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ORIGINAL ARTICLE

Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin uptitration in the treatment of patients with type 2 diabetes: The CompoSIT-M study

Juan P. Frias MD[1] | Zachary Zimmer PhD[2] | Raymond L.H. Lam PhD[2] | Guillermo Amorin Lic[2] | Catherine Ntabadde MPH[2] | Carol Iredale MS[2] | Edward A. O'Neill PhD[2] | Samuel S. Engel MD[2] | Keith D. Kaufman MD[2] | Hideo Makimura MD[2] | Michael F. Crutchlow MD[2]

[1]National Research Institute, Los Angeles, California

[2]MRL, Merck & Co., Inc., Kenilworth, New Jersey

Correspondence
Michael Crutchlow, MD, MRL, Merck & Co., Inc., UG-3CDN004 351 Sumneytown Pike, Upper Gwynedd, PA 19454
Email: michael_crutchlow@merck.com

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Aims: To characterize the glycaemic efficacy and safety of initiation of the dipeptidyl peptidase-4 inhibitor sitagliptin during metformin dose escalation in people with type 2 diabetes (T2D) not at glycated haemoglobin (HbA1c) goal on a sub-maximal dose of metformin.

Materials and methods: Study participants with HbA1c ≥58 mmol/mol and ≤97 mmol/mol (≥7.5% and ≤11.0%) while on 1000 mg/d metformin were randomized to sitagliptin 100 mg once daily or placebo. All were to uptitrate metformin to 2000 mg/d. A longitudinal data analysis model was used to test the primary hypothesis that sitagliptin is superior to placebo when initiated during uptitration of metformin in reducing HbA1c at week 20. [ClinicalTrials.gov Identifier: NCT02791490, EudraCT: 2015-004224-59]

Results: A total of 458 participants (mean HbA1c 71.1 mmol/mol [8.7%], T2D duration 6.3 years) were treated. After 20 weeks, the least squares (LS) mean changes from baseline in HbA1c were −12.1 mmol/mol (−14.0, −10.1) (−1.10% [−1.28, −0.93]) and −7.6 mmol/mol (−9.6, −5.6) (−0.69% [−0.88, −0.51]) with sitagliptin and placebo, respectively; the between-group difference in LS mean changes from baseline HbA1c was −4.5 mmol/mol (−6.5, −2.5) (−0.41% [−0.59, −0.23]); $P < 0.001$. The likelihood of having HbA1c <53 mmol/mol (<7.0%) at week 20 was higher in the sitagliptin group than in the placebo group in the overall population (relative risk 1.7, $P = 0.002$) and in those with a baseline HbA1c ≥69 mmol/mol (≥8.5%) (relative risk 2.4, $P = 0.026$). There were no notable differences between groups with regard to adverse events overall, hypoglycaemia events, changes in body weight or other safety variables.

Conclusion: In participants not at HbA1c goal on a sub-maximal dose of metformin, addition of sitagliptin at the time of metformin dose uptitration improved glycaemic response and HbA1c goal attainment, with similar safety and tolerability, compared to metformin uptitration alone.

KEYWORDS

sitagliptin, metformin, type 2 diabetes, randomised trial

1 | INTRODUCTION

Clinical practice guidelines recommend that hyperglycaemia in patients with type 2 diabetes (T2D) be controlled through a comprehensive management strategy including lifestyle modification and, as needed, pharmacotherapy.[1,2] While glycaemic treatment targets are individualized based on patient-specific considerations, a glycated haemoglobin (HbA1c) concentration of <53 mmol/mol (<7.0%)

is considered a typical treatment target for most patients with T2D, and anti-hyperglycaemic agents (AHAs) are usually initiated and intensified in a stepped-care fashion, based on glycaemic response relative to this goal. Because of its favourable efficacy, safety and cost, metformin is the first-line AHA for most patients with T2D. It is typically initiated at 500-1000 mg/d, with dose escalations occurring as required, based on HbA1c re-assessments, up to doses of 2000 to 2500 mg/d.[2] If dose uptitration of metformin monotherapy does not result in HbA1c goal attainment, one or more other AHAs are added.

This stepped-care approach can substantially delay HbA1c goal attainment in patients who ultimately require two or more AHAs for optimal glycaemic control. A recent analysis of observational data in the United Kingdom indicated that only 25% of patients with T2D with HbA1c ≥53 mmol/mol (≥7.0%) received treatment intensification within 12 months.[3] Further, the likelihood of attaining glycaemic control was significantly lower for patients with delayed intensification. More aggressive approaches may therefore be considered in patients who are well above their HbA1c goal. Clinical practice guidelines recommend that initial treatment with two AHAs be considered for patients presenting with an HbA1c level well above target. For example, HbA1c thresholds for initiation of dual therapy of 58 mmol/mol (7.5%) and 75 mmol/mol (9.0%) have been recommended by the American Association of Clinical Endocrinologists and the American Diabetes Association/European Association for the Study of Diabetes, respectively.[1,2] However, practice recommendations do not yet provide guidance regarding an optimal approach to treatment intensification for patients who are well above their HbA1c target on metformin monotherapy at a sub-maximal dose. For some such patients, it may be reasonable to consider initiation of a second AHA in parallel with, instead of following, metformin dose escalation.

Dipeptidyl peptidase-4 (DPP-4) inhibitors block DPP-4-mediated degradation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, thereby promoting glucose-dependent insulin secretion and improved glucose control. Sitagliptin is among the DPP-4 inhibitors approved for the treatment of T2D as monotherapy and in combination with other AHAs.[4] When used in combination with metformin, sitagliptin provides clinically meaningful improvement in glycaemic control and is generally well tolerated, without body weight gain or increased incidence of hypoglycaemia[5–8]; however, these studies have evaluated sitagliptin as add-on therapy to patients on stable doses of metformin, or as initial co-administration with metformin.

The present study, CompoSIT-M (Comparison of SITagliptin vs. placebo during Metformin uptitration), was designed to characterize, in participants with T2D who were not at HbA1c goal on a sub-maximal dose of metformin, the glycaemic efficacy and safety of metformin dose uptitration, with and without simultaneous initiation of sitagliptin.

2 | METHODS

2.1 | Study population

Eligible study participants were men and women, aged ≥18 years, with T2D, with a body mass index of ≥18 kg/m^2, and either not on any AHA for ≥8 weeks (≥12 weeks if previously taking thiazolidinediones) with HbA1c ≥69 mmol/mol and ≤108 mmol/mol (≥8.5% and ≤12.0%), or on a stable (≥8 weeks) monotherapy regimen of immediate release (IR) or extended release (XR) metformin at a dose of 1000 mg/d, a sulphonylurea, a glinide, or an α-glucosidase inhibitor, with an HbA1c ≥58 mmol/mol and ≤97 mmol/mol (≥7.5% and ≤11.0%). After a 6- to 10-week metformin IR stabilization period, all participants had an HbA1c ≥58 mmol/mol and ≤97 mmol/mol (≥7.5% and ≤11.0%) prior to the start of a 2-week placebo run-in before randomization, and a fasting finger-stick glucose level >6.7 mmol/L and <15.0 mmol/L at randomization.

Participants were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, significant cardiovascular disease, a history of malignancy, or use of any AHA other than as described above. Participants were also excluded for any history of intolerance or hypersensitivity to DPP-4 inhibitors or metformin, including individuals taking metformin 1000 mg/d but with evidence of intolerance to that dose or prior intolerance to a higher dose. Laboratory exclusion criteria included: estimated glomerular filtration rate <60 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease formula[9]); serum alanine aminotransferase or aspartate aminotransferase levels >2 times the laboratory upper limit of normal; haemoglobin <110 g/L (men) or <100 g/L (women); thyroid-stimulating hormone level outside the central laboratory normal range; and triglycerides >6.8 mmol/L.

Written informed consent was obtained from all study participants.

2.2 | Study design

The study was a multinational, double-blind, randomized, placebo-controlled clinical trial, and included the following: a ≤2-week screening period; a period after completion of screening to allow glycaemic stabilization on metformin IR 1000 mg/d (500 mg twice daily) which was ≥10, ≥8 or ≥6 weeks for those on no AHA at screening, those transitioning to metformin IR from a non-metformin AHA, and those already taking 1000 mg/d metformin (IR or XR) at screening, respectively; a 2-week single-blind placebo run-in period; a 20-week double-blind treatment period; a post-treatment telephone call ~2 weeks after the final dose of study medication (Figure 1).

After the placebo run-in period, participants were randomized centrally, using an interactive voice response system, in a 1:1 ratio to sitagliptin or matching placebo. Randomization was stratified based on the participants' use of AHAs at screening (not on AHA; on permissible non-metformin AHA; on metformin IR or metformin XR 1000 mg/d). All participants were to increase the dose of IR to 1500 mg/d (1000 mg morning, 500 mg afternoon) on the day of randomization and to 2000 mg/d (1000 mg twice daily) on day 8. Any participant unable to tolerate metformin IR 1000 mg twice daily by week 6 was to continue on the highest dose of metformin IR they had tolerated for the remainder of the study. Clinic visits occurred at screening, prior to the metformin IR stabilization period (8-12 weeks pre-randomization), prior to the placebo run-in (2 weeks pre-randomization), randomization (week 0) and weeks 6, 14 and 20 post-randomization. Telephone contacts occurred 9 days after randomization to confirm appropriate uptitration of metformin IR, and 14 days after the last dose of study medication.

During the 20-week double-blind study period, participants with fasting plasma glucose (FPG) measurements consistently greater than

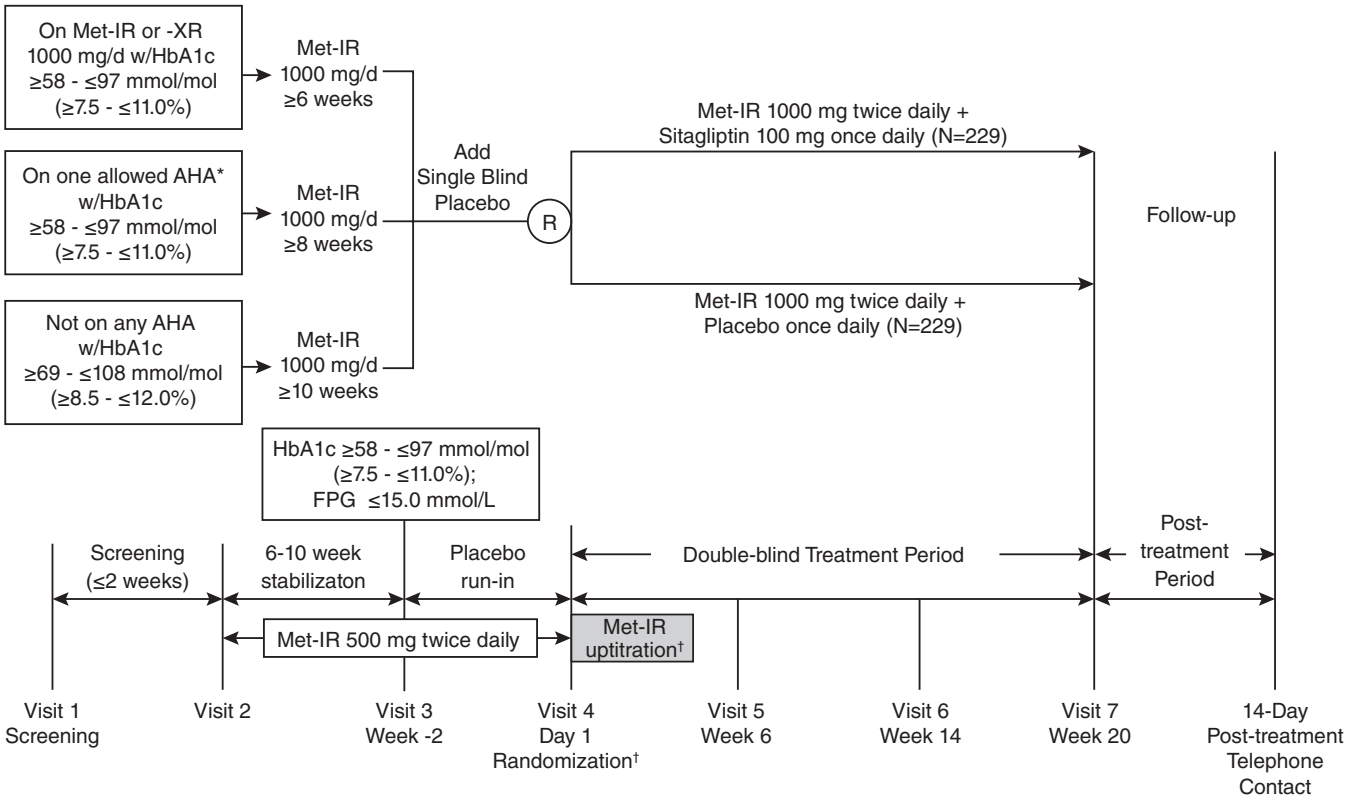

FIGURE 1 Study design. AHA, anti-hyperglycaemic agent; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; Met-IR, metformin immediate release; Met-XR, metformin extended release. *Allowable AHAs at visit 1/screening: α-glucosidase inhibitors, glinides or sulphonylureas. †Begin 1500 mg Met-IR at visit 4/randomization. Met-IR uptitration to 2000 mg/d at ~7 days post-randomization

specified thresholds (FPG >15 mmol/L after randomization and through week 6; FPG >13.3 mmol/L after week 6) were to receive glycaemic rescue therapy while also continuing double-blind study medication. The specific rescue therapy was determined by the investigator but could not include a DPP-4 inhibitor or an increase in the metformin dose.

The study (MK-0431-848; NCT02791490, EudraCT: 2015-004224-59) was conducted in accordance with the principles of Good Clinical Practice and approved by the appropriate institutional review boards and regulatory agencies.

2.3 | Study evaluations

All objectives of this study were to compare the effects of metformin uptitration plus the addition of sitagliptin to those of metformin uptitration alone after 20 weeks of treatment. The primary objectives were to compare (a) the reduction from baseline in HbA1c and (b) overall safety and tolerability. Secondary objectives were to compare (a) the percentage of participants at the HbA1c goal of <53 mmol/mol (<7.0%), (b) the reduction from baseline in FPG, (c) the percentage of participants with baseline HbA1c ≥69 mmol/mol (≥8.5%) at the HbA1c goal of <53 mmol/mol (<7.0%), and (d) the percentage of participants who received glycaemic rescue therapy. Hypotheses were that HbA1c reduction (primary), the proportion at HbA1c goal of <53 mmol/mol (<7.0%) (secondary), and FPG reduction (secondary) would be greater with uptitration of metformin plus the addition of sitagliptin compared to uptitration of metformin alone.

2.4 | Efficacy assessments

Measurements of HbA1c and FPG were collected at the screening visit, prior to the placebo run-in, at baseline (pre-dose on the day of randomization) and at 6, 14 and 20 weeks after randomization.

2.5 | Safety assessments

Adverse events (AEs) were collected at all study visits and during telephone contacts. Protocol-specified safety assessments included physical examinations (week −2 and week 20), body weight (all visits), heart rate and blood pressure measurements (screening and all visits from week −2 to week 20), clinical chemistries (screening, week −2, randomization and week 20) and serum lipids (randomization and week 20). Routine haematology panel and urine dipstick were performed at screening and a 12-lead ECG was performed at week −2. Urine or serum pregnancy tests were performed for women of child-bearing potential at screening and all study visits between randomization and week 20. Documented symptomatic hypoglycaemia was defined as symptoms consistent with hypoglycaemia and a concurrent glucose measurement of ≤3.9 mmol/L. Severe hypoglycaemia was defined as an episode of confirmed or suspected hypoglycaemia which required the assistance of another individual for recovery, regardless of whether such assistance was obtained.

2.6 | Statistical analyses

The primary analysis population for all efficacy endpoints included all randomized participants who received at least one dose of double-blind study medication and had a baseline or post-baseline observation for the analysis endpoint. Safety analyses included all randomized participants who received at least one dose of double-blind study medication. Efficacy analyses excluded data collected after the initiation of glycaemic rescue therapy or after sustained use (defined as >7, not necessarily consecutive, days) of prohibited AHAs (any AHA other than metformin and double-blind study medication). All safety analyses except hypoglycaemia included all data collected, including events that occurred after rescue. For analyses of hypoglycaemia, data collected after the initiation of glycaemic rescue therapy were excluded. Safety analyses included data collected from initiation of treatment up to the 2-week post-treatment follow-up period for AEs and hypoglycaemia, and up to 5 days post-treatment for laboratory endpoints and vital signs. Efficacy analyses included data collected up to 5 days after the last dose of study medication.

For the analyses of change from baseline in HbA1c, a longitudinal data analysis model[10] was used, including terms for treatment (sitagliptin or placebo), AHA status at screening, time (categorical), and the interactions of time by treatment and of time by AHA status at screening, with a constraint that the true mean at baseline is common to both treatment groups within each AHA status group at screening (which is valid as a result of randomization). The same model was used to analyse change from baseline FPG. For the analysis of percentages of individuals at an HbA1c goal, participants were categorized as at goal or not at goal based on observed data (if available); missing data at week 20 were imputed using the longitudinal data analysis model described above. All estimated relative risks, *P* values, and confidence intervals (CIs; HbA1c goal only) and between-group differences in proportion and CIs for efficacy endpoints and safety evaluations were computed based on the Miettinen and Nurminen method.[7]

A sample size of 190 randomized participants per group (total enrolment of 380 participants) was estimated to provide 93% power to establish that uptitration of metformin plus the addition of sitagliptin is superior to uptitration of metformin alone in lowering HbA1c at $\alpha = 0.05$ (two-sided), assuming an underlying treatment difference of −4.4 mmol/mol (−0.4%). As a result of an unexpectedly large number of participants screened at the end of the recruitment period, the number of participants randomized was 458 (229 per group). Based on a post hoc power calculation performed to provide information regarding the impact of over-enrolment, power with the actual sample size was 96%, given the same assumptions used for the original power calculations (except for sample size).

The study-wise type I error rate was controlled at $\alpha = 0.05$ (two-sided) using an ordered testing procedure. First the change from baseline in HbA1c was tested. If the success criterion for HbA1c was met, the first secondary hypothesis for HbA1c goal of <53 mmol/mol (<7.0%) at week 20 would be tested. If the success criterion for the first secondary hypothesis was met, then the second secondary hypothesis for FPG was tested. All three tests were conducted at $\alpha = 0.05$ (two-sided).

3 | RESULTS

3.1 | Patient disposition and characteristics

The study was conducted at 68 sites in eight countries (a list of investigators can be found in Table S1) and was initiated on 21 June 2016 and completed on 1 February 2018. A total of 1100 patients were screened and 458 were randomized.

Baseline demographics and disease characteristics were generally balanced between the treatment groups (Table 1). The mean age of patients in the study was 55.5 years, 60.0% were female, mean body mass index was 31.3 kg/m^2, mean HbA1c was 71.1 mmol/mol (8.7%) and mean duration of T2D was 6.3 years. At screening, 77.9% of participants were taking metformin 1000 mg/d, 15.9% were on no AHA and 6.1% were on a single non-metformin AHA.

Of the 229 participants uptitrating metformin plus sitagliptin (henceforth referred to as the sitagliptin group) and the 229 uptitrating metformin alone (henceforth referred to as the placebo group), a total of 447 (97.6%) completed the study (226 [98.7%] in the sitagliptin group and 221 [96.5%] in the placebo group); and 439 (95.9%) completed the study on blinded study medication (223 [97.4%] in the sitagliptin group and 216 [94.3%] in the placebo group). Reasons for discontinuation from the study were similar in the two groups, with withdrawal by participant choice being the most common (Figure S1). Reasons for withdrawal from study medication were also similar between groups, but more varied (Figure S1). Over 97% of all study participants increased their metformin dose from 1000 mg/d (500 mg twice daily) at randomization to 2000 mg/d (1000 mg twice daily) by 15 days post-randomization as required per protocol, and 94.1% (92.1% on sitagliptin and 96.1% on placebo) were taking 1000 mg twice daily metformin at study completion.

3.2 | Efficacy

After 20 weeks of treatment, the least squares (LS) mean change from baseline in HbA1c was significantly greater with sitagliptin (−12.1 mmol/mol [95% CI −14.0, −10.1] [−1.10% {95% CI −1.28, −0.93}]) compared with placebo (−7.6 mmol/mol [95% CI −9.6, -5.6] [−0.69% {95% CI −0.88, −0.51}]; Table 2 and Figure 2A); the between-group difference was −4.5 mmol/mol (95% CI −6.5, −2.5) (−0.41% [95% CI −0.59, −0.23]); $P < 0.001$. HbA1c decreased from baseline in both groups by week 6, and the extent of HbA1c reduction was greater in the sitagliptin than the placebo group at all post-randomization time points (Figure 2A). As HbA1c was stable from weeks 14 to 20 in the sitagliptin group, but continued to trend downward in the placebo group, the between-group difference in HbA1c response diminished somewhat between week 14 (−6.5 mmol/mol [95% CI −8.3, −4.7] [−0.60% {95% CI −0.76, −0.43}]) and week 20. Between-treatment differences in the HbA1c response in subgroups defined by baseline HbA1c, age, gender and AHA status at screening were generally consistent with those observed in the overall population (Figure S2).

The proportion of participants at HbA1c <53 mmol/mol (<7.0%) after 20 weeks was greater with sitagliptin than with placebo in the overall study population (28.8% vs. 16.6%; relative risk of 1.7 [95% CI 1.2, 2.5]; $P = 0.002$) as well as in the subgroup with baseline HbA1c ≥69 mmol/mol (≥8.5%) (15.6% vs. 5.7%; relative risk of 2.4 [95% CI

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

Characteristic	Sitagliptin N = 229	Placebo N = 229
Age, y	55.6 ± 10.5	55.3 ± 10.4
Female, n (%)	139 (60.7)	136 (59.4)
Race, n (%)		
White	167 (72.9)	155 (67.7)
Multiple	31 (13.5)	39 (17.0)
American-Indian/Alaska native	23 (10.0)	27 (11.8)
Black or African-American	8 (3.5)	7 (3.1)
Asian	0 (0.0)	1 (0.4)
Ethnicity, n (%)		
Hispanic or Latino	147 (64.2)	151 (65.9)
Not Hispanic or Latino	78 (34.1)	70 (30.6)
Not reported/unknown	4 (1.7)	8 (3.5)
Geographic region, n (%)		
Americas	181 (79.0)	186 (81.2)
Europe	48 (21.0)	43 (18.8)
Duration of T2D, y	6.4 ± 5.7	6.3 ± 6.2
Body weight, kg	83.7 ± 19.0	83.4 ± 22.8
BMI, kg/m^2	31.3 ± 5.5	31.2 ± 7.0
HbA1c, mmol/mol	70.9 ± 10.1	71.4 ± 10.6
HbA1c, %	8.6 ± 0.9	8.7 ± 1.0
Baseline HbA1c ≥69 mmol/mol (≥8.5%), n (%)	122 (53.3)	122 (53.3)
FPG, mmol/L[a]	10.1 ± 2.3	10.2 ± 2.5
eGFR, mL/min/1.73 m^2	116.1 ± 34.8	115.3 ± 34.9
AHA status at screening[b], n (%)		
Not on an AHA	36 (15.7)	37 (16.2)
On non-metformin AHA	15 (6.6)	13 (5.7)
On metformin IR or metformin XR 1000 mg/d	178 (77.7)	179 (78.2)

Abbreviations: AHA, anti-hyperglycaemic agent; BMI, body mass index; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IR, immediate release; T2D, type 2 diabetes; XR, extended release.
Values are mean ± SD, unless otherwise indicated.
[a] To convert to mg/dL multiply mmol/L value by 18.
[b] One participant, enrolled in error, was on both metformin and a sulphonylurea at screening and is included in the "On metformin IR or metformin XR 1000 mg/d" row.

1.1, 5.3]; P = 0.026 [Table 2 and Figure 2B]). There was also a greater decrease in FPG after 20 weeks in the sitagliptin group, with a between-group difference in change from baseline in FPG of −0.7 mmol/L (95% CI −1.1, −0.3; P = 0.002 [Table 2 and Figure 2C]). The proportion of participants receiving glycaemic rescue therapy during the study was low in both treatment groups (Kaplan-Meier estimate 1.4% [95% CI 0.4, 3.6] and 3.2% [95% CI 1.4, 6.2] in the sitagliptin and placebo groups, respectively).

3.3 | Safety and tolerability

The incidences of AEs, including those assessed by the investigator as being related to study medication, were similar in the two treatment groups (Table 3). No deaths were reported during the study. The incidence of serious AEs (SAEs) was low and similar in the two groups and no drug-related SAEs were reported. The incidences of specific AEs by system organ class for which ≥4 AEs were reported in at least one treatment group were also generally similar in the two groups (Table S2). The only specific AEs for which the 95% CI for the between-group difference in incidence excluded zero were dyspepsia and tonsillitis, which were both reported at higher incidences in the placebo group. There were no notable changes from baseline or between-group differences in blood pressure, heart rate, body weight, routine chemistry or lipid analyses. The observed incidence of documented symptomatic hypoglycaemia events was low in both groups and the 95% CI for the between-group difference in incidence included zero (difference 1.7 [95% CI −0.8, 4.8]; Table 3). No severe hypoglycaemia events were reported in the study.

4 | DISCUSSION

This study assessed glycaemic response over 20 weeks of treatment in individuals with T2D not at glycaemic target (HbA1c <7.0%) on a stable, sub-maximally efficacious dose of metformin (1000 mg/d), who underwent metformin dose escalation with or without simultaneous initiation of sitagliptin (100 mg/d). The primary and secondary efficacy hypotheses of glycaemic superiority of sitagliptin compared with placebo in this treatment intensification scenario were met, with no meaningful differences in the incidence of AEs or documented symptomatic hypoglycaemia and without body weight gain. These results are consistent with the extensive body of data demonstrating that sitagliptin effectively and safely improves glycaemic control when used in combination with metformin.[5–8]

From a patient management perspective, the observed response to metformin dose escalation alone is notable. Although increasing the dose of metformin from 1000 to 2000 mg/d resulted in a clinically meaningful reduction from baseline HbA1c of 7.6 mmol/mol (0.69%), glycaemic goal attainment was poor, with only approximately one in six participants (16.6%) in the overall population, and one in 18 participants (5.7%) in the sub-population with baseline HbA1c ≥69 mmol/mol (≥8.5%), achieving HbA1c <53 mmol/mol (<7.0%). Two previous 24-week studies assessed HbA1c responses to the same metformin dose increase (from 1000 to 2000 mg/d) as that assessed in the present study. Filozof et al.[11] reported HbA1c reduction of 0.37% from a baseline of 7.3%, with 43.5% of participants at HbA1c of <7.0%, and Weissman et al. reported HbA1c reduction of 0.71% from a baseline of 7.97%, with 48.4% of participants at HbA1c of <7.0%.[12] The higher percentage of participants at HbA1c goal reported in these studies compared with the present study may be largely attributable to the lower baseline HbA1c levels in the earlier studies (7.3% and 7.97%) than in the present study (8.7%). However, the similar rate of HbA1c goal attainment in these two prior studies is surprising given their substantial baseline HbA1c differences and may reflect differences in what is often observed as a "trial effect". Collectively, these two studies and the present study illustrate that the potential for metformin dose uptitration to result in HbA1c goal attainment is substantially determined by proximity to the HbA1c target at the time of dose uptitration. Future analyses of data from the present study may better

TABLE 2 Efficacy endpoints at week 20

Parameter	Sitagliptin	Placebo
HbA1c	***N* = 229**	***N* = 229**
Baseline, mmol/mol (%)	70.9 ± 10.1 (8.6 ± 0.9)	71.4 ± 10.6 (8.7 ± 1.0)
Week 20, mmol/mol (%)	59.6 ± 12.5 (7.6 ± 1.1)	63.2 ± 12.4 (7.9 ± 1.1)
Change from baseline[a], mmol/mol (%)	−12.1 (−14.0, −10.1)	−7.6 (−9.6, −5.6)
	(−1.10 [−1.28, −0.93])	(−0.69 [−0.88, −0.51])
Change vs. placebo[b], mmol/mol (%)	−4.5* (−6.5, −2.5)	—
	(−0.41* [−0.59, −0.23])	—
HbA1c < 53 mmol/mol (<7.0%) at Week 20		
Overall population	***N* = 229**	***N* = 229**
% (*n*)	28.8 (66)	16.6 (38)
Difference vs. placebo	12.9 (4.9, 20.9)	—
Relative risk (95% CI)	1.7** (1.2, 2.5)	—
Baseline HbA1c ≥69 mmol/mol (≥8.5%)	***N* = 122**	***N* = 122**
% (*n*)	15.6 (19)	5.7 (7)
Difference vs. placebo	9.5 (1.2, 18.1)	—
Relative risk (95% CI)	2.4*** (1.1, 5.3)	—
FPG[c], mmol/L	***N* = 229**	***N* = 229**
Baseline	10.1 ± 2.3	10.2 ± 2.5
Week 20	8.6 ± 2.4	9.1 ± 2.6
Change from baseline[a]	−1.6 (−2.1, −1.2)	−0.9 (−1.4, −0.5)
Change vs. placebo[b]	−0.7** (−1.1, −0.3)	—

Abbreviation: FPG, fasting plasma glucose. Values are mean ± standard deviation unless otherwise noted.
[a] Least squares (LS) mean (95% CI).
[b] Difference in LS means (95% CI).
[c] To convert to mg/dL multiply mmol/L value by 18.
*$P < 0.001$.
**$P = 0.002$.
***$P = 0.026$.

delineate the relationship between baseline HbA1c and the likelihood of glycaemic goal attainment with metformin dose uptitration alone to clarify the patient population most appropriate for initiation of a second AHA prior to metformin dose uptitration.

In the context of the present study, an additional patient management consideration is clinical or therapeutic inertia, i.e. the failure to initiate or intensify therapy when indicated. This is a common, long-recognized factor limiting HbA1c goal attainment in many patients with T2D, attributed to multiple clinician-related factors including lack of treatment target awareness and concerns regarding patient adherence and potential for medication side effects.[13–18] Multiple studies, including those in patients on metformin monotherapy, have demonstrated median delays in excess of 1 year to appropriate treatment intensification for patients with T2D not at HbA1c goal.[19] Given its multifactorial nature, clinical inertia is a challenging issue to address; however, safe, effective and convenient treatment-intensification strategies should be enabling in this regard. Given the favourable efficacy and safety results of the present study, sitagliptin addition at the time of metformin dose uptitration may be an appropriate treatment-intensification strategy for many patients. Approaches such as this for initiating appropriately aggressive treatment strategies in a timely fashion have the potential to address clinical inertia effectively and accelerate HbA1c goal attainment. This is of particular importance in the context of treatment with medications that require dose titration. Reassessment of the likelihood of goal attainment in a dynamic manner, during the dose escalation process, can reduce patients' overall hyperglycaemic burden.

Strengths of the present study include the randomized, double-blind design, the high completion rate and the high degree of adherence to protocol-mandated metformin uptitration. Additionally, the study used broad enrolment criteria, resulting in a study population generally representative of the T2D population receiving metformin, although there was minimal enrolment of black or Asian participants. The study was limited by assessment focused only on early initiation with sitagliptin at the time of metformin uptitration. Given the clinical profile similarities across the DPP-4 inhibitor drug class, other members of the same drug class may well have similar effects, and use of other AHA classes may also be beneficial in this treatment paradigm. Future studies on other AHAs would help to clarify optimal patient-specific treatment-intensification options in this scenario.

In summary, sitagliptin was both efficacious and well tolerated when initiated simultaneously with metformin dose escalation, compared with the more conservative approach of metformin dose escalation alone. These data indicate that early initiation of sitagliptin may be a safe and effective treatment-intensification strategy for many patients with T2D who are not at HbA1c goal on a sub-maximal dose of metformin. Early initiation of sitagliptin may therefore effectively

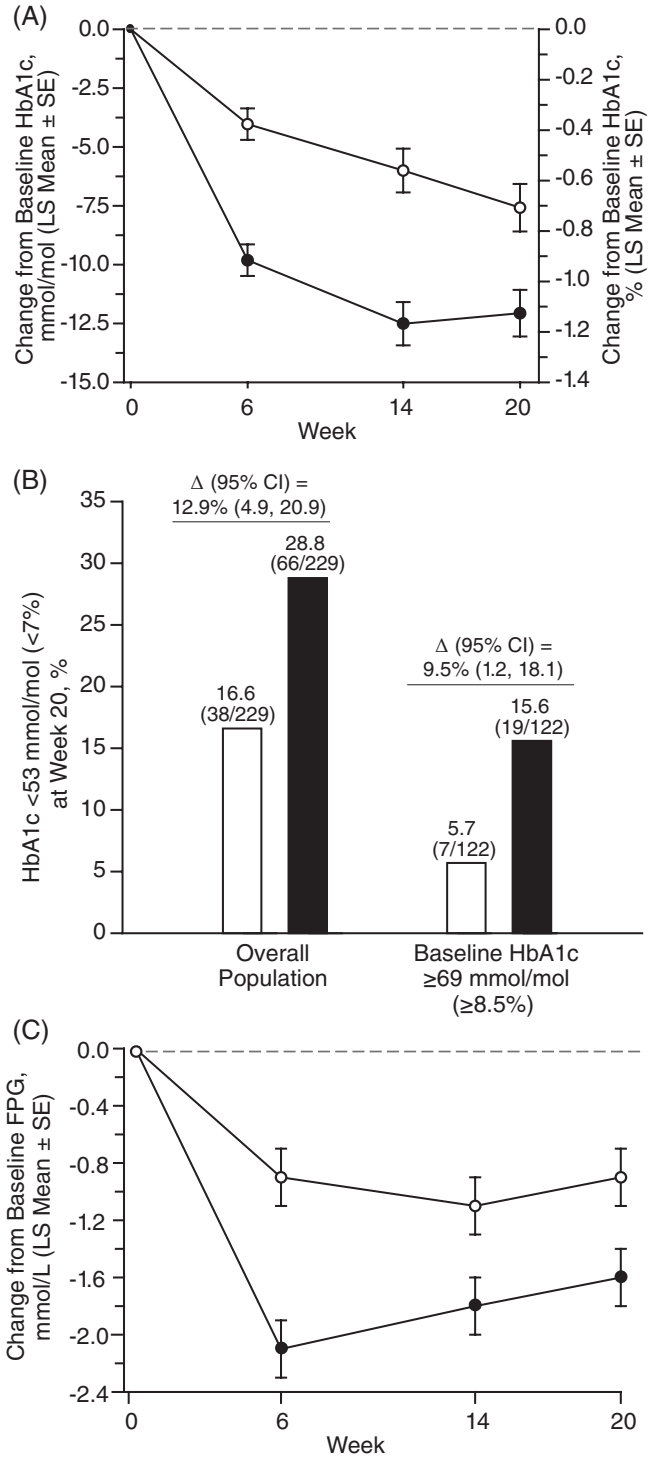

FIGURE 2 Glycaemic efficacy endpoints. Open circles = metformin uptitration + placebo; filled circles = metformin uptitration + sitagliptin. Data in all figures were calculated using the longitudinal data analysis model as described in methods. A, Least squares (LS) mean ± SE change from baseline glycated haemoglobin (HbA1c); B, Percentage of participants at HbA1c <7.0% at week 20 and percentage of participants with baseline HbA1c ≥8.5% at HbA1c <7.0% at week 20. C, LS mean ± SE change from baseline fasting plasma glucose (FPG). RR, relative risk

address clinical inertia and speed HbA1c goal attainment for many patients who are unlikely to achieve target glycaemic control through metformin dose uptitration alone.

TABLE 3 Adverse events and hypoglycaemia summary

Participants, n (%)	Sitagliptin N = 229	Placebo N = 229	Difference[a]
With one or more			
AEs	101 (44.1)	105 (45.9)	−1.7 (−10.8, 7.4)
Drug-related[b] AEs	3 (1.3)	1 (0.4)	0.9
Serious AEs	3 (1.3)	4 (1.7)	−0.4 (−3.3, 2.2)
Serious drug-related[b] AEs	0 (0.0)	0 (0.0)	0
Who died	0 (0.0)	0 (0.0)	0
Who discontinued study medication due to			
An AE	2 (0.9)	0 (0.0)	0.9
A drug-related[b] AE	0 (0.0)	0 (0.0)	0
A serious AE	2 (0.9)	0 (0.0)	0.9
A serious drug-related[b] AE	0 (0.0)	0 (0.0)	0
With one or more episodes of documented symptomatic hypoglycaemia[c]	6 (2.6)	2 (0.9)	1.7 (−0.8, 4.8)
Severe[d]	0 (0.0)	0 (0.0)	0

Abbreviations: AE, adverse event; CI, confidence interval.

[a] Difference in % vs placebo; estimate (95% CI) 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] Documented symptomatic: episode with clinical symptoms attributed to hypoglycaemia with a documented plasma glucose concentration of ≤3.9 mmol/L.

[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.

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CONFLICTS OF INTEREST

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Author contributions

J.P.F., Z.Z., R.L.H.L., G.A., C.N., C.I., E.A.O.N., S.S.E., K.D.K., H.M. and M.F.C. are responsible for the work described in this paper. C.I., S.S.E., K.D.K. and M.F.C. conceived, designed, and/or planned the study. J.P.F., G.A., C.N., C.I. and H.M. acquired the data. Z.Z., R.L.H.L., G.A., E.A.O.N. and H.M. analysed the data. J.P.F., Z.Z., R.L.H.L., G.A., S.S.E.,

K.D.K. and M.F.C. interpreted the results. Z.Z., G.A., E.A.O.N. and M.F.C. drafted the manuscript. J.P.F., R.L.H.L., G.A., C.N., C.I., S.S.E., K.D.K. and H.M. 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.msd.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.

ORCID

Juan P. Frias https://orcid.org/0000-0001-9486-1255
Samuel S. Engel https://orcid.org/0000-0002-4439-6356
Michael F. Crutchlow https://orcid.org/0000-0002-9686-9047

REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. *Endocr Pract*. 2018;24:91-120.
3. Desai U, Kirson NY, Kim J, et al. Time to treatment intensification after monotherapy failure and its association with subsequent glycemic control among 93,515 patients with type 2 diabetes. *Diabetes Care*. 2018;41:2096-2104.
4. U.S. prescribing information for JANUVIA (sitagliptin) Tablets, 2006 [updated 02/2018]. http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf. Accessed August 8, 2018.
5. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab*. 2011;13:160-168.
6. Brazg R, Xu L, Dalla MC, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:186-193.
7. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006;29:2638-2643.
8. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007;30:1979-1987.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-470.
10. Liang KY, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. *Indian J Stat*. 2000;62:134-148.
11. Filozof C, Schwartz S, Foley J. Effect of vildagliptin as add-on therapy to a low-dose metformin. *World J Diabetes*. 2010;1:19-26.
12. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE study. *Curr Med Res Opin*. 2005;21(12):2029-2035.
13. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. *Ann Intern Med*. 2001;135:825-834.
14. Zafar A, Davies M, Azhar A, Khunti K. Clinical inertia in management of T2DM. *Prim Care Diabetes*. 2010;4:203-207.
15. Strain WD, Cos X, Hirst M, et al. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2014;105:302-312.
16. Pantalone KM, Misra-Hebert AD, Hobbs TM, et al. Clinical inertia in type 2 diabetes management: evidence from a large, real-world data set. *Diabetes Care*. 2018;41:e113-e114.
17. Pantalone KM, Wells BJ, Chagin KM, et al. Intensification of diabetes therapy and time until A1C goal attainment among patients with newly diagnosed type 2 diabetes who fail metformin monotherapy within a large integrated health system. *Diabetes Care*. 2016;39:1527-1534.
18. Rajpathak SN, Rajgopalan S, Engel SS. Impact of time to treatment intensification on glycemic goal attainment among patients with type 2 diabetes failing metformin monotherapy. *J Diabetes Complications*. 2014;28:831-835.
19. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. *Diabetes Obes Metab*. 2018;20:427-437.

SUPPORTING INFORMATION

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

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