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CLINICAL TRIAL

Sitagliptin added to stable insulin therapy with or without metformin in Chinese patients with type 2 diabetes

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ABSTRACT

Introduction: We evaluated the tolerability and efficacy of the addition of sitagliptin in Chinese patients with type 2 diabetes mellitus receiving stable insulin therapy alone or in combination with metformin.

Materials and Methods: A total of 467 patients with inadequate glycemic control on insulin (glycated hemoglobin [HbA1c] ≥7.5% and ≤11%) were randomized 1:1 to receive sitagliptin 100 mg once daily or a matching placebo for 24 weeks. Randomization was stratified based on metformin use (on or not on metformin) and type of insulin (pre-mixed vs intermediate-/long-acting) at screening. The primary end-point was the change from baseline at week 24 in HbA1c.

Results: The addition of sitagliptin led to a significantly ($P < 0.001$) greater week 24 HbA1c reduction (0.7%) compared with the reduction (0.3%) with placebo. A significantly ($P = 0.013$) greater proportion of patients taking sitagliptin (16%) had an HbA1c of <7.0% at week 24 compared with placebo (8%). The addition of sitagliptin significantly ($P < 0.001$) reduced 2-h post-meal glucose by 26.5 mg/dL (1.5 mmol/L) relative to placebo. Reductions from baseline in fasting plasma glucose were observed in both the sitagliptin (14.4 mg/dL reduction) and placebo (10.7 mg/dL reduction) groups; the between-group difference was not significant. A total of 64 (27.4%) patients taking sitagliptin and 51 (21.9%) taking placebo experienced adverse events of hypoglycemia (symptomatic or asymptomatic). Neither group had a significant change from baseline in bodyweight.

Conclusions: After 24 weeks, sitagliptin added to stable insulin therapy (±metformin) was generally well tolerated and improved glycemic control in Chinese patients with type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus affects more than 380 million people worldwide, including more than 96 million people in China[1]. For type 2 diabetes mellitus patients who are not able to reach treatment targets using oral antihyperglycemic agents (AHAs), insulin is typically added. A standard approach in China is to start with 'basal' insulin, using either neutral protamine Hagedorn or a long-acting insulin analog added to an AHA. If adequate glycemic control is not achieved, intensive insulin therapy (neutral protamine Hagedorn plus regular insulin, long-acting insulin analog plus short-acting insulin analog or an insulin pump) is usually implemented[2]. The most common AHA used in combination with insulin is metformin. Although some type 2 diabetes mellitus patients reach treatment goals with this combination, many patients, despite aggressive titration of insulin, fail to achieve current glycated hemoglobin (HbA1c) goals of <7.0% and/or <6.5%. Even the use of pre-mixed insulin, which includes short-acting insulin to address prandial requirements, is often insufficient. One reason for the

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failure to achieve HbA1c goals with insulin therapy is that glucose excursions after meals are not adequately controlled. Studies have shown postmeal glucose excursions contribute substantially to the elevation in HbA1c, especially when HbA1c levels are only mildly to moderately elevated. Indeed, recent studies have shown that 42–88% of patients fail to reach HbA1c <7% despite aggressive titration of basal insulin[3–10].

Sitagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, and is approved as an adjunct to diet and exercise for the treatment of patients with type 2 diabetes mellitus. Sitagliptin has been shown to improve glycemic control as monotherapy and as combination therapy with other AHAs (metformin, a thiazolidinedione, a sulfonylurea, or a sulfonylurea or thiazolidinedione in combination with metformin) and with insulin (with or without metformin). The efficacy and safety of sitagliptin in combination with insulin (with or without metformin) were shown in a previous 24-week, placebo-controlled, phase III, multinational study[11]. This previous study showed that in patients who had inadequate glycemic control (HbA1c 7.5–11.0% at screening) on insulin therapy (with or without metformin), sitagliptin was well tolerated and provided a significant improvement in HbA1c compared with placebo, with a between-group difference in HbA1c change from baseline at week 24 of −0.6%. Fasting plasma glucose (FPG) and 2-h postmeal glucose (2-h PMG) were also significantly improved compared with placebo, with between-group differences of −15.0 mg/dL (−0.8 mmol/L) and −36.1 mg/dL (−2.0 mmol/L), respectively.

The present study was carried out in China to assess the efficacy and safety of sitagliptin compared with placebo in patients with type 2 diabetes mellitus who had failed to achieve adequate glycemic control with insulin, alone or in combination with metformin.

MATERIALS AND METHODS

Patients

Patients were eligible to participate in the present study if they were aged 18–79 years with type 2 diabetes mellitus and were on a stable insulin (intermediate- or long-acting, or premixed insulin) regimen for ≥10 weeks with or without metformin ≥1,500 mg/day, and had inadequate glycemic control (screening HbA1c 7.5–11%). Exclusion criteria included a site fasting fingerstick glucose of <130 mg/dL (7.2 mmol/L) or >260 mg/dL (14.4 mmol/L) at day 1, type 1 diabetes mellitus, New York Heart Association class III–IV congestive heart failure, unstable cardiac disease, marked renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2 or, for patients taking metformin, creatinine ≥1.4 mg/dL [124 μmol/L] in men and ≥1.3 mg/dL [115 μmol/L] in women), triglycerides >600 mg/dL, or elevated (>twofold upper limit of normal) aspartate aminotransferase or alanine aminotransferase. Treatment with any AHA other than the protocol-required insulin (alone or with metformin) within 12 weeks of study entry or having ever been treated with a DPP-4 inhibitor or a glucagon-like peptide-1 analog were also excluded. All patients were counseled throughout the study regarding diet and exercise based on the recommendations of the American Diabetes Association.

Study design

The present randomized, double-blind, placebo-controlled, parallel-group study (Protocol 254; clinicaltrials.gov: NCT01590797) was carried out at 28 clinical sites in China. Eligible patients taking stable-dose insulin ± metformin entered a 2-week, single-blind, placebo run-in. At the end of the run-in period, patients had baseline measurements and then were randomized (1:1) to receive sitagliptin 100 mg q.d. or placebo for 24 weeks. Patients were randomized based on their use of metformin (taking or not taking metformin) and the type of insulin (premixed vs intermediate-/long-acting) at screening. Approximately equal numbers of patients were randomized in each metformin stratum. The proportion of patients using premixed insulin was capped at 75%. Insulin and metformin doses were to remain stable throughout the study, except if a reduction in insulin dose was required because of the occurrence of, or to prevent, hypoglycemia.

Patients not achieving glycemic targets were eligible for glycemic rescue therapy, which consisted of an increase by more than 10% of the patient's stable insulin dose (i.e., insulin dose at day 1). Glycemic rescue criteria were as follows: FPG consistently >270 mg/dL (>14.99 mmol/L) after randomization to week 6, FPG consistently >240 mg/dL (>13.32 mmol/L) after week 6 to week 12, and FPG consistently >200 mg/dL (>11.10 mmol/L) after week 12. The investigator used his/her clinical judgment to manage the adjustment in insulin dose(s) for glycemic rescue.

Downtitration of insulin was to be carried out if a patient had an unexplained (i.e., not explained by a missed meal, excessive physical activity etc.) hypoglycemic episode (symptomatic or asymptomatic) or the patient was considered at risk of hypoglycemia based on the investigator's review of the patient's self-monitored blood glucose values. If any of these criteria were met, the investigator could reduce the dose of insulin by a minimum of 2–4 IU/day until the patient was no longer judged by the investigator to be at risk for hypoglycemia. If the patient continued to experience hypoglycemic episodes on this lowered dose, they were to be evaluated for discontinuation from the study.

This study was carried out in accordance with the Declaration of Helsinki and good clinical practice, and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided written informed consent before participating in the trial.

Efficacy end-points

The primary efficacy end-point was change from baseline at week 24 in HbA1c. Secondary efficacy end-points included the proportion of patients with an HbA1c <7% at week 24, FPG and 2-h PMG. Additional end-points included fasting lipids

(triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol and total cholesterol).

A standard meal tolerance test was carried out at baseline and week 24. Study medication was taken, and insulin was injected after the meal tolerance test on day 1. At week 24, study medication was taken 30 min before ingestion of the standard meal. Open-label insulin (for those patients taking morning insulin) was given when appropriate after collection of the 2-h blood sample for the meal tolerance test. Patients taking metformin took their metformin after fasting blood samples had been collected and immediately before ingestion of the standard meal. Patients consumed the standard meal within 15 min after starting to ingest it; at week 24, patients were to eat the same proportion of the standard meal as they had done on day 1. The meal consisted of approximately 460 kcal, with 18 g protein, 75 g carbohydrate and 9 g fat. Blood was collected 120 min after the start of the meal for determination of the 2-h PMG.

Safety end-points

Safety end-points included clinical adverse events, bodyweight, laboratory data, physical examinations, vital signs and electrocardiograms. Investigators assessed adverse events for the relationship to study medication and intensity. Laboratory assessments included urinalysis, hematology and blood chemistry.

Investigators instructed patients on how to carry out fingerstick glucose measurements and the frequency with which they were to carry out these measurements, with a recommended minimum number of two fasting fingerstick glucose determinations per week. Investigators also counseled patients regarding hypoglycemia symptoms and how to manage these symptoms. Patients were provided a hypoglycemia assessment log and were instructed on how to record hypoglycemia episodes. Hypoglycemia events were categorized as events that did not require assistance, events that required non-medical assistance and events that met the prespecified definition of severe hypoglycemia (associated with markedly depressed level of consciousness, including seizure or loss of consciousness, or requiring medical or non-medical intervention).

Laboratory measurements were analyzed at a central laboratory (PPD Global Central Labs, Beijing, China) as described previously[12].

Statistical analysis

An analysis of covariance (ANCOVA) model was used to analyze the change from baseline in HbA1c at week 24, based on the assumption that the ANCOVA model-based residuals follow a normal distribution. If the distribution of the ANCOVA residuals was highly non-normal ($P < 0.001$), the primary analysis was to be carried out using a robust regression approach. The analysis model controlled for treatment, metformin stratum (±metformin), type of insulin (premixed or intermediate-/long-acting) and baseline HbA1c value. The estimated least squares (LS) mean treatment difference under the model was used to assess the primary hypothesis regarding superiority of sitagliptin compared with placebo in decreasing HbA1c. The LS mean change (or percent change) from baseline at week 24 was estimated using this model. This analysis excluded data obtained after initiation of glycemic rescue therapy. The last-observation-carried-forward method was used to impute missing data. The planned sample size of 230 patients per treatment group was expected to provide 90% power to detect a difference of 0.29% in the mean change from baseline in HbA1c between the treatment groups (two-sided test, $\alpha = 0.05$) based on a standard deviation of 0.9% and a patient discontinuation rate of approximately 13%.

All other continuous efficacy end-points (except for triglycerides) were analyzed using the aforementioned ANCOVA method (or robust regression method in the case in which the ANCOVA residuals were highly non-normal) described for HbA1c, substituting the relevant baseline efficacy value as the covariate. For analyses in the individual metformin strata, the terms of use of metformin were not included in the model. An ANCOVA based on Tukey's normalized ranks was used to analyze the change from baseline in triglycerides[13].

The Miettinen and Nurminen method was used to analyze the proportion of patients achieving the HbA1c goal of <7.0% at week 24[14]. The analysis was stratified by the use of metformin (±metformin).

The Kaplan–Meier estimate and the log–rank test were used to carry out a time-to-glycemic rescue analysis.

The Miettinen and Nurminen method was used to assess between-treatment differences for the incidence of hypoglycemic events[14]. The ANCOVA model described above was used to analyze the between-group difference in change from baseline in bodyweight. Data obtained after glycemic rescue therapy were excluded from the analyses of bodyweight and hypoglycemia.

RESULTS

A total of 740 insulin-treated patients were screened, among whom 273 were not enrolled and 467 were randomized to sitagliptin ($n = 234$) or placebo ($n = 233$). A total of 434 patients (93%) completed the study (Figure 1). A similar proportion of patients in each treatment group discontinued (Figure 1). The two treatment groups were similar with respect to demographics and baseline characteristics (Table 1). At baseline, the mean HbA1c for all patients was 8.7% (range 6.9%–12.4%) and the mean FPG was 185 mg/dL (10.2 mmol/L). The mean duration of diabetes was 11.2 years. A total of 75% of patients were taking premixed insulin and 25% were taking intermediate- or long-acting insulin. A total of 49% of patients were on both insulin and metformin therapy. The median daily dose of metformin at baseline was 1,500 mg/day. There was no change from baseline in the median daily dose of metformin throughout the study (data not shown). The overall mean treatment

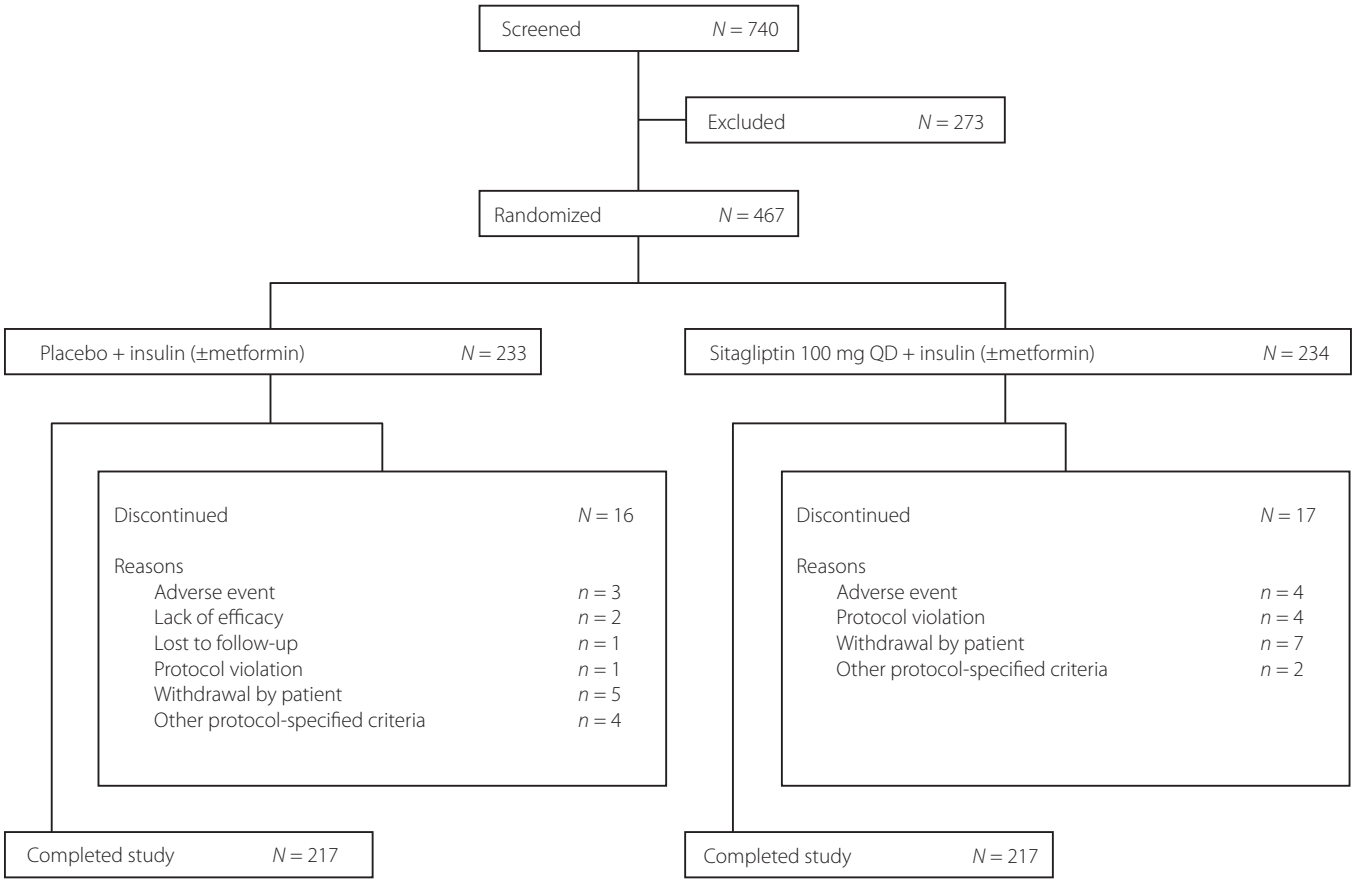

Figure 1 | Patient disposition.

compliance rate was 99%, and was comparable between the two treatment groups.

Efficacy

After 24 weeks, HbA1c was significantly ($P < 0.001$) reduced by 0.7% from a baseline of 8.7% in the sitagliptin group compared with a decrease of 0.3% from a baseline of 8.8% in the placebo group (Table 2). Figure 2 shows change from baseline in HbA1c over time. The HbA1c response across subgroups defined by baseline demographics, disease-related and anthropometric characteristics, and insulin stratum (premixed insulin or intermediate- and long-acting acting insulin), was similar to that seen in the overall study population (data not shown). The HbA1c treatment response was also similar for patients taking metformin compared with those not taking metformin (Table 2).

At week 24, a significantly ($P = 0.013$) greater percentage of patients taking sitagliptin (16%) had an HbA1c <7.0% compared with placebo (8%).

There was a significant reduction from baseline in 2-h PMG in the sitagliptin group compared with the placebo group (Table 2). The 2-h PMG treatment response was similar for patients taking metformin compared with those not taking metformin (Table 2).

There were significant LS mean reductions from baseline in FPG at week 24 in both the sitagliptin and placebo groups; the between-group difference was not significant (Table 2). Consistent with these results, the between-group difference for change from baseline in FPG at week 24 was not significant in either metformin stratum (Table 2).

Mean doses of intermediate- and long-acting insulins at baseline with sitagliptin and placebo were 23 IU/day and 19 IU/day, respectively. Mean doses of premixed insulin at baseline with sitagliptin and placebo were 38 IU/day and 39 IU/day, respectively. There was minimal overall mean (standard deviation) change in insulin dose at study end, 0.4 IU (2.6) with sitagliptin and 0.5 IU (2.5) with placebo.

The percentage of patients requiring glycemic rescue therapy was numerically smaller in the sitagliptin group (9.4%) compared with the placebo group (12.4%), with $P = 0.297$ for the between-group difference.

There were no meaningful between-group differences in lipid parameters in the overall cohort or in the individual metformin strata (Table S1).

Table 1 | Demographics and baseline disease characteristics for randomized patients

Characteristic	Placebo + insulin (±metformin) *n* = 233	Sitagliptin 100 mg q.d. + insulin (±metformin) *n* = 234
Age (years)	56.7 ± 9.1	58.6 ± 8.4
Male	116 (49.8)	130 (55.6)
Body mass index (kg/m^2)	26.1 ± 2.9	25.9 ± 3.0
HbA1c (%)	8.8 ± 0.9	8.7 ± 0.9
(Range)†	(7.1–11.1)	(6.9–12.4)
HbA1c distribution at baseline		
<8%	55 (23.6)	62 (26.5)
≥8% to <9%	84 (36.1)	92 (39.3)
≥9% to <10%	65 (27.9)	54 (23.1)
≥10%	29 (12.4)	26 (11.1)
Fasting plasma glucose (mg/dL)	188.6 ± 44.4	182.1 ± 40.3
Duration of diabetes (years)	11.3 ± 5.8	11.0 ± 5.0
Diabetic complications		
Diabetic retinopathy	27 (11.6)	20 (8.5)
Diabetic neuropathy	34 (14.6)	41 (17.5)
Diabetic nephropathy	20 (8.6)	17 (7.3)
Type of insulin		
All patients	233 (100)	234 (100)
Total daily dose (IU/day)	34.5 ± 14.7	34.5 ± 14.1
Premixed	176 (75.5)	173 (73.9)
Total daily dose (IU/day)	40.0 ± 13.4	38.6 ± 14.2
Long- or intermediate-acting	57 (24.5)	61 (26.1)
Total daily dose (IU/day)	19.3 ± 5.8	23.3 ± 7.6
On metformin	116 (49.8)	115 (49.2)
Metformin dose (mg/day)	1,500 (1,500, 1,500)	1,500 (1,500, 1,500)
Prior lipid modifying agents	27 (11.6)	43 (18.4)

Data are expressed as mean ± standard deviation (median [interquartile range] for metformin dose) or frequency (*n* [%]), unless otherwise indicated. †Patients were eligible for the 2-week placebo run-in period before randomization if glycated hemoglobin (HbA1c) was in the range of 7.5–11%. Baseline measurements were obtained after this run-in period (at the randomization visit), and thus HbA1c might be outside the range specified in the eligibility criteria.

Safety

The two treatment groups were generally similar with regard to overall incidences of adverse events, drug-related adverse events, serious adverse events, drug-related serious adverse events, adverse events leading to discontinuation and drug-related adverse events leading to discontinuation (Table 3). No deaths were reported in the present study.

Four patients (1.7%) taking sitagliptin discontinued treatment as a result of an adverse event. One of these four patients was discontinued as a result of a serious adverse event – acute myocardial infarction – which was determined by the investigator as not being related to the study medication. Of the other three patients in the sitagliptin group who discontinued as a result of an adverse event, one each was discontinued due to increased blood glucose, decreased glomerular filtration rate and insomnia. Two patients taking placebo discontinued as a result of an adverse event, one due to fibula fracture and the other due to diabetic ketoacidosis.

One or more adverse events of symptomatic or asymptomatic hypoglycemia were reported in 64 (27.4%) patients in the sitagliptin group and 51 (21.9%) patients in the placebo group. The incidence of symptomatic hypoglycemia was numerically higher in patients treated with sitagliptin (24.8% [58/234]) compared with placebo (19.7% [46/233]) ($P = 0.191$ for between-group difference). A total of 18 (7.7%) patients in the sitagliptin group and 16 (6.9%) patients in the placebo group had severe symptomatic hypoglycemic episodes (i.e., showed symptoms of marked severity or required medical assistance). No patients taking sitagliptin compared with two patients taking placebo required medical assistance for severe symptomatic hypoglycemia. A total of 53 (22.6%) patients in the sitagliptin group and 42 patients (18.0%) in the placebo group reported adverse events of hypoglycemia associated with known precipitating factors, with the most commonly reported precipitating factor being 'skipped, delayed or smaller meal/snack.'

In addition to hypoglycemia, five other adverse events were reported with an incidence of ≥2% in one or more treatment groups: upper respiratory tract infection (2.0% and 4.0%), urinary tract infection (5.6% and 4.4%), hyperglycemia (2.8% and 1.2%), hyperlipidemia (3.2% and 6.0%), and hyperuricemia (3.6% and 2.4%) for sitagliptin and placebo, respectively. For each of these events, the 95% CIs for the between-treatment difference included zero. No adverse events of acute pancreatitis were reported during the present study.

The change from baseline in bodyweight at week 24 was similar in the two treatment groups (mean change [standard deviation] of 0.1 kg [2.8] in both groups).

DISCUSSION

The addition of sitagliptin led to a significantly greater reduction from baseline in HbA1c compared with placebo after 24 weeks in Chinese patients with type 2 diabetes mellitus receiving stable insulin therapy (±metformin). A similar HbA1c response was observed in patients receiving concomitant metformin therapy compared with those not receiving such therapy, and in those taking intermediate- or long-acting insulin compared to those taking premixed insulin. The addition of sitagliptin enabled a greater proportion of patients to achieve the HbA1c target <7.0% compared with placebo. The addition of sitagliptin also led to a statistically significant improvement in 2-h PMG compared with placebo. Although the addition of sitagliptin led to a numerically greater reduction from baseline in FPG than placebo, the between-group difference was not significant.

Table 2 | Efficacy results

Parameter	*n*	Week 0 (baseline) Mean ± SD	Week 24 Mean ± SD	LS mean change from baseline (95% CI)	Difference LS mean change from baseline (95% CI) (sitagliptin vs placebo)
HbA1c (%)					
Overall cohort					
Placebo + insulin	219	8.7 ± 0.9	8.4 ± 1.1	−0.3 (−0.4, −0.2)†	−0.3 (−0.5, −0.2)***†
Sitagliptin 100 mg q.d. + insulin	223	8.7 ± 0.9	8.0 ± 1.0	−0.7 (−0.8, −0.6)†	
On metformin					
Placebo + insulin	104	8.7 ± 0.9	8.4 ± 1.1	−0.3 (−0.5, −0.2)†	−0.4 (−0.6, −0.1)**†
Sitagliptin 100 mg q.d. + insulin	109	8.6 ± 0.9	7.9 ± 1.1	−0.7 (−0.9, −0.6)†	
Not on metformin					
Placebo + insulin	115	8.7 ± 0.9	8.4 ± 1.0	−0.3 (−0.5, 0.2)‡	−0.3 (−0.5, −0.1)*‡
Sitagliptin 100 mg q.d. + insulin	114	8.8 ± 1.0	8.2 ± 1.0	−0.6 (−0.8, −0.4)‡	
2-h Postmeal glucose (mg/dL)					
Overall cohort					
Placebo + insulin	203	324.7 ± 72.1	305.9 ± 71.3	−21.3 (−30.3, −12.3)‡	−26.5 (−38.4, −14.7)***‡
Sitagliptin 100 mg q.d. + insulin	209	321.4 ± 68.1	278.8 ± 64.0	−47.9 (−57.0, −38.8)‡	
On metformin					
Placebo + insulin	102	319.2 ± 72.6	295.5 ± 73.8	−21.5 (−34.2, −8.9)‡	−28.2 (−45.5, −11.0)***‡
Sitagliptin 100 mg q.d. + insulin	104	305.1 ± 66.6	262.2 ± 62.1	−49.8 (−62.5, −37.1)‡	
Not on metformin					
Placebo + insulin	101	330.2 ± 71.5	316.4 ± 67.4	−22.1 (−35.4, −8.8)‡	−24.4 (−40.9, −8.0)**‡
Sitagliptin 100 mg q.d. + insulin	105	337.5 ± 66.1	295.2 ± 62.0	−46.6 (−60.0, −33.2)‡	
Fasting plasma glucose (mg/dL)					
Overall cohort					
Placebo + insulin	226	188.2 ± 44.3	175.3 ± 46.9	−10.7 (−16.9, −4.6)‡	−3.7 (−11.8, 4.4)‡
Sitagliptin 100 mg q.d. + insulin	228	182.5 ± 40.3	170.0 ± 43.5	−14.4 (−20.6, −8.2)‡	
On metformin					
Placebo + insulin	111	190.0 ± 46.8	175.4 ± 49.0	−9.1 (−17.4, −0.7)‡	−3.9 (−15.4, 7.5)‡
Sitagliptin 100 mg q.d. + insulin	112	176.7 ± 34.7	167.1 ± 40.0	−13.0 (−21.4, −4.6)‡	
Not on metformin					
Placebo + insulin	115	186.5 ± 41.9	175.1 ± 45.0	−13.5 (−22.9, −4.1)‡	−2.9 (−14.5, 8.7)‡
Sitagliptin 100 mg q.d. + insulin	116	188.2 ± 44.5	172.7 ± 46.7	−16.4 (−25.8, −7.0)‡	

***$P \leq 0.001$, **$P < 0.01$, *$P < 0.05$. †Least squares (LS) means estimated using robust regression approach due to the distribution for the residuals of the ANCOVA model being highly non-normal ($P < 0.001$). ‡LS means estimated using ANCOVA model. CI, confidence interval; HbA1c, glycated hemoglobin; SD, standard deviation.

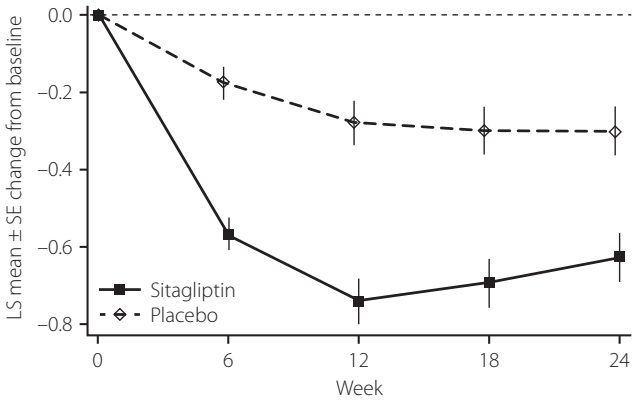

Figure 2 | Change from baseline in HbA1c (%) over time. LS, least squares; SE, standard error of the mean.

Table 3 | Adverse events

No. patients (%)	Placebo + insulin (±metformin) *n* = 233	Sitagliptin 100 mg q.d. + insulin (±metformin) *n* = 234
One or more adverse events	116 (49.8)	126 (53.8)
Drug-related† adverse events	39 (16.7)	47 (20.1)
Serious adverse events	9 (3.9)	4 (1.7)
Serious drug-related† adverse events	0	0
Deaths	0	0
Discontinued due to an adverse event	2 (0.9)	4 (1.7)
Discontinued due to a drug-related† adverse event	0	2 (0.9)
Discontinued due to a serious adverse event	2 (0.9)	1 (0.4)
Discontinued due to a serious drug-related† adverse event	0	0

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

The results of the present study carried out in China are generally consistent with those of a similarly-designed, multinational, sitagliptin add-on to insulin study carried out in several countries including the USA and European nations[11]. There were some differences in the study design and the baseline demographics between the two studies. In the present study compared with the multinational study, by design, ~75% of patients were taking long- or intermediate-acting insulin compared with ~25%, 50% of patients were taking metformin compared with ~72%, and patients had a lower body mass index (~26 kg/m^2 compared with 31 kg/m^2) and a lower dose of insulin (~35 IU/day compared with ~51 IU/day).

The LS mean reduction from baseline in HbA1c resulting from the addition of sitagliptin in the present add-on to insulin study in Chinese patients (−0.7%, 95% confidence interval [CI]: −0.8, −0.6) was consistent with that observed in the previous sitagliptin add-on to insulin multinational study (−0.6%, 95% CI: −0.7, −0.5). A modest decrease from baseline in HbA1c was also observed in the placebo group in the present study (LS mean change from baseline: −0.3%, 95% CI: −0.4, −0.2), whereas no change was observed in the placebo group in the multinational study (LS mean change from baseline: 0.0%, 95% CI: −0.1, 0.1). Similar placebo effects have been reported in other clinical trials carried out in Chinese patients with type 2 diabetes mellitus[15–19]. Possible reasons for the modest reduction in HbA1c observed in the placebo group at week 24 in the present study include patient awareness of blood glucose levels affected by home blood glucose monitoring, and increased compliance to diet and lifestyle modification as a consequence of participation in a clinical trial and the attendant regular clinic visits.

In the present study, reductions in FPG from baseline at week 24 were observed both in the sitagliptin and the placebo groups (for the overall cohort and the individual metformin strata); however, the between-group difference was not significant. The lack of a significant between-group difference in FPG in the present study suggests that the primary mode of improvement in overall glycemic control was brought about through the observed improvement in 2-h PMG, which was clinically important and statistically significant. As optimizing control of PMG in patients taking insulin – either basal insulin (e.g., insulin glargine) or premixed insulins (e.g., 70/30) – can be challenging, the improvement observed in 2-h PMG with sitagliptin in the present study provides important clinical value.

Sitagliptin was generally well tolerated. The incidences of adverse events, serious adverse events and adverse events leading to discontinuation were comparable between the two treatment groups. The overall incidence of adverse events of hypoglycemia was numerically higher in the sitagliptin group compared with the placebo group. The incidence of symptomatic hypoglycemia showed a similar numerical increase in the sitagliptin group, but was not significantly different from that in the placebo group (P = 0.191). An increase in the incidence of symptomatic hypoglycemia has been reported when agents, such as sitagliptin, that are not by themselves associated with hypoglycemia are added to insulin therapy[20–22], as was observed in the previous, similarly-designed, multinational study[11]. This observation is most likely related to improved glycemic control; by lowering ambient glucose levels closer to the normoglycemic range, the risk of insulin-induced hypoglycemia increases. Despite the modest numerical increase in the occurrence of hypoglycemia, the incidence of severe events of hypoglycemia was not notably higher in the sitagliptin group compared with the placebo group, and there were no hypoglycemic events requiring medical assistance in the sitagliptin group.

The incidence of symptomatic hypoglycemia was higher in both treatment groups in the present study relative to the

incidences reported in the prior multinational sitagliptin add-on to insulin study[11]. Previous placebo-controlled, add-on to insulin studies with other DPP-4 inhibitors also reported higher incidences of hypoglycemia (DPP-4 inhibitor groups 18.4–22.9%; placebo groups 19.9–29.6%)[23–25]. However, the between-group difference in symptomatic hypoglycemia was not notably different in the present study relative to the prior multinational sitagliptin add-on to insulin study. In the present study, 24.8% and 19.7% of patients had symptomatic hypoglycemia in the sitagliptin and placebo groups, respectively; whereas it was 15.5% and 7.8%, respectively, in the previous study. This higher occurrence of hypoglycemia seen in both treatment groups in the present study might be due to the much higher background use of premixed insulins relative to the use in the prior multinational study (~75% relative to 25%), which would be expected to be associated with hypoglycemia. As previously noted, there was also a greater placebo response in HbA1c-lowering in the present study relative to that in the previous study, which might have led to the higher incidence of hypoglycemia in the placebo group in the present study.

Increased bodyweight can be an unwanted side-effect of some AHAs in patients with type 2 diabetes mellitus[26]. Insulin therapy is typically associated with weight gain as a result of improvement in glycemic control[27]. In the present study, the improvement in glycemic control with sitagliptin when added to ongoing insulin therapy with or without metformin was not associated with an increase in bodyweight compared with baseline or placebo.

In summary, in the present study of Chinese patients with type 2 diabetes mellitus and inadequate glycemic control receiving stable insulin therapy with or without metformin, the addition of sitagliptin led to significant and clinically meaningful improvements in glycemic control compared with placebo, and was generally well tolerated. The efficacy and safety profile was generally consistent with that observed with sitagliptin in a similarly designed, multinational trial.

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DISCLOSURE

R Ravi Shankar, Lei Xu, and Samuel S Engel are employees of Merck & Co., Inc., Kenilworth, New Jersey, USA, and may own stock options or stock in the company. Fan Wu was an employee of MSD China at the time this study was carried out, and may own stock options or stock in the company. Yuqian Bao, Ping Han, Ji Hu, Jianhua Ma, Yongde Peng and Weiping Jia declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1| Lipid results.