A Randomized, Trial to Assess Safety and Efficacy of Sitagliptin in Chinese Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Sulfonylurea Alone or Combined with Metformin

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Abstract

**Background:** Type 2 diabetes mellitus (T2DM) is a significant burden in China where approximately 114 million patients have been diagnosed with diabetes. Chinese patients present with prominent \( \beta \)-cell failure with resultant deficiency in insulin secretion, particularly early phase insulin secretion leading to postprandial hyperglycemia. Sitagliptin, a selective once-daily oral dipeptidyl peptidase-4 (DPP-4) inhibitor, has been shown to improve glycemic control as monotherapy and in combination with other antihyperglycemic agents including sulfonylureas and metformin.

**Methods:** This was a multicenter, randomized, double-blind, placebo-controlled study conducted in China. The study assessed the safety and efficacy of the addition of sitagliptin 100 mg once daily vs placebo on the change from baseline at Week 24 in HbA1c, fasting plasma glucose (FPG) and 2-hour post-meal glucose (PMG). Patients 18-79 years had T2DM with inadequate glycemic control taking a sulfonylurea with or without metformin.

**Results:** After 24 weeks, sitagliptin reduced HbA1c, FPG and 2-hr PMG significantly more than placebo (between-treatment differences: HbA1c: -0.61%; FPG: -16.8 mg/dL; 2-hr PMG: -32.9 mg/dL; all p <0.001). The addition of sitagliptin was generally well tolerated, with a comparable incidence of adverse events and drug-related adverse events in both treatment groups. The sitagliptin group had a higher incidence of symptomatic hypoglycemia vs the placebo group [25/248 (10.1%) vs 13/249 (5.2%), respectively; p=0.042].

**Conclusions:** Sitagliptin 100 mg once daily significantly improved glycemic control in Chinese patients with T2DM who had inadequate glycemic control with sulfonylurea with or without metformin therapy. The addition of sitagliptin was generally well tolerated (clinicaltrials.gov: NCT01590771).

**Keywords:** HbA1c; hypoglycemia; sitagliptin; sulfonylurea; China
Key points

Significant findings of the study:

The addition of sitagliptin resulted in significantly greater glycemic control vs placebo among Chinese patients with T2DM inadequately controlled on a sulfonylurea with or without metformin. The safety profile was generally consistent with that observed in similarly designed global trials.

What this study adds:

The current study was conducted in a Chinese population and yielded results generally consistent with a similarly designed multinational study. Taken together, these results demonstrate the consistency of effect of sitagliptin across multiple populations.

Introduction

Worldwide, 387 million people are estimated to be living with diabetes mellitus.\(^1\) In China, diabetes affected 113.9 million adults in 2010, indicating that China had more people with diabetes than any other country.\(^2\) The American Diabetes Association (ADA) and the International Diabetes Federation (IDF) recommend a glycemic treatment target for hemoglobin A1c (HbA1c) of approximately 7.0% or less for most patients.\(^1,3,4\) A more aggressive HbA1c treatment goal of 6.5% has been recommended by the IDF and the American Association of Clinical Endocrinologists (AACE),\(^4,5\) as well as the ADA in individual patients if it can be achieved without significant hypoglycemia or other adverse events.\(^3\) Despite these recommendations many patients fail to achieve optimal glycemic control.
The progressive nature of type 2 diabetes mellitus (T2DM) contributes to the failure of glycemic target achievement for many patients, and as a result, treatment with a combination of different antihyperglycemic agents (AHAs) is now widely accepted. Given the β-cell failure noted in patients with T2DM, treatment with sulfonylureas with or without metformin is a common paradigm. Sulfonylureas improve blood glucose levels by stimulating insulin secretion from pancreatic β-cells in a non-glucose–dependent manner and metformin, a biguanide, acts primarily by lowering hepatic glucose production and may also improve insulin resistance. However, patients treated with a sulfonylurea or with the combination of a sulfonylurea and metformin may not achieve or maintain glycemic control, and the addition of other oral AHA medications, including thiazolidinediones [TZDs], dipeptidyl peptidase IV (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, or sodium/glucose cotransporter 2 (SGLT2) inhibitors are recommended by the ADA and the European Association for the Study of Diabetes (EASD).

Sitagliptin (JANUVIA®) is an orally active, selective DPP-4 inhibitor approved in many countries, including China, as an adjunct to diet and exercise for the treatment of patients with T2DM. In global studies sitagliptin treatment improved glycemic control as monotherapy and in combination with metformin in Chinese patients, and as monotherapy and in combination with other oral agents (metformin, a TZD, a sulfonylurea or a sulfonylurea or TZD in combination with metformin) and insulin (with or without metformin). Previously, a global study of the safety and efficacy of the addition of sitagliptin treatment in patients failing glimepiride alone or in combination with metformin was conducted. That study showed that in patients who had failed to achieve adequate glycemic control (i.e., HbA1c 7.5%-10.5%) on glimepiride therapy (with or without metformin), sitagliptin was generally well-tolerated and provided significant improvements in HbA1c, fasting plasma glucose (FPG) and 2-hour post-meal glucose (2-hr PMG) compared
with placebo. The current study, conducted in China, assessed the safety and efficacy of sitagliptin compared with placebo in Chinese patients with T2DM who had failed to achieve adequate glycemic control with a sulfonylurea (either glimepiride or gliclazide), alone or in combination with metformin.

Methods

Patients

Men and women ≥18 to ≤79 years of age with T2DM on stable doses of gliclazide (modified release ≥60 mg/day or immediate release ≥160 mg/day) or glimepiride (≥3 mg/day) with or without metformin (≥1500 mg/day) for at least 10 weeks and HbA1c ≥7.5% and ≤11.0% were eligible for this study. At screening, patients were excluded if they had a history of type 1 diabetes; or intolerance, hypersensitivity or contraindication to sitagliptin, gliclazide/glimepiride, or metformin. Patients with active liver disease (including chronic active hepatitis B or C, primary biliary cirrhosis, or symptomatic gallbladder disease); new or worsening signs of coronary heart disease within 3 months (including acute coronary syndrome, coronary artery intervention, stroke or transient ischemic neurological disorder); severe peripheral vascular disease; or exclusionary laboratory values were also excluded. Women with a positive pregnancy test were excluded, and those with reproductive potential were required to remain abstinent or use an acceptable method of birth control throughout the study period.

Study design

This was a 24-week, Phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial conducted at 32 centers in China from July 2012 to June 2014 (Merck protocol PN253). The study was conducted in conformance with Good Clinical Practice standards and applicable country and local statutes and regulations regarding ethical
committee review; written informed consent was obtained from each subject prior to performing any study-related procedure.

Sitagliptin 100 mg or matching placebo was supplied as an oral tablet in a blinded manner. In addition to ongoing open-label therapy with stable doses of gliclazide/glimepiride with or without metformin, during the 2-week, single-blind placebo run-in period, patients were instructed to take one tablet of placebo matching sitagliptin 100 mg per day. The randomized allocation schedule for study treatment assignment was performed via a computer-generated allocation schedule and implemented by an interactive voice response system (IVRS). Patients who met inclusion criteria at the end of the placebo run-in period were randomized via the IVRS in a 1:1 ratio to sitagliptin or placebo treatment. During the 24-week double-blind treatment period, patients were instructed to take one tablet of sitagliptin 100 mg or matching placebo per day. Open-label gliclazide, glimepiride and metformin were administered as recommended in the China drug label through the end of the double-blind treatment period and doses kept constant unless down-titration was required for hypoglycemia.

A meal tolerance test (MTT) was conducted at randomization and Week 24. At Visit 2 (Week 2-2), the first dose of single-blind sitagliptin placebo was taken at the clinic as a witnessed dose after completion of all procedures. At Visit 3 (Day 1), the first dose of double-blind sitagliptin or matching placebo was taken at the clinic after completion of all procedures and after the blood sample for the MTT was taken, which was taken 120 minutes following the start of the standard meal (consisting of approximately 460 kcal, including 75 g carbohydrate, 9 g fat and 18 g protein). At Week 24, the last dose of double-blind sitagliptin or matching placebo was taken at the clinic as a witnessed dose after fasting blood samples were collected and 30 minutes prior to ingesting the standard meal for the MTT. Open-label
study medications (gliclazide/glimepiride with or without metformin) were taken after fasting blood samples were collected and just prior to ingesting the standard meal for the MTT.

Study assessments

The primary efficacy endpoint was the change from baseline in HbA1c after 24 weeks of add-on treatment with sitagliptin compared with placebo in patients taking a sulfonylurea, alone or in combination with metformin (overall cohort). Secondary efficacy endpoints included the change from baseline in HbA1c, 2-hr PMG (following a standard meal) and FPG after 24 weeks of add-on treatment with sitagliptin compared with placebo in each metformin stratum and the overall cohort. The percent of patients at HbA1c goals (<7.0% and <6.5%) at Week 24, and the changes from baseline in fasting insulin, Homeostasis Model Assessment of β-cell function (HOMA-β), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and Quantitative Insulin Sensitivity Check Index (QUICKI) were assessed at Week 24. Changes from baseline in lipids, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were also measured in the individual metformin strata and the overall cohort.

Safety and tolerability were assessed by physical examination, collection of adverse events (AEs), vital signs, body weight, laboratory safety studies, and locally read ECGs. Laboratory safety studies included blood chemistry (including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, and creatine phosphokinase), hematology (including complete blood count [CBC], differential, and absolute neutrophil count, platelet count), urinalysis, and urine pregnancy testing.

Statistical analyses
It was expected that 200 patients per treatment group would be available for the analysis for the primary hypothesis. Based on a standard deviation (SD) of 1.0%, this sample size would provide 90% (80%) power to detect a difference of 0.32% (0.28%) in the mean change from baseline in HbA1c between the treatment groups (2-sided test, \( \alpha = 0.05 \)).

The Full Analysis Set (FAS) population was used for all efficacy analyses, defined separately for each analysis endpoint, and was comprised of all patients who received \( \geq 1 \) dose of study therapy, except for the following: For analyses that use the ANCOVA method, the FAS excluded patients who did not have \( \geq 1 \) observation for the analysis endpoint subsequent to the first dose of study treatment, or who did not have baseline data for the analysis endpoint. For analyses that use the constrained longitudinal data analysis (cLDA) model, the FAS population excluded patients who did not have \( \geq 1 \) measurement for the analysis endpoint (baseline or subsequent to the first dose of study treatment). For analyses that use the Miettinen and Nurminen method, the FAS excluded patients who did not have \( \geq 1 \) observation for the analysis endpoint subsequent to the first dose of study treatment. The change from baseline in HbA1c at Week 24 was analyzed using an analysis of covariance (ANCOVA) model controlled for treatment, metformin stratum (on or not on metformin), and baseline HbA1c value. The primary hypothesis regarding superiority of sitagliptin compared with placebo in decreasing HbA1c was assessed using the estimated treatment difference under the ANCOVA model. This model was based on the assumption that model-based residuals follow a normal distribution. For highly non-normal residuals (\( p < 0.001 \)), the primary analysis for the above parameters was conducted using a robust regression (RREG) approach (See supplementary materials for results). Endpoints related to HbA1c for each individual metformin stratum were evaluated only if the primary efficacy endpoint test was successful. A constrained longitudinal data analysis method proposed by Liang and Zeger\(^{16}\) was used as a secondary method for handling missing data for primary and secondary
efficacy endpoints. The Hochberg method was used for multiplicity adjustment to control the overall type I error rate at $\alpha=0.05$ across the first two secondary endpoints.

The secondary endpoints were supportive and were evaluated in a conditional manner with priority order. The 2-hr PMG related endpoints were tested only if the corresponding HbA1c endpoint tests were successful; and the FPG related endpoints were tested only if the corresponding 2-hr PMG endpoint test was successful. Analyses of the percentages of patients at the HbA1c goals of <7.0% and <6.5% at Week 24 were conducted using the Miettinen and Nurminen method. The differences in proportions and relative risks, along with the corresponding 95% CIs were calculated. The LOCF method was used to determine whether a value met the goal when the HbA1c result at Week 24 was not available. Safety analyses were conducted in the All-Patients-as-Treated (APaT) populations, which included all patients who received $\geq 1$ dose of study drug.

**Results**

A total of 764 patients were screened and 498 were randomized (249 each to sitagliptin or placebo; Figure 1). The most common reason for screen failure was not meeting the HbA1c entry criteria, followed by not meeting other required laboratory values. Fifty-eight (11.6%) patients discontinued from the study, with more patients discontinuing from the placebo group (n=39) than the sitagliptin group (n=19). The most common reasons for discontinuation were withdrawal by subject and protocol-specified criteria (Figure 1). In total, 230 patients in the sitagliptin group and 210 patients in the placebo group completed the 24-week double-blind treatment period.
Baseline assessments of demographic, anthropometric, disease characteristics and efficacy endpoints were comparable between the treatment groups (Table 1). For the overall cohort, the mean duration of T2DM was 7.0 years and the mean HbA1c level was 8.5%. There were no meaningful differences between treatment groups in frequency or type of baseline medical conditions or use of other concomitant medications. Mean compliance to study medication was 98.6% in both treatment groups.

The reduction in HbA1c from baseline at Week 24 was significantly greater in the sitagliptin group than that in the placebo group, with an estimated between-treatment difference (95% CI) of $-0.61\%$ ($-0.77\%, -0.44\%$; $p<0.001$; Table 2). The reduction in HbA1c from baseline over time to Week 24 in the overall cohort is shown in Figure 2. The addition of sitagliptin treatment resulted in greater HbA1c reductions from baseline at Week 24 compared with placebo in each metformin stratum (Table 2; $p<0.001$). The least squares mean change (95% CI) from baseline in the sitagliptin group was similar across each metformin stratum, while the change from baseline in the placebo group was greater in the subgroup of patients on metformin than that in the subgroup of patients not on metformin (Table 2).

The addition of sitagliptin treatment significantly increased the proportion of patients with HbA1c values <7.0% at Week 24 compared with placebo in the overall cohort [24.7% (60/243) vs 12.3% (29/236), respectively; $p<0.001$], in the subgroup of patients on metformin, [27.9% (31/111) vs 13.4% (15/112), respectively; $p=0.007$], and in the subgroup of patients not on metformin [22.0% (29/132) vs 11.3% (14/124), respectively; $p=0.023$].

Sitagliptin reduced 2-hr PMG significantly more than placebo at Week 24 in the overall cohort and in each metformin stratum (Table 2). The between-treatment differences (95% CI) in least squares mean change from baseline were $-32.9$ mg/dL ($-45.4$ mg/dL, $-20.4$ mg/dL; $p<0.001$) for the overall cohort, $-27.2$ mg/dL ($-41.2$ mg/dL, $-13.2$ mg/dL; $p<0.001$)
for the subgroup of patients on metformin, and −37.7 mg/dL (−56.9 mg/dL, -18.4 mg/dL; p<0.001) for the subgroup of patients not on metformin.

Similarly, the reduction in FPG was significantly greater with sitagliptin than with placebo at Week 24 in the overall cohort and in each metformin stratum (Table 2 and Supplementary Figure 1). The estimated between-treatment difference (95% CI) in least squares mean change from baseline was −16.8 mg/dL (−23.3 mg/dL, -10.2 mg/dL; p<0.001) in the overall cohort, −16.5 mg/dL (−25.3 mg/dL, -7.8 mg/dL; p<0.001) in the subgroup of patients on metformin, and −17.0 mg/dL (−26.9 mg/dL, -7.1 mg/dL; p<0.001) in the subgroup of patients not on metformin.

No statistically significant difference was observed between the treatment groups in the overall cohort for change from baseline at Week 24 in fasting insulin [LS mean difference (95% CI): -0.4 (-3.0, 2.1); p=0.739], HOMA-β [147.1 (-180.1, 474.3); p=0.377], HOMA-IR [-0.3 (-1.3, 0.6); p=0.494], or QUICKI [-0.0 (-0.0, 0.0); p=0.371] (Supplementary Table 1).

There were no statistically significant differences observed between the treatment groups in the percent change from baseline at Week 24 in the overall cohort for lipids (for details, see supplementary section and Supplementary Table 2).

Of the 498 patients randomized in this study, 497 patients received double-blind study medication (248 patients in the sitagliptin group and 249 patients in the placebo group) and were included in the analyses of safety. A summary of AEs is presented in Table 3. The proportion of patients reporting AEs was generally comparable between the sitagliptin and placebo groups. No deaths occurred during the study. A significantly higher proportion of patients in the sitagliptin group [25/248 (10.1%)] had one or more events of symptomatic hypoglycemia compared with the placebo group [13/249 (5.2%); between group difference = 4.9%; P=0.042]. The percentage of patients reporting symptomatic or asymptomatic hypoglycemia was higher in the sitagliptin group [35/248 (14.1%)] compared to the placebo.
The percentage of patients reporting severe symptomatic hypoglycemia was higher in the sitagliptin group compared with the placebo group [13/248 (5.2%) vs 2/249 (0.8%); between-treatment difference (95% CI): 4.4 (1.6, 8.1)]. None of the events of severe symptomatic hypoglycemia required medical assistance.

There were 3 SAEs related to CV events subject to adjudication by an expert committee blinded to treatment assignment. Of these, 2 were confirmed as cardiovascular SAEs and 1 was not able to be adjudicated. Confirmed adjudicated cardiovascular events included an event of unstable angina pectoris in a patient in the sitagliptin group and an event of hemorrhagic stroke in a patient in the placebo group.

During the study there were no clinically meaningful changes from baseline or between-group differences in the percentage of patients meeting criteria for the pre-defined limits of change (PDLC) for all selected laboratory endpoints. Mean changes in PDLC were generally low and comparable between the sitagliptin group and the placebo group. No clinically relevant changes from baseline or between-group differences were observed at any time point for pulse rate, systolic blood pressure, diastolic blood pressure or weight change (supplementary Table 3); and no consistent trends over time were noted.

**Discussion**

Overall, 24 weeks of add-on treatment with sitagliptin to sulfonylurea, alone or in combination with metformin, resulted in significantly greater reductions in HbA1c, 2-hr PMG, and FPG compared with the addition of placebo. Moreover, the proportion of patients achieving HbA1c levels <7.0% was greater in the sitagliptin 100 mg group than in the placebo group. The addition of sitagliptin 100 mg was generally well-tolerated with a low incidence of AEs and SAEs, although the proportion of patients with symptomatic
hypoglycemia was higher with sitagliptin compared with placebo. To complement the HbA1c efficacy endpoint, measured primarily to identify the average plasma glucose concentration over the prior 2 to 3 months, PMG and FPG were also assessed. The greater reduction from baseline in both the 2-hr PMG and in FPG compared with the placebo group after 24 weeks are consistent with the overall superior reduction in HbA1c observed in the sitagliptin group.

Results of global studies of the addition of sitagliptin or other DPP-4 inhibitors in patients being treated with sulfonylurea monotherapy or sulfonylurea and metformin have been reported previously. However, since the pathophysiology and evolution of type 2 diabetes mellitus in East Asian patients may not be identical to that observed in Caucasian patients previously studied in global trials, demonstration of the safety and efficacy and of the addition of a DPP-4 inhibitor (sitagliptin) in Chinese patients being treated with sulfonylurea monotherapy or sulfonylurea and metformin is important and addresses a gap in the current knowledge about these agents. The current study, conducted in a Chinese population, yielded results generally consistent with a similarly-designed multinational study, demonstrating that the addition of sitagliptin to a sulfonylurea with or without metformin in patients with inadequate glycemic control resulted in statistically significant and clinically meaningful reductions in HbA1c in the sitagliptin group compared with placebo.

The results from the current study are generally consistent with those from previous global studies where DPP-4 inhibitors have been added to sulfonylureas. In an 18-week study of linagliptin added to sulfonylurea monotherapy, the change from baseline in HbA1c was numerically lower than the change from baseline in HbA1c at Week 24 in the current study among the subgroup of patients taking sulfonylurea monotherapy. Similarly, the change in baseline observed in the subgroup of patients taking sulfonylurea monotherapy in the present study was numerically higher than the change from baseline in HbA1c.
observed in the saxagliptin 2.5 mg- and 5 mg-dose groups at Week 24\textsuperscript{21}, or at Week 26 in a study in which alogliptin 12.5 mg, or 25 mg was added to sulfonylurea monotherapy.\textsuperscript{22}

The mean change from baseline in HbA1c observed in the subgroup of patients on sulfonylurea and metformin in the current study was also numerically higher than the change from baseline in HbA1c at Week 24 observed when 5 mg saxagliptin was added to sulfonylurea and metformin treatment.\textsuperscript{23} The change from baseline in HbA1c observed at Week 24 in the subgroup of patients on sulfonylurea and metformin was consistent with that observed in another global study in which sitagliptin was added to patients taking sulfonylurea and metformin.\textsuperscript{24}

The results from the current study suggest that the glycemic efficacy of the addition of sitagliptin to patients taking sulfonylurea (with or without metformin) is consistent to that observed when sitagliptin was used as monotherapy (Chinese subgroup from a study conducted in Chinese, Korean, and Indian patients\textsuperscript{12}), or when added to metformin in Chinese patients with type 2 diabetes mellitus.\textsuperscript{13} Furthermore, consistent with the mechanism of action of sitagliptin, the incidence of hypoglycemia observed in this study when sitagliptin was added to sulfonylurea, an agent associated with hypoglycemia, was higher than when it was used in monotherapy,\textsuperscript{12} or added to metformin, an agent not associated with hypoglycemia, in Chinese patients with type 2 diabetes mellitus.\textsuperscript{13}

Some limitations of this study should be noted. The short duration of this trial precludes evaluation of long-term glycemic control and adverse events. In addition, the study was conducted only in Chinese patients living in China and the results may not be generalizable to other populations. However, the results were consistent with a similarly designed multinational study,\textsuperscript{15} and with a similarly designed study conducted in other Asian populations,\textsuperscript{13, 14} supporting the results of the current study.
Conclusion

The results of this study demonstrated that in Chinese patients with T2DM with inadequate glycemic control on a sulfonylurea with or without metformin, the addition of sitagliptin treatment resulted in significantly greater improvements in glycemic control compared with the addition of placebo. Sitagliptin was generally safe and well tolerated, with an efficacy and safety profile that was generally consistent with that observed in similarly designed global trials.

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Conflict of Interest

P. Han, G. Yuan, Z. Mo, C. Pan and J. Ba have nothing to disclose. F. Wu, L. Xu, M.E. Hanson, S.S. Engel, and R.R. Shankar are all current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock/stock options in the company. F. Wu also reports employment at Novartis Pharmaceuticals.
Disclosure

J. Ba, P. Han, G. Yuan, Z. Mo, C. Pan, F. Wu, L. Xu, M.E. Hanson, S. S. Engel and R.R. Shankar are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data in addition to drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Reference List


Table 1. Baseline demographic, anthropometric, disease characteristic and efficacy endpoint data for all patients randomized

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<th>Sitagliptin n=249</th>
<th>Placebo n=249</th>
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<tr>
<td>Males, n (%)</td>
<td>117 (47.0)</td>
<td>132 (53.0)</td>
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<tr>
<td>Age, years</td>
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<td>BMI, kg/m2</td>
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<td>HbA1c distribution, n (%)</td>
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<td>28 (11.2)</td>
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<td>2-hr PMG, mg/dL (n)</td>
<td>296.5 ± 68.0 (248)</td>
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<td>FPG, mg/dL</td>
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<td>0.32 ± 0.03 (230)</td>
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BMI, body mass index; FPG, fasting plasma glucose; HOMA, homeostatic model assessment; QUICKI, quantitative insulin sensitivity check index; PMG, post-meal glucose; T2DM, type 2 diabetes mellitus

Data are expressed as mean ± standard deviation unless otherwise indicated.
Table 2. Least squares mean change from baseline to Week 24 in glycemic and meal tolerance test endpoints for the full study cohort and subsets of patients receiving and not receiving metformin

<table>
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<th>Efficacy parameter</th>
<th>Entire cohort</th>
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<th>Subset of patients not on metformin</th>
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<tr>
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<td>Sitagliptin n=111 Placebo n=112 Difference in LS means (95% CI)¶</td>
<td>Sitagliptin n=132 Placebo n=124 Difference in LS means (95% CI)¶</td>
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<td>-0.85 -0.05 -0.80 (-10.7, -0.53)</td>
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<td>FPG, mg/dL 2-hr PMG, mg/dL</td>
<td>-24.4 -7.7 -16.8 (-23.3, -10.2)</td>
<td>-22.2 -5.7 -16.5 (-25.3, -7.8)</td>
<td>-26.3 -9.30 -17.0 (-26.9, -7.1)</td>
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<tr>
<td></td>
<td>-40.7 -6.0 -32.9 (-45.4, -20.4)</td>
<td>-33.4 -6.2 -27.2 (-41.2, -13.2)</td>
<td>-49.5 -11.90 -37.7 (-56.9, -18.4)</td>
</tr>
</tbody>
</table>

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LS, least squares; PMG, post-meal glucose

†HbA1c and 2-hr PMG analyses were based on robust regression using M-estimation with terms for treatment and the metformin stratum, and baseline efficacy parameter as a covariate. FPG was based on robust regression using M-estimation with terms for treatment and the metformin stratum, and baseline FPG as a covariate.

‡HbA1c was based on an ANCOVA model with terms for treatment and baseline efficacy parameter as a covariate. 2-hrPMG and FPG were based on robust regression using M-estimation with terms for treatment and baseline efficacy parameter as a covariate.

§HbA1c and 2-hr PMG were based on an ANCOVA model with terms for treatment and baseline efficacy parameter as a covariate. FPG was based on robust regression using M-estimation with terms for treatment and baseline Fasting Plasma Glucose as a covariate.

¶All differences were statistically significant at the p<0.001 level.
<table>
<thead>
<tr>
<th>Event</th>
<th>Sitagliptin 100 mg</th>
<th>Placebo</th>
<th>Difference in % Sitagliptin 100 mg vs. Placebo Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in population</td>
<td>248 (n)</td>
<td>249 (n)</td>
<td></td>
</tr>
<tr>
<td>≥1 AE</td>
<td>106 (42.7)</td>
<td>98 (39.4)</td>
<td>3.4 (-5.3, 12.0)</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>24 (9.7)</td>
<td>21 (8.4)</td>
<td>-3.4 (-12.0, 5.3)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>7 (2.8)</td>
<td>7 (2.8)</td>
<td>0.0 (-3.2, 3.3)</td>
</tr>
<tr>
<td>Serious drug-related AEs</td>
<td>0</td>
<td>3 (1.2)</td>
<td>-1.2</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Discontinued§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to an AE</td>
<td>3 (1.2)</td>
<td>7 (2.8)</td>
<td>-1.6 (-4.6, 1.0)</td>
</tr>
<tr>
<td>Due to a drug-related§ AEs</td>
<td>0</td>
<td>2 (0.8)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Due to a serious AE</td>
<td>2 (0.8)</td>
<td>4 (1.6)</td>
<td>-0.8 (-3.3, 1.5)</td>
</tr>
<tr>
<td>Due to a serious drug-related§ AEs</td>
<td>0</td>
<td>2 (0.8)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Hypoglycemia (symptomatic or asymptomatic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>35 (14.1)</td>
<td>17 (6.8)</td>
<td>7.3 (2.0, 12.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>25 (10.1)</td>
<td>13 (5.2)</td>
<td>4.9 (0.2, 9.8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>12 (4.8)</td>
<td>2 (0.8)</td>
<td>3.2 (0.1, 6.9)</td>
</tr>
<tr>
<td>Hypoglycemia (symptomatic or asymptomatic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall gastrointestinal AEs</td>
<td>11 (4.4)</td>
<td>7 (2.8)</td>
<td>1.6 (-1.8, 5.3)</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; n, number of patients in population

†Based on Miettinen & Nurminen method.

‡Considered by the investigator to be related to the study medication.

§Study medication withdrawn.

Every patient is counted a single time for each applicable row.

Asymptomatic episode: Episode without symptoms attributed to hypoglycemia, but with a glucose level ≤70 mg/dL.

Symptomatic episode: Episode with clinical symptoms attributed to hypoglycemia, without regard to glucose level.

Severe episode: Episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure are classified as having required medical assistance, whether or not medical assistance was obtained.
Figure 1
Figure 2

HbA1c (%) over weeks for Sitagliptin 100 mg (n=231-248) and Placebo (n=213-249).