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ORIGINAL ARTICLE

Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: The CompoSIT-I Study

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Aims: To compare the effects of continuing versus discontinuing sitagliptin when initiating and intensively titrating insulin glargine.

Materials and methods: Eligible patients had inadequately controlled type 2 diabetes on metformin (≥1500 mg/d) in combination with a dipeptidyl peptidase-4 (DPP-4) inhibitor and/or a sulphonylurea. Those on metformin + sitagliptin were directly randomized; all others were switched to metformin + sitagliptin (discontinuing other DPP-4 inhibitors and sulphonylureas) and stabilized during a run-in period. At randomization, patients were allocated to continuing sitagliptin or discontinuing sitagliptin, with both groups initiating insulin glargine and titrating to a target fasting glucose of 4.0 to 5.6 mmol/L.

Results: A total of 743 participants (mean glycated haemoglobin [HbA1c] 72.6 mmol/mol [8.8%], disease duration 10.8 years), were treated. After 30 weeks, the mean HbA1c and least squares (LS) mean change from baseline in HbA1c were 51.4 mmol/mol (6.85%) and −20.5 mmol/mol (−1.88%) in the sitagliptin group and 56.4 mmol/mol (7.31%) and −15.5 mmol/mol (−1.42%) in the placebo group; the difference in LS mean changes from baseline HbA1c was −5.0 mmol/mol (−0.46%; $P < 0.001$). The percentage of participants with HbA1c <53 mmol/mol (<7.0%) was higher (54% vs. 35%) and the mean daily insulin dose was lower (53 vs. 61 units) in the sitagliptin group. Despite lower HbA1c, event rates and incidences of hypoglycaemia were not higher in the sitagliptin group. Adverse events overall and changes from baseline in body weight were similar between the two treatment groups.

Conclusion: When initiating insulin glargine therapy, continuation of sitagliptin, compared with discontinuation, resulted in a clinically meaningful greater reduction in HbA1c without an increase in hypoglycaemia. ClinicalTrials.gov Identifier: NCT02738879.

KEYWORDS

clinical trial, insulin therapy, sitagliptin, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is a progressive disease and, over time, most patients will require intensification of therapy to maintain glycaemic control. While clinical practice guidelines provide comprehensive recommendations for the intensification of pharmacological treatment which take into consideration drug-specific and patient factors, they provide limited guidance regarding the continuation or discontinuation of anti-hyperglycaemic agents (AHAs) that are part of a patient's existing regimen at the time of initiating insulin therapy.[1,2] Nonetheless, continuation of oral agents is consistent with practice guidelines, and when insulin therapy is initiated, basal insulin is often prescribed for use in combination with metformin and sometimes additional AHAs.

Prior to the initiation of insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used as part of dual or triple combination therapy with metformin to achieve glycaemic control; therefore, when combination oral therapy becomes inadequate for maintaining glycaemic control and insulin therapy is initiated, a commonly encountered decision is that of whether to continue a DPP-4 inhibitor. There are limited data available that provide an evidence base with regard to this clinical issue.

The continued use of DPP-4 inhibitors when initiating insulin therapy has theoretical advantages. While the use of basal insulin targets the reduction of fasting and pre-meal blood glucose (BG) levels, the progressive diminution in insulin secretory capacity in patients with type 2 diabetes can lead to poor postprandial and, as a consequence, overall glycaemic control. DPP-4 inhibitors, which improve postprandial glycaemic control by stabilizing the endogenous incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), directly address this pathophysiology. In addition, it has been shown that event rates of hypoglycaemia increase as basal insulin is progressively titrated to achieve glycated haemoglobin (HbA1c) targets consistent with scientific society guidance,[3–6] which probably plays a role in the inability to achieve glycaemic goals in many patients. Continuation of DPP-4 inhibitors might result in reduced rates of hypoglycaemia at lower HbA1c targets because of a reduced requirement for insulin and/or because of the glucagonotropic effects of GIP during hypoglycaemia.[7–10]

While there may be advantages to continuing DPP-4 inhibitors when initiating basal insulin, DPP-4 inhibitors are often discontinued under these circumstances.[11] The impact of discontinuing DPP-4 inhibitors when initiating basal insulin on glycaemic control and hypoglycaemia has not been studied. The CompoSIT-I (**Comp**arison **o**f **Sit**agliptin vs. placebo during Initiation of **I**nsulin) trial was designed to evaluate the impact of continuation versus discontinuation of sitagliptin when initiating and intensively titrating insulin glargine therapy.

2 | METHODS

2.1 | Study population

At screening, eligible patients were men and female, aged ≥18 years, with type 2 diabetes and on a stable regimen (>12 weeks) of metformin (≥1500 mg/d) in dual or triple combination therapy with a DPP-4 inhibitor (maximum labelled dose) and/or a sulphonylurea. Metformin could be immediate-release, extended-release or part of a fixed-dose combination. Patients on dual combination therapy with metformin and a DPP-4 inhibitor or metformin and a sulphonylurea were required to have an HbA1c concentration ≥58 mmol/mol and ≤97 mmol/mol (≥7.5% and ≤11.0%). Patients on triple combination therapy (metformin, DPP-4 inhibitor and a sulphonylurea) were required to have an HbA1c concentration ≥53 mmol/mol and ≤86 mmol/mol (≥7.0% and ≤10.0%). At randomization, eligible patients were required to have a fasting finger-stick glucose level >7.2 mmol/L and <15.0 mmol/L.

Patients were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, active liver disease, significant cardiovascular disease, a history of malignancy or haematological disorders, if they had been treated with any AHAs other than specified above within 12 weeks prior to screening, or if they had a history of two or more episodes of hypoglycaemia resulting in seizure, coma or loss of consciousness, or recurrent (≥3 times per week) episodes of hypoglycaemia within 8 weeks prior to screening. For patients assessed by the investigator as possibly having type 1 diabetes, C-peptide level was measured and those with a C-peptide <0.23 nmol/L were excluded. Laboratory exclusion criteria included estimated glomerular filtration rate <60 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease formula), serum alanine aminotransferase or aspartate aminotransferase levels >2 times the upper limit of normal, haemoglobin <110 g/L (men) or <100 g/L (female), triglycerides >6.8 mmol/L or thyroid-stimulating hormone outside the central laboratory normal range.

2.2 | Study design

The study was a multinational, double-blind, randomized, placebo-controlled trial conducted at 149 sites in 22 countries (Supporting Information Table S1). The study included a 1-week screening period, a 4- to 8-week run-in period (for participants taking metformin + a DPP-4 inhibitor other than sitagliptin, ± a sulphonylurea at screening, a 4-week period for sitagliptin initiation and dose stabilization and sulphonylurea washout if required; for participants taking metformin + sulphonylureas at screening, an 8-week period for sitagliptin initiation and dose stabilization and sulphonylurea washout was included; for participants taking metformin + sitagliptin at screening, no run-in period was required), a 30-week double-blind treatment period and 2-week follow-up were included (Supporting Information Figure S1). Participants on a fixed-dose combination of a DPP-4 inhibitor and metformin (immediate-release or extended-release) were switched to co-administration of sitagliptin and metformin immediate-release or extended-release as appropriate. Participants were trained to perform self-monitoring of BG using a BG meter and to self-administer insulin subcutaneously. After the run-in period, participants were randomized centrally, using an interactive voice response system, in a 1:1 ratio, to either continue sitagliptin or switch to a placebo matching sitagliptin. All participants initiated insulin glargine (LANTUS, U-100, Sanofi, Bridgewater, NJ, USA) on the evening of the day of randomization with a starting dose of 10 units. Participants were instructed to administer their insulin in the evening at the same time every day.

Participants were instructed to titrate insulin throughout the entire study period, based on their pre-breakfast fasting BG level using an algorithm that targeted a fasting value of 4.0 to 5.6 mmol/L. If, on 3 consecutive days the fasting BG was >5.6 mmol/L but ≤7.8 mmol/L, the insulin dose was increased by 2 units; if fasting BG was >7.8 mmol/L, the insulin dose was increased by 4 units. If the fasting BG was ≤3.9 mmol/L, the insulin dose was reduced by 4 units after consultation with the investigator. Participants were instructed to maintain a hypoglycaemia assessment log that was used to record hypoglycaemia events, including symptoms, and to document associated finger-stick glucose measurements.

The study (MK-0431-845; NCT02738879, EudraCT: 2015–004990-34) was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was obtained from all study participants.

2.3 | Efficacy objectives

All objectives of this study were to assess the effects of continuing sitagliptin relative to discontinuing sitagliptin after 30 weeks. The primary objectives were to assess the change from baseline in HbA1c and the event rate of documented symptomatic hypoglycaemia with BG ≤3.9 mmol/L. "Event rate" was defined as the total number of events (including multiple events in the same participant) divided by the total follow-up time.

Secondary objectives were to assess the incidence of documented hypoglycaemia (with symptoms and regardless of symptoms) with a BG ≤3.9 mmol/L, the event rate and incidence of documented hypoglycaemia (with symptoms and regardless of symptoms) with BG ≤3.1 mmol/L, and daily insulin dose. "Incidence" was defined as the percentage of participants with at least one event. Other secondary objectives were to assess the percentage of participants with HbA1c of <53 mmol/mol (<7.0%), the percentage of participants with the composite endpoint of HbA1c of <53 mmol/mol (<7.0%) without any documented hypoglycaemia (BG ≤3.9 mmol/L), and fasting plasma glucose (FPG) levels.

2.4 | Safety evaluations

Safety assessment included adverse events, changes from baseline in standard laboratory blood chemistry (eg, electrolytes, liver and renal safety tests), lipid panel and vital signs (including systolic and diastolic blood pressure and heart rate) and body weight.

2.5 | Statistical analyses

The population for all efficacy endpoints included all randomized participants who received at least one dose of study treatment and, with the exception of the endpoint of hypoglycaemia, who had at least one measurement of the respective endpoint. Type 1 error was controlled at 0.05 using the method described by Maurer and Bretz[12] (Supporting Information Figure S2). Safety analyses included all randomized and treated participants.

For the analyses of change from baseline in HbA1c, a longitudinal data analysis model[13] was used to evaluate the non-inferiority (margin = 0.3%) and superiority of continuing sitagliptin versus discontinuing sitagliptin. The model included terms for treatment, AHA treatment at screening, time (categorical), and the interactions of time by treatment and of time by AHA treatment at screening. The same model was used to analyse FPG and daily insulin dose.

For event rate analyses related to hypoglycaemia, a negative binomial regression model with a log-link function was used, with the number of events for each participant being the response variable. The model included terms for treatment, race, region, AHA treatment at screening, baseline HbA1c value, baseline body weight, and an offset for follow-up time (on the natural log scale).

For incidence analyses related to HbA1c goals and hypoglycaemia, the Miettinen and Nurminen method[14] was used. For endpoints related to HbA1c goals, missing values at week 30 were imputed as "not at goal". For endpoints related to hypoglycaemia, a missing data imputation method was used as described in the Supporting Information.

A sample size of ~350 participants per treatment group was estimated to provide >99% power to establish that continuing sitagliptin was non-inferior to withdrawing sitagliptin and 93% power for HbA1c superiority, assuming an underlying treatment difference of 0% and −0.3%, respectively. The study had 93% power to detect a rate ratio of 0.6 for documented symptomatic hypoglycaemia events with BG ≤3.9 mmol/L.

3 | RESULTS

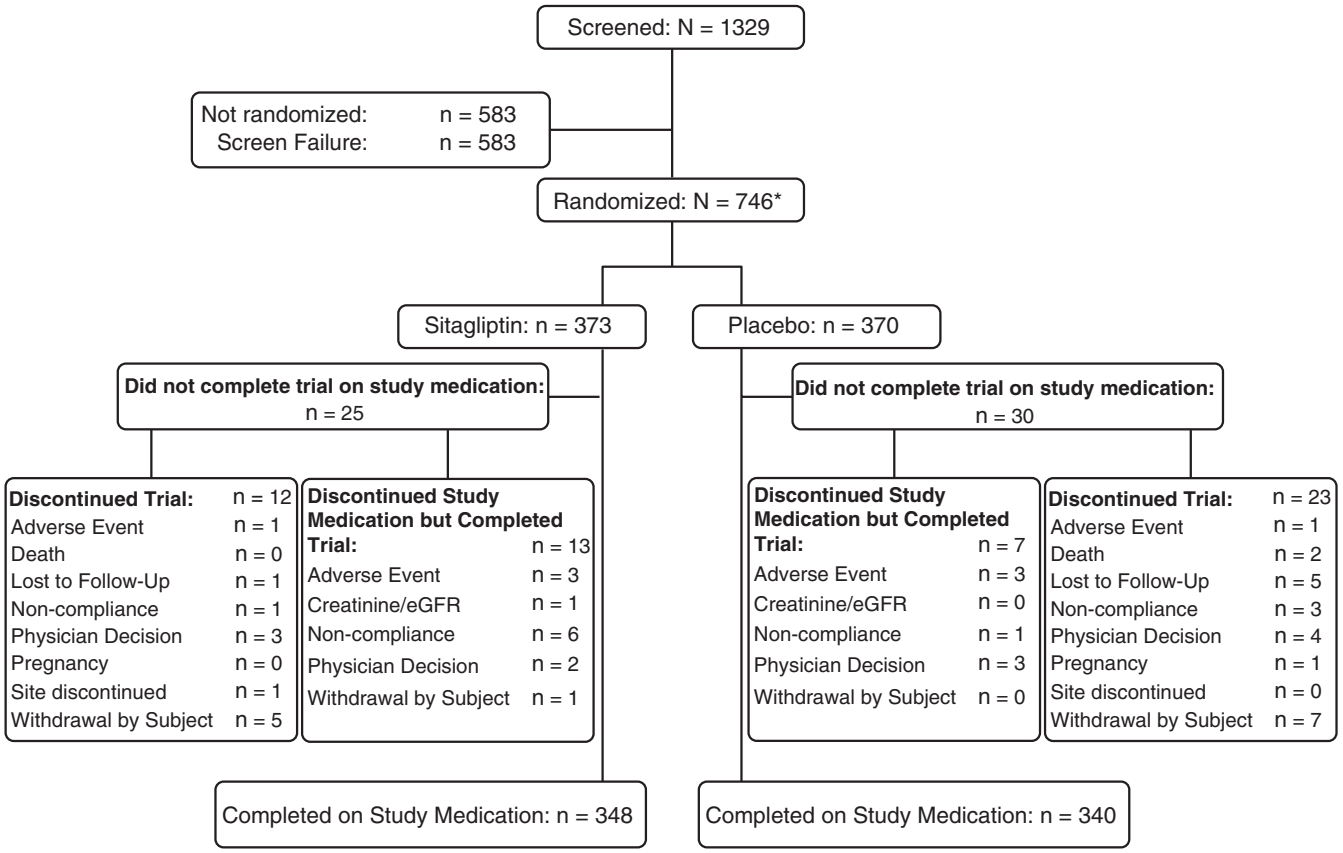
3.1 | Participant disposition and characteristics

A total of 1329 patients were screened, 746 were randomized and 743 were treated (373 continuing sitagliptin and 370 discontinuing sitagliptin [henceforth referred to as the placebo group]); 688 (92.2%) completed the study on study medication (Figure 1). The most common reason for excluding patients at screening was not meeting the prior antihyperglycaemic therapy and HbA1c requirements or meeting exclusionary laboratory values. The study was initiated on 18 May, 2016 and the last visit was on 30 January, 2018.

Baseline demographics and efficacy variables were balanced between treatment groups (Table 1). The participants' mean ± SD age was 58.3 ± 9.6 years, ~50% were female, the mean ± SD baseline HbA1c was 72.6 ± 10.2 mmol/mol (8.8 ± 0.9%), body mass index was 31.1 ± 5.8 kg/m^2, and duration of diabetes was 10.8 ± 6.8 years.

3.2 | Efficacy

After 30 weeks of treatment, the mean ± SD HbA1c achieved and the least squares (LS) mean change from baseline in HbA1c were 51.4 ± 9.0 mmol/mol (6.85% ± 0.83%) and −20.5 mmol/mol (95% confidence interval [CI] −21.6, −19.4; −1.88% [95% CI −1.98, −1.78]), respectively, with sitagliptin, and 56.4 ± 10.4 mmol/mol (7.31% ± 0.95%) and −15.5 mmol/mol (95% CI −16.6, −14.4; −1.42% [95% CI −1.52, −1.32]), respectively, with placebo. The between-group difference in LS



*Three participants were randomized (one in the sitagliptin group and two in the placebo group) but took no study medication.

FIGURE 1 Participant disposition. Abbreviation: eGFR, estimated glomerular filtration rate

mean change from baseline in HbA1c at week 30 was −5.0 mmol/mol (95% CI −6.4, −3.7; −0.46% [95% CI −0.58, −0.34]; $P < 0.001$ [Figure 2A]). Between-group differences in HbA1c were observed by week 6, the first post-randomization measurement (Figure 2A).

The event rate of documented symptomatic hypoglycaemia with BG ≤3.9 mmol/L over 30 weeks was significantly lower in the sitagliptin group compared with the placebo group (event rate ratio = 0.73; $P = 0.039$ [Table 2]). Two participants (both in the sitagliptin group) were excluded from the primary analysis of this endpoint because of missing values for a model covariate (race); in a post hoc analysis of a model in which race was excluded, thereby including the two participants noted above, the event rate ratio was 0.76 ($P = 0.073$). In a post hoc analysis of the time course of hypoglycaemia events by 6-week intervals, which corresponded to scheduled clinic visits (Supporting Information Figure S3), during the initial 6 weeks of insulin titration, when insulin doses were lowest, the event rates were also lowest in both groups. With further insulin titration, the event rates increased in both treatment groups, but were notably lower in the sitagliptin group compared with the placebo group in all but one of the periods (weeks 18-24).

The results of analyses of the primary endpoints (ie, change from baseline in HbA1c at week 30 and event rate of documented symptomatic hypoglycaemia with BG ≤3.9 mmol/mol at week 30) across subgroups defined by baseline HbA1c levels (<75 mmol/mol [<9.0%], ≥75 mmol/mol [≥9.0%]), age, sex, region, and AHA treatment at screening were consistent with the primary analyses (95% CIs for the between-group differences overlapped for all factor levels, Supporting Information Tables S2 and S3).

The first key secondary objective was the assessment of the incidence of documented symptomatic hypoglycaemia with BG ≤3.9 mmol/L over 30 weeks, which was 33.5% in the sitagliptin group and 37.7% in the placebo group, with a between-group difference of −4.1 (95% CI −11.2, 2.9; $P = 0.250$). According to the prespecified testing strategy (Supporting Information Figure S2), subsequent hypotheses were not tested for statistical significance, although nominal P values are provided for descriptive purposes.

All key secondary objectives related to hypoglycaemia had incidences (95% CI) that were similar between the sitagliptin and placebo groups (Table 2). An analysis of the distribution of the total number of episodes of hypoglycaemia (1229 in the sitagliptin group and 1441 in the placebo group) is shown in Supporting Information Table S4.

At week 30, the mean ± SD FPG level was 6.5 ± 1.9 mmol/L in the sitagliptin group and 6.8 ± 2.1 mmol/L in the placebo group; the between-group difference for LS mean change from baseline in FPG was −0.36 mmol/L (95% CI −0.66, −0.06; $P = 0.020$). The maximum reduction in FPG was observed by week 12 and remained generally stable thereafter (Figure 2B). The percentage of participants at week 30 who had FPG within the insulin titration algorithm target FPG range of 4.0 to 5.6 mmol/L was 30.2% in the sitagliptin group and 30.9% in the placebo group. The percentage of participants at HbA1c goal of <53 mmol/mol (<7.0%) was greater in the sitagliptin group (54.2%) compared with the placebo group (35.4%), with a

TABLE 1 Baseline demographic, anthropometric and disease characteristics of study treatment groups, based on all treated patients

	Sitagliptin N = 373	Placebo N = 370
Age, years	58.6 ± 9.5	58.1 ± 9.7
Female, n (%)	203 (54.4)	180 (48.6)
Race, n (%)		
White	258 (69.2)	270 (73.0)
Asian	42 (11.3)	36 (9.7)
Multiple	34 (9.1)	34 (9.2)
American Indian/Alaska native	19 (5.1)	17 (4.6)
Black or African American	12 (3.2)	12 (3.2)
Native Hawaiian or other Pacific islander	6 (1.6)	1 (0.3)
Missing	2 (0.5)	0 (0.0)
Ethnicity, n (%)		
Not Hispanic or Latino	247 (66.2)	239 (64.6)
Hispanic or Latino	122 (32.7)	129 (34.9)
Not reported	4 (1.1)	2 (0.5)
Geographic region, n (%)		
Asia	36 (9.7)	26 (7.0)
Europe	158 (42.4)	172 (46.5)
Latin America	84 (22.5)	82 (22.2)
North America	80 (21.4)	77 (20.8)
Other	15 (4.0)	13 (3.5)
Body weight, kg	84.8 ± 19.8	85.6 ± 18.9
Body mass index, kg/m^2	31.2 ± 5.8	31.1 ± 5.7
HbA1c		
mmol/mol	72.5 ± 9.8	72.7 ± 10.6
%	8.8 ± 0.9	8.8 ± 1.0
FPG, mmol/L	11.0 ± 2.8	11.2 ± 2.9
eGFR, mL/min/1.73 m^2	103.7 ± 30.3	106.4 ± 28.1
Duration of type 2 diabetes, years	10.4 ± 6.8	11.1 ± 6.9
Background medication, n (%)		
Metformin + DPP-4 inhibitor	184 (49.3)	182 (49.2)
Metformin + DPP-4 inhibitor + SU	87 (23.3)	86 (23.2)
Metformin + SU	102 (27.3)	102 (27.6)

Abbreviations: DPP-4, dipeptidyl peptidase; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SU, sulphonylureas.
Values are mean ± SD, unless otherwise indicated.

between-group difference of 18.8 (95% CI 11.6, 25.7; $P < 0.001$). The percentage of participants at HbA1c goal of <53 mmol/mol (<7.0%) without having any episode of documented hypoglycaemia with BG ≤3.9 mmol/L was greater in the sitagliptin group (15.3%) compared with the placebo group (10.0%), with a between-group difference of 5.3 (95% CI 0.5, 10.1; $P = 0.030$).

The LS mean daily insulin dose at week 30 was lower in the sitagliptin group (53.2 units [95% CI 48.5, 58.0]) compared with the placebo group (61.3 units [95% CI 56.5, 66.0]), with a between-group difference of −8.0 (95% CI −14.6, −1.5; $P = 0.016$ [Figure 2C]). The daily insulin dose increased over time in both treatment groups (Figure 2C). At week 6, the daily dose of insulin was higher in the placebo group compared with the sitagliptin group, and remained higher throughout the remainder of the treatment period.

3.3 | Safety and tolerability

The incidences of adverse events, including those assessed by the investigator as drug-related, were similar between the treatment groups (Table 3). Two deaths (both cardiovascular-related) were reported, both in the placebo group. There were no clinically meaningful differences in adverse events between treatment groups.

There were no clinically meaningful findings related to laboratory safety measures or vital signs in either treatment group. At week 30, mean ± SD changes from baseline in body weight were 1.5 kg ± 3.4 (sitagliptin) and 1.7 kg ± 3.9 (placebo).

4 | DISCUSSION

A recent published retrospective study of a healthcare claims database reported that 32% of patients on dual therapy with metformin and a DPP-4 inhibitor discontinued DPP-4 inhibitor therapy within 3 months after initiating insulin.[11] Further analysis of this dataset indicates that ~57% of patients discontinued DPP-4 inhibitor therapy within 12 months of insulin initiation (unpublished data). The reasons for this discontinuation have not been fully elucidated and the impact of this discontinuation on disease management has not been extensively studied.

The present double-blind, randomized study in participants with type 2 diabetes evaluated the efficacy and safety of continuing sitagliptin, compared with discontinuing sitagliptin, when initiating basal insulin therapy. The key results of the study are that continued use of sitagliptin compared with discontinuation did not result in an increase in hypoglycaemia despite a statistically significant and clinically meaningful greater improvement in glycaemic control in patients initiating and intensively titrating basal insulin. The greater proportion of participants achieving an HbA1c target of <53 mmol/mol [<7.0%] and the greater proportion of participants achieving target HbA1c without hypoglycaemia episodes in the sitagliptin group provide additional data to demonstrate the clinically meaningful glycaemic benefits of continuing sitagliptin in this setting.

In the present study the reduction from baseline FPG at week 30 was also greater in the sitagliptin group than in the placebo group, but in neither treatment group did the mean FPG level reach the study target level of 4.0 to 5.6 mmol/L, and only ~30% of participants were at the target level at week 30. Both investigators and participants were instructed to adhere to the insulin titration algorithm, and intensification of insulin therapy was to be limited only by hypoglycaemia events or target achievement. Because the dose of insulin increased throughout the study in both treatment groups, the fact that most participants in both groups did not reach the target FPG range is consistent with uptitration in both groups being limited by a hypoglycaemic event. This result is similar to that observed in another study, in which formulations of insulin glargine were titrated guided by an FPG-based dosing algorithm to a target level of 3.9 to 5.6 mmol/L over 24 weeks[15]; in that study the mean FPG levels achieved were 6.6 and 6.8 mmol/L.

It has been demonstrated that the burden of hypoglycaemia, as assessed by event rate and incidence, increases as insulin is titrated to

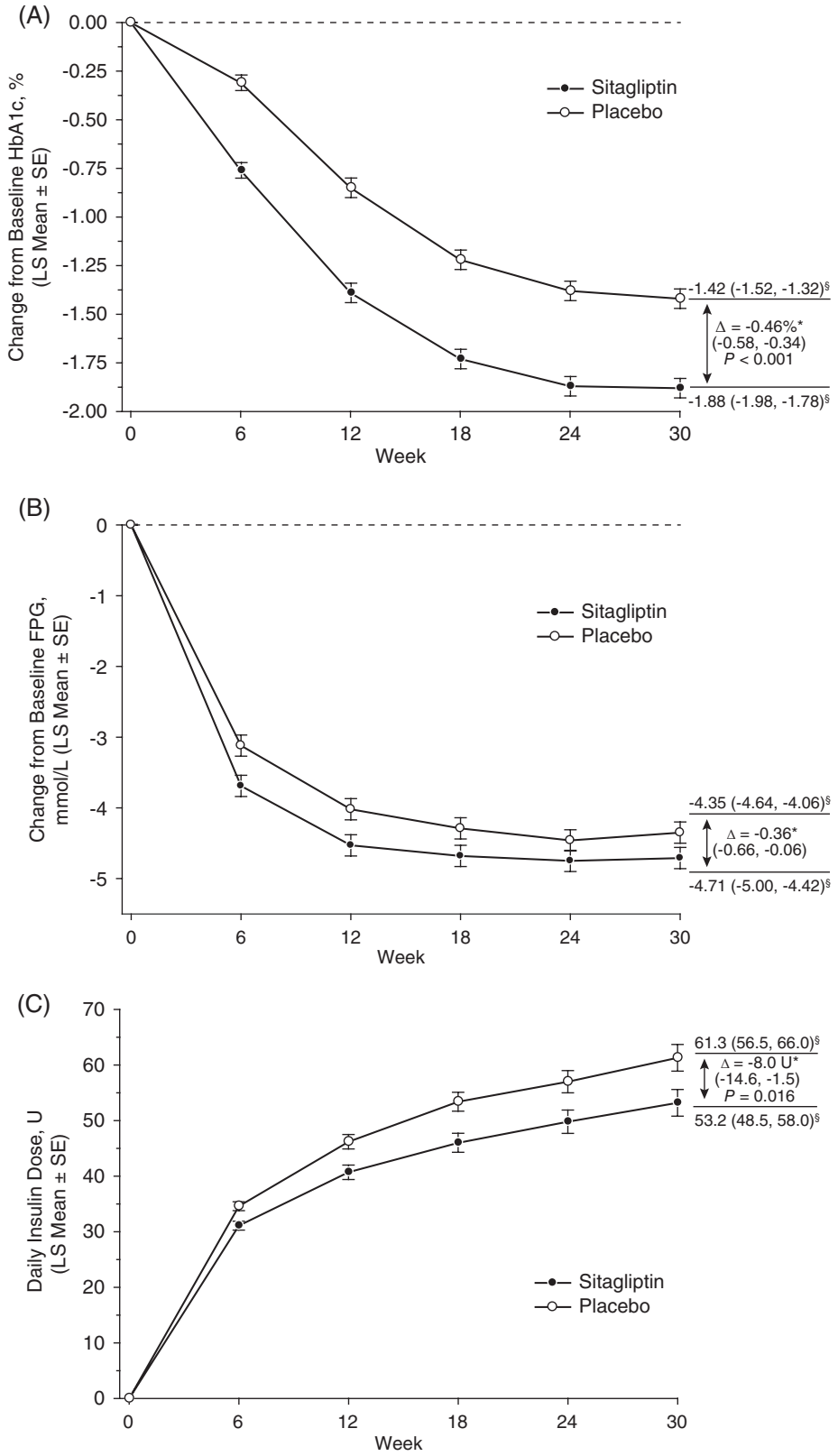


FIGURE 2 Least squares (LS) mean ± SE change from baseline in **A,** glycated haemoglobin (HbA1c), % **B,** fasting plasma glucose (FPG), mmol/L and **C,** daily insulin dose, units (U) up to week 30. Black circles, sitagliptin; open circles, placebo. [§]Least squares (LS) mean (95% confidence interval) change from baseline. [*]Between-group difference and *P* value are model-based

achieve HbA1c ranges consistent with commonly recommended treatment targets.[1,3–6] The present study evaluated event rates and incidences of hypoglycaemia and hypothesized that they might be lower in the group continuing sitagliptin compared with the group discontinuing sitagliptin. While the point estimate of the event rate ratio of documented symptomatic hypoglycaemia with BG ≤3.9 mmol/L over 30 weeks (second primary endpoint) favoured sitagliptin over placebo, the result was only marginally statistically

TABLE 2 Hypoglycaemia endpoints

Hypoglycaemia	Sitagliptin	Placebo	*P*
Documented symptomatic: BG ≤3.9 mmol/L	n = 371	n = 370	
Event rate[a]	1.55 (1.22, 1.96)	2.12 (1.70, 2.66)	
Event rate ratio[b]	0.73 (0.54, 0.98)	––	0.039
Documented symptomatic: BG ≤3.9 mmol/L	n = 373	n = 370	
Incidence[c]	33.5 (28.5, 38.6)	37.7 (32.7, 42.6)	
Difference in percent values[d]	−4.1 (−11.2, 2.9)	––	0.250
Documented symptomatic: BG ≤3.1 mmol/L	n = 371	n = 370	
Event rate[a]	0.17 (0.10, 0.28)	0.22 (0.14, 0.36)	
Event rate ratio[b]	0.76 (0.40, 1.44)	––	0.394[e]
Documented any: BG ≤3.9 mmol/L	n = 373	n = 370	
Incidence[c]	66.8 (61.9, 71.7)	68.0 (63.2, 72.9)	
Difference in percent values[d]	−1.2 (−8.2, 5.8)	––	0.740[e]
Documented symptomatic: BG ≤3.1 mmol/L	n = 373	n = 370	
Incidence[c]	7.6 (4.9, 10.3)	8.3 (5.4, 11.2)	
Difference in percent values[d]	−0.7 (−4.7, 3.2)	––	0.712[e]

Abbreviation: BG, blood glucose; CI, confidence interval.
[a] Estimate of events/participant year (95% CI).
[b] Sitagliptin/placebo (95% CI).
[c] % of participants with one or more events during treatment period + 2 weeks (95% CI).
[d] Sitagliptin – placebo (95% CI).
[e] As the *P* value for the analysis of documented symptomatic hypoglycaemia, BG ≤3.9 mmol/L was >0.05, testing of hypotheses lower in the testing hierarchy could not proceed; therefore this *P* value is presented only to assist in the comprehensive assessment of hypoglycaemia in the study.

TABLE 3 Adverse events summary

	Sitagliptin N = 373 n (%)	Placebo N = 370 n (%)	Difference[a] (95% CI)
Participants with:			
≥ 1 AE	216 (57.9)	222 (60.0)	−2.1 (−9.1, 5.0)
≥ 1 drug-related[b] AE	15 (4.0)	11 (3.0)	1.0 (−1.7, 3.9)
≥ 1 serious AE	14 (3.8)	18 (4.9)	−1.1(−4.2, 1.9)
≥ 1 serious drug-related[b] AE	0 (0.0)	0 (0.0)	0
Participants who died	0 (0.0)	2 (0.5)	−0.5
Participants who discontinued study medication due to:			
An AE	5 (1.3)	6 (1.6)	−0.3 (−2.3, 1.7)
A drug-related[b] AE	1 (0.3)	0 (0.0)	0.3
A serious AE	0 (0.0)	2 (0.5)	−0.5
A serious drug-related[b] AE	0 (0.0)	0 (0.0)	0
With one or more episodes of hypoglycaemia	247 (66.2)	244 (65.9)	0.3 (−6.5, 7.1)
Symptomatic[c]	135 (36.2)	143 (38.6)	−2.5 (−9.4, 4.5)
Severe[d]	11 (2.9)	18 (4.9)	−1.9 (−4.9, 0.9)
Asymptomatic[e]	189 (50.7)	188 (50.8)	−0.1 (−7.3, 7.0)

Abbreviation: AE, adverse event.
[a] Difference in % vs. placebo; estimate was computed only for AE summary and hypoglycaemia endpoints with at least four participants having events in one or more treatment groups.
[b] Assessed by the investigator as related to study drug.
[c] Symptomatic hypoglycaemia: episode with clinical symptoms attributed to hypoglycaemia, without regard to glucose level.
[d] Severe hypoglycaemia: episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure were classified as having required medical assistance, whether or not medical assistance was obtained.
[e] Asymptomatic hypoglycaemia: finger-stick glucose values ≤3.9 mmol/L without symptoms.

significant. The point estimates for all of the secondary endpoints related to hypoglycaemia likewise favoured sitagliptin over placebo, but none was statistically significant. Consistent with the overall study results, in a post hoc analysis, event rates over time increased with the increase in insulin dose in both treatment groups but were lower in the sitagliptin group throughout the study, with the exception of the time period of weeks 18 to 24, when event rates were similar. The lack of statistical significance for the hypoglycaemia-related endpoints may be attributable to the fact that the observed event rate was lower than anticipated, rendering the study underpowered for the assessment of hypoglycaemia. Nevertheless, all available evidence from the study supports the concept that continuing sitagliptin does not increase hypoglycaemia compared with discontinuing sitagliptin, despite attainment of greater glycaemic control.

An alternate approach to evaluation of hypoglycaemia would be to consider that if the changes in HbA1c observed over time in the sitagliptin group were replicated in the placebo group (ie, if glycaemic equipoise between the two groups had been achieved in the study, with both groups achieving a mean HbA1c of 51.4 mmol/mol [6.85%]), one would anticipate that greater rates and incidences of hypoglycaemia would have been observed in the placebo group than were observed in the present study. That robust insulin titration was achieved in this study, as evidenced by the titration to an average of 50 to 60 units during the double-blind treatment period, and the fact that there was greater insulin titration in the placebo group, supports the validity of the comparisons of efficacy and of safety as assessed by hypoglycaemia.

As monotherapy, sitagliptin and other DPP-4 inhibitors do not cause hypoglycaemia because of their glucose-dependent mechanism of action; however, when a DPP-4 inhibitor is added to stable doses of insulin, rates of hypoglycaemia can be affected. In a placebo-controlled study in which sitagliptin was added on to ongoing therapy with a stable dose of insulin (with or without metformin), better glycaemic control was accompanied by a higher event rate (1.06 vs. 0.51 events/participant-year) and incidence (16% vs. 8%; *P* = 0.003) of symptomatic hypoglycaemia with sitagliptin compared to placebo.[16,17] Alogliptin,[18] linagliptin[19] and saxagliptin[20,21] added to stable, ongoing insulin treatment did not increase the risk of hypoglycaemia compared with placebo; vildagliptin addition to stable, ongoing insulin treatment has been reported to be associated with both similar[22] and reduced[23] hypoglycaemia rates compared with placebo. In a different treatment paradigm, in participants with inadequate control on insulin (with or without metformin) in which sitagliptin was added on to basal insulin and insulin was intensively titrated,[24] compared with placebo, a lower

event rate (1.7 vs. 3.6 events/participant-year) and incidence of symptomatic hypoglycaemia (25.2% vs. 36.8%; $P = 0.001$) was observed with sitagliptin compared to placebo.[25] In the present study, which used a clinical treatment paradigm from all previously conducted studies that evaluated the use of DPP-4 inhibitor with insulin in the literature (ie, insulin added on to DPP-4 inhibitor as opposed to DPP-4 inhibitor added on to insulin), the incidence and event rate of hypoglycaemia were similar compared to placebo despite improvements in glycaemic control. Taken together, the results of these studies indicate that it is important to consider how combination therapy with sitagliptin and insulin is initiated when assessing the risk of hypoglycaemia.

Possible mechanisms for the superior glycaemic control without increased hypoglycaemia observed with sitagliptin compared to placebo include the lower dose of insulin used in the sitagliptin group and the DPP-4 inhibitory effect of sitagliptin that stabilizes endogenous GIP. GIP has been demonstrated in preclinical and clinical studies to enhance the glucagon counter-regulatory response during fasting and hypoglycaemic conditions.[7–10] The stabilization of endogenous GIP with a DPP-4 inhibitor may contribute to attenuation of the tendency for insulin-induced hypoglycaemia.

The effects of combination therapy with a DPP-4 inhibitor and insulin on glycaemic control and hypoglycaemia have some analogies to combination therapy with a GLP-1 agonist and insulin. In studies that compared insulin degludec with a fixed ratio of insulin degludec + liraglutide, significant improvements in glycaemic control were observed.[26,27] In one of these studies,[26] in which the baseline HbA1c (72 – 73 mmol/mol [8.7%-8.8%]) was similar to that in the present study, the change from baseline in HbA1c at 26 weeks (21 mmol/mol [−1.92%] in the degludec + liraglutide group) was also similar to the results observed in the present study (−20.5 mmol/mol [−1.88%] in the glargine + sitagliptin group). In the degludec + liraglutide studies, the incidences of hypoglycaemia were either similar between the treatment groups when the insulin doses were equivalent,[26] or lower in the degludec + liraglutide group when the mean insulin dose was lower in that group.[27] Similar findings have been observed with the fixed-ratio combination of glargine + lixisenitide.[28–30] As with DPP-4 inhibitor + insulin therapy, the GLP-1 agonist component or these fixed-ratio combinations might have beneficial glucose-dependent effects on both α-cell (glucagon-secreting) and β-cell (insulin-secreting) function.

In most studies in which DPP-4 inhibitors were added on to insulin, no significant changes from baseline or between-group differences in doses of insulin were observed; however, in those studies, insulin doses were intended to remain stable.[31] In the above-mentioned study in which sitagliptin was added on to insulin therapy, which was then intensively titrated,[24] the increase from baseline in daily insulin dose was smaller in the sitagliptin group compared with the placebo group (19.0 vs. 23.8 units; difference −4.7 [$P = 0.009$]). Similarly, in the present study, the daily insulin dose at week 30 was lower in the sitagliptin group compared with the placebo group.

The present study extends the findings of an open-label, randomized study of patients with type 2 diabetes on stable doses of metformin (>1000 mg/d) and sitagliptin (100 mg/d) who continued or discontinued sitagliptin at the time at which therapy with biphasic insulin aspart 30 twice daily was initiated. In that study, participants who continued on sitagliptin had superior glycaemic control (between-group difference in HbA1c −0.24 [95% CI −0.06, −0.43]; $P = 0.01$), a lower incidence of hypoglycaemia (regardless of symptoms) with BG ≤3.1 mmol/L (25.9% vs. 36.5%) and a greater percentage achieving an HbA1c goal of <53 mmol/mol (<7.0%) (59.8% vs 49.7%).[32]

In a recently published database analysis, it was observed that titration of basal insulin was characterized by substantial treatment inertia in the real world.[33] This may be attributable to the reluctance of patients and physicians to titrate insulin for many reasons, including fear of hypoglycaemia. In the present study, continuation of sitagliptin when initiating and intensively titrating insulin glargine led to participants achieving greater glycaemic control and no evidence of an increased hypoglycaemic burden typically associated with intensifying insulin glargine. The present study provides a high level of evidence (ie, randomized clinical trial data), which can be used to make evidence-based medicine decisions and inform medical society recommendations related to the continuation of oral AHAs (other than metformin) when initiating insulin therapy. The results of this study are anticipated to be useful to clinicians making individualized patient decisions about intensification of treatment for patients with type 2 diabetes when initiating basal insulin therapy.

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CONFLICT OF INTEREST

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Author contributions

R.R., S.D.G., Y.Z., S.S., C.D., R.R.S., G.T.G., R.L.H.L., E.A.O.N., I.G., K.D.K. and S.S.E. are responsible for the work described in this paper. S.D.G., Y.Z., C.D., R.R.S., G.T.G. and S.S.E. conceived, designed and/or planned the study. S.D.G., S.S. and C.D. acquired the data. S.D.G., Y.Z., S.S., G.T.G. and I.G. analysed the data. R.R., S.D.G., Y.Z., G.T.G., R.L.H.L., E.A.O.N., I.G., K.D.K. and S.S.E. interpreted the results. G.T.G., E.A.O.N. and I.G. drafted the manuscript. R.R., S.D.G., Y.Z., S.S., C.D., R.R.S., G.T.G., R.L.H.L., I.G., K.D.K. and S.S.E. critically reviewed and/or revised 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.

Data availability

Merck & Co., Inc.'s data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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SUPPORTING INFORMATION

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

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