respectively, discontinued due to drug-related AEs.

Treatment with Sita/Met FDC resulted in a significant reduction in body weight compared with glimepiride (–0.83 vs +0.90; LS mean difference – 1.72 kg; P < 0.001; Fig. 2d). The incidence of hypoglycemia was higher in the glimepiride group than in the Sita/Met FDC group (20.1 % vs 5.5 % patients reporting at least one hypoglycemic episode; Fig. 2e), with a significant (P < 0.001) between-group difference of –14.7 %. Similarly, the number of hypoglycemic episodes differed between the two groups, with 53 and 12 episodes occurring in the glimepiride and Sita/Met FDC groups, respectively. There was only one episode of hypoglycemia in the glimepiride group that was reported to require medical assistance or to have exhibited marked severity (defined as markedly depressed level of consciousness, loss of consciousness, or seizure) compared with no episode in the Sita/Met FDC group.
No clinically meaningful change from baseline or between-group difference was observed for other vital signs, blood chemistry, plasma lipids, or other hematological assessments.

**Discussion**

The present multicenter double-blind study in Korean patients with T2D demonstrated that treatment with Sita/Met FDC was superior to treatment with glimepiride in reducing HbA1c and FPG levels after 30 weeks as an initial treatment. A significantly greater proportion of patients in the Sita/Met FDC group met the target HbA1c level of <7.0 % (53 mmol/mol). Although both treatments improved glycemic control, treatment with glimepiride resulted in patients gaining weight, whereas treatment with Sita/Met FDC led to slight weight loss and less hypoglycemia. Overall, both therapies were relatively well tolerated.

Combination therapy with sitagliptin and metformin has been shown previously to be effective in achieving adequate glycemic control, being well tolerated, weight neutral, and associated with a low risk of hypoglycemia. The results of the present study provide further evidence for the use of Sita/Met as an FDC therapy in patients with T2D. Per current practices, glimepiride is the first-line therapy for T2D in Korea. The results of the present study suggest that Sita/Met FDC is probably a good candidate for initial therapy in patients with T2D compared with glimepiride monotherapy. Given the current recommendations on the use of combination therapy for early initial treatment if target HbA1c levels are not achieved, these findings have important clinical implications in diabetes management in Korea.

Earlier studies that assessed the efficacy and safety of combination therapy with sitagliptin and metformin in the Korean population have found this dual therapy to be efficacious and well-tolerated. A recent study comparing the glycemic effectiveness of metformin-based combination therapies with either sitagliptin, a sulfonylurea (glimepiride or gliclazide-modified release), or pioglitazone in 116 drug-naïve Korean patients showed that the three dual therapies had similar glycemic effectiveness across a wide range of baseline HbA1c levels. In another study, when Korean patients on previous...
combination therapies (dual- or triple-combination ther-
apies with metformin) were treated with sitagliptin
100 mg/day, a significant improvement in glycemic con-
trol was observed. In fact, in the group that switched
from glimepiride to sitagliptin, the incidence of hypogly-
cemic events decreased, suggesting that switching from
glimepiride to sitagliptin should be considered for pa-
tients with recurrent fasting hypoglycemia.30 Despite
combination therapy having been shown to be effective,
Sita/Met as an FDC has not been analyzed previously in
Korea, and the present study being the first such study.

The benefits of using FDC therapies have been demon-
strated for other dual-drug combinations in T2D. In a
randomized open label parallel-group multicenter study,
when 209 Korean patients with T2D who were inade-
quately controlled by low-dose metformin monotherapy
received glimepiride/metformin FDC or metformin up-
titrations for 24 weeks, glimepiride/metformin FDC was
found to be more effective in glycemic control than
metformin up-titration.31 An evidence-based review
concluded that metformin/pioglitazone FDC in insulin-
resistant patients with T2D is an effective option when
monotherapy fails in the achievement of the recom-
manded standards of care.32 A large retrospective
database analysis of 16928 subjects found that rosiglitazone/metformin FDC yielded significant im-
provements in medication adherence rates compared
dual therapy regimens.33 Overall, the use of FDCs may
not only improve adherence in patients, but has also been
shown to have a favorable tolerability profile with im-
proved patient convenience and potential cost benefits.34
The use of Sita/Met FDC in the present study could be
a factor in the high compliance rates (~95 %) observed.

Almost 40 % of the patients enrolled in the present
study were treatment naïve, with no previous therapy
with AHAs. The efficacy of initial therapy with a
Sita/Met FDC in drug-naïve patients with T2D has been
evaluated in a few previous studies.35–37 The efficacy and
safety of Sita/Met FDC compared with pioglitazone was
recently assessed in two large studies comprising approx-
inately 500 patients, each of which found that treatment
with Sita/Met led to significantly greater improvement
in glycemic control.35,37 Moreover, patients in the Sita/Met
group showed a reduction in weight, with patients in
the pioglitazone group gaining weight. Another double-blind
randomized study of 1250 drug-naïve patients treated
with Sita/Met FDC or metformin found that, compared
with metformin monotherapy, initial treatment with
Sita/Met FDC provided superior glycemic improvement
with a similar degree of weight loss and lower incidences
of abdominal pain and diarrhea.38 In two early, well-
designed clinical trials in treatment-naïve patients with
T2D, the improvements in glycemic control seen with
Sita/Met therapy after 18 or 24 weeks were greater than
those observed with monotherapy with either drug
and/or placebo, and sustained over treatment durations
of up to 2 years.28 Considering there was a wash-off
run-in period in the study design, the superior treatment
effect of Sita/Met FDC observed in the present study
could partially reflect the fact that many patients in the
study were treatment naïve.

A higher incidence of hypoglycemia was observed in
the glimepiride group compared with the Sita/Met
FDC group (20.1 % vs 5.5 %). With >46 % of patients
being administered a maximum or final dose of 1 mg,
and only approximately 17 % treated with 6 mg as the
maximum or final dose, the results are not surprising.
Although glimepiride could be up-titrated in the present
study by physicians at their discretion, note that the
treatments were blind to the physician because of the
nature of the double-blind study. Therefore, this study re-
veals the real-world practice of passively up-titrating
the dosage of glimepiride. Interestingly, a higher inci-
dence of hypoglycemia was observed in the glimepiride
group with a relatively low dosage. Considering factors
like concern about hypoglycemia, a treatment regimen
with sulfonylureas may delay the achievement of glyce-
ic goals. Furthermore, hypoglycemia caused by sulfo-
nylureas has been shown to be dose related, and is also
correlated inversely with gain in BMI,39 which may be
a plausible explanation for the weight gain observed in
the glimepiride group in the present study.

A relatively lower discontinuation rate was observed
in the Sita/Met FDC group compared with the
glimepiride group (17.7 % vs 25.5 %). Although the dis-
continuation rates of both groups seemed to be high,
considering the long study period of 39 weeks the rates
could be considered within a reasonable range.

The present study compared the effectiveness and
safety of a monotherapy (glimepiride) with dual therapy
(Sita/Met FDC). Numerous previous studies have
compared monotherapies with combination ther-
apies31,36,37; therefore, any debate regarding the choice
of study drugs is not entirely valid. Moreover, because
glimepiride is the first-line therapy for T2D in Korea,
this further justifies the choice of the comparator group
used in the present study.

Although 628 patients were screened for the present
trial, only 292 patients were randomized to either treat-
ment arm. Most screening failures were because of very
low or very high HbA1c levels, low creatinine clearance,
and other parameters that did not meet the study eligibil-
ity criteria. Many patients failed eligibility during the
run-in period because of low HbA1c levels, perhaps
due to changes in patients’ lifestyles during the 6-week
run-in period, itself an indication of the positive effect


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imparted by a healthy lifestyle on diabetes management. Finally, as discussed previously, the up-titration of glimepiride may not have been sufficient, and this could have affected the study results.

In summary, the use of combination therapy for early initial treatment is the current practice in diabetes management. The present study is the first to evaluate the safety and efficacy of Sita/Met FDC compared with glimepiride in patients with T2D as initial management in Korea. The results of the study suggest that Sita/Met FDC may be a good candidate for initial therapy in patients with T2D compared with glimepiride monotherapy. Further research is needed to analyze the long-term effects of Sita/Met FDC, and its effect on CV endpoints and mortality in patients with T2D.

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Disclosure

SJL is an employee of MSD Korea Ltd; all other authors have no conflicts of interest to declare.

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