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ORIGINAL ARTICLE

The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus

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Aims: This study was conducted to compare the glycaemic efficacy and safety of initial combination therapy with the fixed-dose combination of sitagliptin and metformin versus metformin monotherapy in drug-naive patients with type 2 diabetes.
Methods: This double-blind study (18-week Phase A and 26-week Phase B) randomized 1250 drug-naïve patients with type 2 diabetes [mean baseline haemoglobin A1c (HbA1c) 9.9%] to sitagliptin/metformin 50/500 mg bid or metformin 500 mg bid (uptitrated over 4 weeks to achieve maximum doses of sitagliptin/metformin 50/1000 mg bid or metformin 1000 bid). Results of the primary efficacy endpoint (mean HbA1c reductions from baseline at the end of Phase A) are reported herein.
Results: At week 18, mean change from baseline HbA1c was −2.4% for sitagliptin/metformin FDC and −1.8% for metformin monotherapy ($p < 0.001$); more patients treated with sitagliptin/metformin FDC had an HbA1c value <7% ($p < 0.001$) versus metformin monotherapy. Changes in fasting plasma glucose were significantly greater with sitagliptin/metformin FDC (−3.8 mmol/l) versus metformin monotherapy (−3.0 mmol/l; $p < 0.001$). Homeostasis model assessment of β-cell function (HOMA-β) and fasting proinsulin/insulin ratio were significantly improved with sitagliptin/metformin FDC versus metformin monotherapy. Baseline body weight was reduced by 1.6 kg in each group. Both treatments were generally well tolerated with a low and similar incidence of hypoglycaemia. Abdominal pain (1.1 and 3.9%; $p = 0.002$) and diarrhoea (12.0 and 16.6%; $p = 0.021$) occurred significantly less with sitagliptin/metformin FDC versus metformin monotherapy; the incidence of nausea and vomiting was similar in both groups.
Conclusion: Compared with metformin monotherapy, initial treatment with sitagliptin/metformin FDC provided superior glycaemic improvement with a similar degree of weight loss and lower incidences of abdominal pain and diarrhoea.
Keywords: diabetes, GLP-1, GIP, metformin, sitagliptin, type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease that arises from a complex pathophysiology involving insulin resistance, reduced insulin secretion and increased hepatic glucose output [1]. On the basis of data from the UK Prospective Diabetes Study (UKPDS) Group [2] and the Diabetes Control and Complications Trial (DCCT) study [3], there is broad consensus regarding the importance of glycaemic control in all patients with diabetes mellitus. The American Diabetes Association recommends a general glycaemic treatment target for HbA1c <7.0%. Another expert group, the International Diabetes Federation, recommends an even lower HbA1c goal <6.5%. Despite these recommendations, many patients fail to achieve optimal glycaemic control. Data from the Third National Health and Nutrition Examination Survey (NHANES III 1988–1994) and NHANES 1999–2000 showed that rates of attainment of HbA1c levels below 7.0% were only 44.3 and 37%, respectively [4].

Monotherapy with metformin, a biguanide agent that primarily acts to lower hepatic glucose output [5,6], is the most widely prescribed first-line oral antihyperglycaemic agent (AHA). As with all AHAs, monotherapy with metformin is often unsuccessful in achieving or maintaining adequate glycaemic control [4,7,8]. Furthermore, patients who initially get to goal with monotherapy frequently require additional agents over time in order to maintain glycaemic control due to the progressive nature of T2DM [7]. Initial combination therapy offers an alternative approach to single-agent therapy for the treatment of T2DM, especially in patients with moderate-to-high HbA1c levels for which the use of initial combination therapy is considered a potential treatment option supported by practice guidelines [9].

Sitagliptin is an oral, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with

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T2DM [10]. Sitagliptin delays the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), the major incretins involved in glucose homeostasis, thereby increasing insulin release and lowering glucagon secretion in a glucose-dependent manner [11,12]. Treatment with sitagliptin 100 mg once daily leads to improvements in glycaemic control in patients with T2DM, including reductions in fasting and postprandial glucose concentrations. Sitagliptin has not been associated with an increased risk of hypoglycaemia when administered as either monotherapy or in combination with agents not known to cause hypoglycaemia [13–17]. The combined use of sitagliptin and metformin is an effective method of lowering glucose levels in T2DM. A Phase III study that randomized patients with baseline HbA1c of 7.5–11% (mean 8.8%) showed additive effects of initial co-administration with sitagliptin and metformin [18]. The glycaemic effects were sustained and the combination was generally well tolerated for up to 54 weeks of treatment [19].

A fixed-dose combination (FDC) tablet has been developed and approved for use in many countries for the treatment of patients with T2DM [20,21]. The purpose of this study was to assess the efficacy and safety/tolerability of initial therapy with the FDC of sitagliptin/metformin compared with metformin monotherapy in drug-naïve patients with T2DM and moderate-to-severe hyperglycaemia while on a diet/exercise regimen.

Methods

Patients

Study participants included drug-naïve [defined as not on AHA therapy within the 4 months (or longer) preceding the screening visit] men and women (aged 18–78 years) with T2DM and an HbA1c $\geq$7.5% while on a diet/exercise regimen. Additional glycaemic entry criteria to be satisfied included a fingerstick glucose test $\geq$7.2 and $\leq$17.8 mmol/l. Patients with type 1 diabetes, unstable cardiac disease, elevated [more than twofold the upper limit of normal (ULN)] alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) or any contraindication for use of metformin were excluded from this study.

Study Design

This was a randomized, double-blind, parallel-group study (Merck Protocol Number MK-0431A P079; Clinialtrials.gov: NCT00482729) consisting of a 1-week screening period (visits 1–2) and an 18-week active-controlled treatment period (i.e. Phase A encompassing visits 2–5). After completion of Phase A (26 June 2007 to 3 November 2008), patients continued to receive double-blind treatment during a 26-week treatment period (i.e. Phase B). The current report presents results of the initial 18-week Phase A portion of the study, addressing the primary and secondary prespecified study hypotheses. This study was conducted at 229 sites in the USA (224 sites) and Puerto Rico (5 sites). The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided written, informed consent before the initiation of any study procedures. The institutional review board or independent ethics committee for each study site approved the final protocol and informed consent form.

Following completion of the 1-week screening period, eligible patients were randomized in a 1 : 1 ratio to bid oral treatment with sitagliptin/metformin FDC or metformin monotherapy. Metformin, either as monotherapy or as the metformin component of the sitagliptin/metformin FDC, was uptitrated over 4 weeks in both arms in order to improve gastrointestinal tolerability. The starting dose of sitagliptin/metformin FDC was 50/500 mg bid. The dose was uptitrated after 2 weeks to 50/500 mg in the morning and 50/1000 mg in the evening, and to 50/1000 mg bid after 4 weeks. The starting dose of metformin 500 mg bid was uptitrated after 2 weeks to 500 mg in the morning and 1000 mg in the evening, and then to 1000 mg bid after 4 weeks. Patients who did not tolerate the maximum doses of these treatments were downtitrated to a minimum dose of sitagliptin/metformin 50/500 mg bid or metformin 500 mg bid, respectively. Patients who were not able to tolerate the minimal doses of sitagliptin/metformin 50/500 mg bid or metformin 500 mg bid at 6 weeks after initiation were discontinued. Patients received counselling on exercise and a weight management diet consistent with American Diabetes Association recommendations throughout the study.

During the study, patients not meeting progressively stricter glycaemic goals were to initiate additional antihyperglycaemic therapy with sulfonylureas, meglitinides or thiazolidinediones if fasting plasma glucose (FPG) exceeded specific criteria, as follows: >16.7 mmol/l after visit 2 (day 1 of treatment) to visit 3 (week 6); >14.4 mmol/l after visit 3 (week 6) to visit 4 (week 12) and >12.8 mmol/l and after visit 4 (week 12) to visit 5 (week 18). Patients were to be discontinued if the investigator considered that add-on therapy with sulfonylureas, meglitinides or thiazolidinediones was inappropriate for a given patient meeting these FPG criteria.

Study Endpoints

Efficacy Assessments. Patients were required to fast overnight for $\geq$10 h prior to each scheduled clinic visit. HbA1c, FPG and body weight were assessed at baseline and every clinic visit from week 6 to week 18. The primary efficacy endpoint was change in HbA1c from baseline (i.e. randomization visit, prior to first dose) to week 18. Secondary endpoints included proportions of patients with HbA1c <7.0 and <6.5% and changes from baseline in FPG, proinsulin/insulin ratio, homeostasis model assessment of β-cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR), lipids and body weight at week 18.

All laboratory measurements were performed at a central laboratory (PPD Global Central Labs, LLC, Highland Heights, KY, USA) by technicians blinded to the patients' treatment assignments.

Safety Assessment. Visits included assessment of vital signs, physical examinations, adverse experiences (AEs) and laboratory assessments. All AEs were rated by the investigators for intensity and relationship to study drug. Predefined clinical

adverse experiences of interest included hypoglycaemia and selected gastrointestinal AEs: abdominal pain (including the terms lower abdominal pain, upper abdominal pain, abdominal pain, abdominal discomfort and epigastric pain), nausea, vomiting and diarrhoea. Laboratory safety was collected during the study and included complete blood counts and blood chemistry (including ALT, AST, total bilirubin, alkaline phosphatase, creatinine and urinalysis).

Patients were counselled to self-monitor their blood glucose levels and immediately notify investigators if they experienced symptoms of hypoglycaemia (e.g. sweating, anxiety, palpitations, headache, blurred vision, clouding of consciousness) for assessment of hypoglycaemic events during the study. Hypoglycaemia was assessed by the study site investigators by reviewing the patient's self-reports of signs and symptoms of hypoglycaemia. A fingerstick blood glucose determination concurrent with the episode was not required to determine whether an episode was considered an adverse experience of hypoglycaemia, although investigators could include the fingerstick glucose measurement, if available, in their assessment of the episode.

Statistical Analyses

All efficacy analyses were performed on the full analysis set (FAS) defined as all randomized patients who received at least one dose of study drug and who had valid measurements both at baseline and at least one postbaseline measurement (occurring prior to initiation of additional AHAs). Change from baseline in HbA1c at week 18 was analyzed using an analysis of covariance (ANCOVA) model with a term for treatment and baseline HbA1c as a covariate. To assess the treatment effects of sitagliptin/metformin FDC and metformin monotherapy on efficacy parameters independent of the initiation of additional AHAs, data obtained after the initiation of additional AHAs were treated as missing. The last-observation-carried-forward method was used to impute missing data. The within-group differences [least squares (LS) mean changes from baseline at week 18] with 95% confidence intervals (CI) were summarized for the efficacy endpoints. Differences in LS mean changes (or percent changes, as appropriate) from baseline and 95% CIs were calculated to estimate the between-group differences. A p value of <0.050 was considered statistically significant.

A logistic regression model with terms for treatment and baseline HbA1c was used to analyze the proportions of patients with HbA1c values <7.0 and $<6.5\%$ at week 18. Changes from baseline (or percent change, as appropriate) in other secondary efficacy endpoints were analyzed using the ANCOVA model as specified for HbA1c but with the corresponding baseline value as a covariate. Percent changes from baseline in triglycerides (TG) and TG/HDL-C (high-density lipoprotein cholesterol) ratio were analyzed using a nonparametric ANCOVA model using ranks based upon Tukey's normalized scores with terms for treatment and baseline value.

Multiplicity adjustments were made for the primary and two key secondary efficacy hypotheses (i.e. % patients with HbA1c $<7\%$ and change from baseline in FPG). The first key secondary efficacy hypothesis (i.e. % patients with HbA1c $<7\%$) was only considered significant if $p < 0.05$ (two-sided) and the primary hypothesis was confirmed. Furthermore, the secondary efficacy endpoint of change from baseline in FPG was declared significant if $p < 0.05$ (two-sided)—the primary hypothesis and the first secondary hypothesis both were confirmed.

Although no formal statistical testing was performed, prespecified subgroup analyses of change from baseline in HbA1c were performed to explore the consistency of the treatment effect across subgroups defined by gender, age ($<$ or $\geq$65 years), race, baseline body mass index, baseline HbA1c and known duration of T2DM.

Safety analyses were performed on the all-patients-as-treated population (APaT) defined as all patients who took at least one dose of study drug. The analysis of safety parameters used a multitiered approach. Between-group differences in adverse experiences of hypoglycaemia and prespecified selected gastrointestinal AEs (i.e. abdominal pain, nausea, vomiting, diarrhoea) were tested for statistical significance. For other adverse experiences and predefined limits of change in laboratory variables, the between-group differences and associated 95% CIs were provided. Tests and confidence intervals comparing differences in proportions of events used the method of Miettinen and Nurminen [22].

Results

Demographics and Baseline Characteristics

The overall disposition of patients enrolled and subsequently randomized to treatment is shown in figure 1. Of the 2045 patients who were screened, a total of 1250 patients satisfied the eligibility criteria and were randomized to study treatment. After completion of this study, one investigational site was found to be non-compliant with the requirements of Good Clinical Practice. For this reason, data from the patients randomized at this site ($n = 4$) were deemed unreliable and were excluded from all analyses (efficacy and safety). Of the remaining 1246 patients, 965 completed Phase A (week 18) of the study. The proportions of patients discontinuing during Phase A were similar in the sitagliptin/metformin FDC and metformin monotherapy groups (23 vs. 22%, respectively) (figure 1). Of all randomized patients, 22.6% discontinued before week 18. A slightly higher proportion of patients with an A1C $\geq$11% at baseline discontinued before week 18 (28.7%). In addition, the A1C at baseline of patients who discontinued was slightly higher compared with patients who completed week 18 (mean baseline A1C 10.2 vs. 9.8%).

Of all randomized patients, 14.6% discontinued because of 'lost to follow-up' or 'withdrew consent', whereas in the subgroup of patients with an A1C $\geq$11% at baseline this proportion was slightly higher (20.2%).

The baseline demographic, anthropometric and disease characteristics of the randomized population were similar across the treatment groups (Table 1). For the entire study population, the average reported duration of diabetes was 3.3 years, average baseline HbA1c was 9.9%; 54% of patients had a baseline HbA1c $<10\%$ and the average baseline FPG was 12.2 mmol/l. The baseline glycaemic (Table 1) and lipid values (data not shown) were generally balanced across the treatment groups.

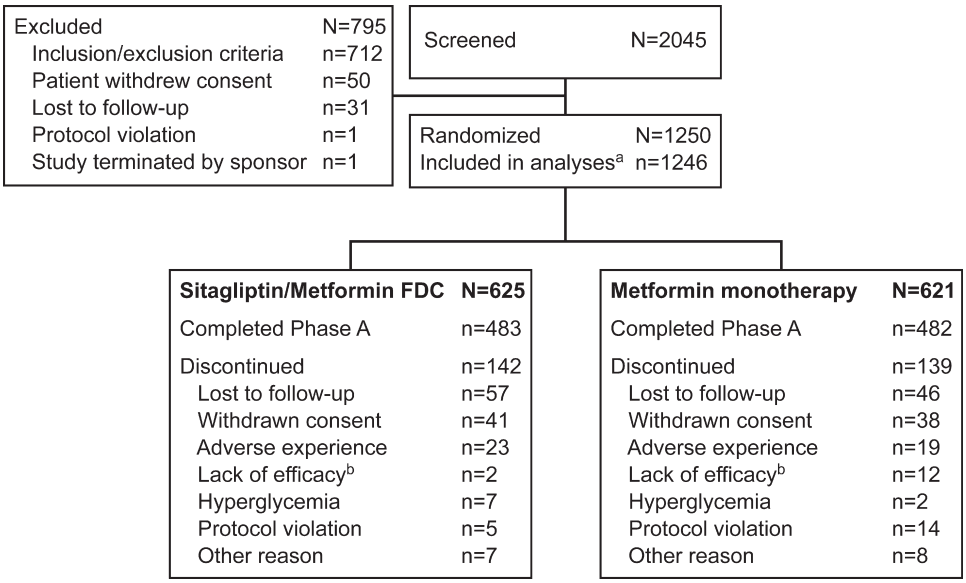

Figure 1. Overall disposition of screened and randomized patients. [a]One investigational site was identified as non-compliant with some of the requirementes of Good Clinical Practice. For this reason, data from all 4 randomized patients at this site were deemed unreliable and were excluded from all analyses (efficacy and safety). [b]Includes patients not meeting the progressively stricter, protocol-specified glycaemic rescue citeria and/or not meeting the investgator's expectations of glycaemic improvement.

Table 1. Baseline demographics and disease characteristics of randomized patients.

Parameter	Sitagliptin/ metformin FDC N = 625	Metformin monotherapy N = 621
Age, years (mean ± s.d.)	49.4 ± 10.5	50.0 ± 10.5
Gender, n (%)		
Male	353 (56)	356 (57)
Female	272 (44)	265 (43)
Race, n (%)		
Caucasian	508 (81)	489 (79)
Black	82 (13)	88 (14)
Asian	17 (3)	24 (4)
Other	18 (3)	20 (3)
Ethnicity, n (%)		
Hispanic or Latino	224 (36)	184 (30)
Not Hispanic or Latino	401 (64)	437 (70)
Body weight, kg (mean ± s.d.)	94.7 ± 23.4	97.2 ± 25.5
Body mass index, kg/m^2 (mean ± s.d.)	32.9 ± 7.2	33.7 ± 7.8
Known duration of type 2 diabetes, years (mean ± s.d.)	3.5 ± 4.5	3.2 ± 4.3
HbA1c, % (mean ± s.d.) [range]	9.9 ± 1.8 [6.9–16.6]	9.8 ± 1.8 [6.7–16.8]
HbA1c distribution at baseline, n (%)		
<8%	100 (16)	112 (18)
≥8 to <9%	130 (21)	118 (19)
≥9 to <10%	107 (17)	105 (17)
≥10 to <11%	108 (17)	122 (20)
≥11%	178 (29)	160 (26)
Fasting plasma glucose, mmol/l (mean ± s.d.)	12.3 ± 3.8	12.1 ± 3.9

FDC, fixed-dose combination; HbA1c, haemoglobin A1c.

Efficacy

At week 18, the mean HbA1c change from baseline was −2.4% (95% CI: −2.5, −2.2) for sitagliptin/metformin FDC and −1.8% (95% CI: −1.9, −1.6) for metformin monotherapy, resulting in a significant between-group difference of −0.6% (95% CI: −0.8, −0.4; $p < 0.001$) (Table 2). For both the sitagliptin/metformin FDC and metformin monotherapy groups, the largest decrease in HbA1c was observed during the first 12 weeks of treatment with a smaller further decrease seen between weeks 12 and 18 (figure 2). The reductions in HbA1c were larger in the sitagliptin/metformin FDC group compared with metformin monotherapy at the earliest measurement (week 6) and at every time point examined thereafter.

At week 18, a significantly greater proportion of patients in the sitagliptin/metformin FDC group had HbA1c values <7.0% relative to the metformin monotherapy group (49.2 vs. 34.2%, respectively; $p < 0.001$) or <6.5% (31.8 vs. 16.0%, respectively; $p < 0.001$) (figure 3). Fewer patients required initiation of additional AHAs based on the prespecified criteria for FPG by week 18 in the sitagliptin/metformin FDC group compared with the metformin group [2.7% (17/625) vs. 5.2% (32/621); *post hoc* p value of 0.012].

Reductions from baseline in HbA1c at week 18 in both treatment groups were greater among patients with baseline levels higher than the median baseline value (i.e. >9.70%) compared with patients with baseline levels at or below the median baseline value (i.e. ≤9.70%). Consistent with the primary endpoint, there was a significantly greater reduction observed for the sitagliptin/metformin FDC group relative to the metformin monotherapy group for both subgroups, with the between-group difference being larger for patients with a

Table 2. Baseline and change from baseline in fasting glycaemic endpoints at week 18 for the FAS population.

Parameter†	Sitagliptin/ metformin FDC	Metformin monotherapy
HbA1c (%)		
n	559	564
Baseline	9.9 ± 1.8	9.8 ± 1.8
Change from baseline	−2.4 (−2.5, −2.2)	−1.8 (−1.9, −1.6)
Difference vs. MET alone	−0.6 (−0.8, −0.4)**	—
Fasting plasma glucose (mmol/l)		
n	560	566
Baseline	12.2 ± 3.7	12.1 ± 3.9
Change from baseline	−3.8 (−4.1, −3.6)	−3.0 (−3.2, −2.7)
Difference vs. MET alone	−0.9 (−1.2, −0.5)**	—
Proinsulin/insulin ratio‡		
n	469	458
Baseline	0.556 ± 1.256	0.518 ± 0.388
Change from baseline	−0.238 (−0.260, −0.215)	−0.186 (−0.209, −0.162)
Difference vs. MET alone	−0.052 (−0.085, −0.020)*	—
HOMA-β		
n	465	456
Baseline	50.5 ± 56.6	62.4 ± 113.8
Change from baseline	54.6 (43.6, 65.5)	31.8 (20.7, 42.8)
Difference vs. MET alone	22.8 (7.2, 38.4)*	—
HOMA-IR		
n	465	456
Baseline	8.3 ± 6.4	9.0 ± 8.2
Change from baseline	−1.3 (−2.1, −0.5)	−2.2 (−3.0, −1.4)
Difference vs. MET alone	0.9 (−0.2, 2.1)	—

AHA, antihyperglycaemic agents; FAS, full analysis set; FDC, fixed-dose combination; HbA1c, haemoglobin A1c; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metformin.

*$p < 0.050$ versus MET monotherapy.

**$p < 0.001$ versus MET monotherapy.

†Baseline data are expressed as mean ± s.d.; changes from baseline and differences versus MET monotherapy are expressed as least squares mean (95% confidence interval). Excludes data obtained after the initiation of additional AHAs.

‡Insulin concentration was converted to pmol/l for calculation of the proinsulin/insulin ratio.

baseline HbA1c greater than the median than in patients with a baseline HbA1c at or below the median (figure 4).

The larger reductions in HbA1c seen with sitagliptin/metformin FDC compared with those with metformin monotherapy were generally similar across patient subgroups defined by age (≤ and >65 years), gender (male, female), race (Asian, Black, White, Other), baseline body mass index (median baseline body mass index: ≤ and >32.0 kg/m^2), duration of T2DM (median duration: ≤ and >1.5 years), baseline homeostasis model assessment of insulin resistance (HOMA-IR; median baseline value: ≤ and >6.7) and baseline HOMA-β (median baseline value: ≤ and >33.0) (data not shown).

At week 18, treatment with sitagliptin/metformin FDC led to a significantly larger decrease from baseline in FPG (−3.8 mmol/l) compared with metformin monotherapy

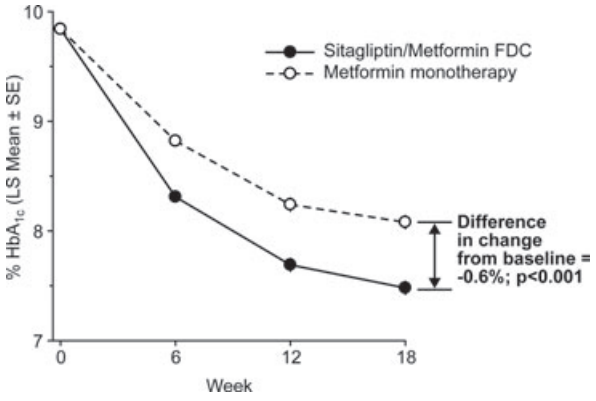

Figure 2. Haemoglobin A1c (HbA1c) over time.

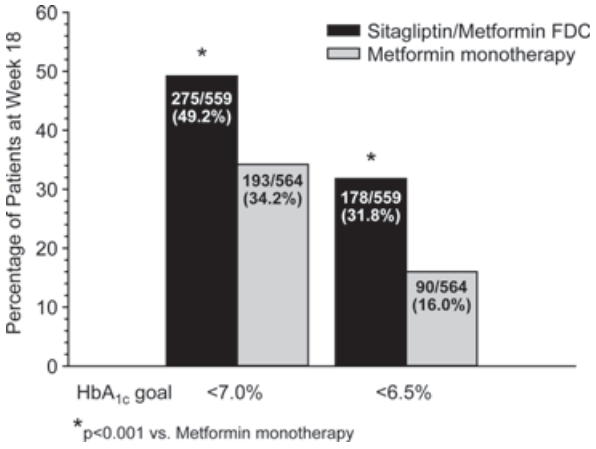

Figure 3. Percentages of patients with haemoglobin A1c (HbA1c) values <7 and <6.5% at week 18.

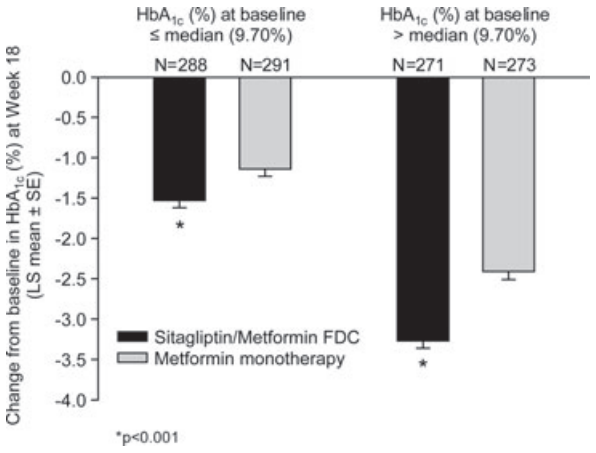

Figure 4. Change from baseline in haemoglobin A1c (HbA1c) at week 18 presented by baseline HbA1c subgroup.

(−3.0 mmol/l), resulting in a significant between-group difference of 0.9 mmol/l ($p < 0.001$) (Table 2). The FPG profiles over time showed that maximal reductions in FPG were achieved by week 6 for both treatment groups; these reductions remained generally stable through week 18 (data not shown).

Significant improvements in measures of β-cell function (i.e. HOMA-β and proinsulin/insulin ratio) were observed following treatment with sitagliptin/metformin FDC compared with metformin monotherapy at week 18 (Table 2). Both treatments led to small reductions from baseline in insulin resistance as measured by HOMA-IR (Table 2).

At week 18, body weight change from baseline was −1.6 kg (95% CI: −2.1, −1.1) in both the sitagliptin/metformin FDC and metformin monotherapy groups. Progressive reductions in mean body weight were observed over the first 12 weeks of treatment, with evidence of a plateau between weeks 12 and 18 (data not shown).

The sitagliptin/metformin FDC and metformin monotherapy groups showed small improvements from baseline in total cholesterol (TC) [−4.2% (95% CI: −5.7, −2.8) vs. −3.8% (95% CI: −5.2, −2.3), respectively], HDL-C [4.8% (95% CI: 3.3, 6.3) vs. 5.8% (95% CI: 4.3, 7.3), respectively], TG [−8.4% (95% CI: −12.4, −4.4) vs. −2.1% (95% CI: −6.3, 2.1), respectively] and non-HDL-C [−5.6% (95% CI: −7.6, −3.7) vs. −5.4% (95% CI: −7.3, −3.4), respectively]. Small numerical decreases in low-density lipoprotein cholesterol (LDL-C) were observed for both treatment groups [−1.3% (95% CI: −3.8, 1.2) vs. −4.2% (95% CI: −6.8, −1.7)]. The mean percent changes from baseline in LDL-C, TC, HDL-C, TG and non-HDL-C were generally similar between the two groups, with the exception of a significantly greater between-group reduction in TG seen with sitagliptin/metformin FDC compared with metformin monotherapy ($p = 0.049$).

Safety

In this study, initial therapy with sitagliptin/metformin FDC was generally well tolerated, as was metformin monotherapy. Over the 18-week treatment period, the incidence of adverse experiences was similar in the sitagliptin/metformin FDC and the metformin monotherapy groups (43 vs. 48%, respectively; Table 3). No meaningful differences were observed between the two groups with respect to the incidences of drug-related adverse experiences, serious adverse experiences, serious drug-related adverse experiences, discontinuations due to adverse experiences, discontinuations due to drug-related adverse experiences, discontinuations due to serious adverse experiences or discontinuations due to serious drug-related adverse experiences.

Table 3. Summary of adverse experiences for the APaT population over 18 weeks of metformin monotherapy or treatment with sitagliptin/metformin FDC.*

Parameter	Number (%) of patients	
	Sitagliptin/ metformin FDC N = 625	Metformin monotherapy N = 621
One or more AEs	271 (43.4)	301 (48.5)
Drug-related† AEs	109 (17.4)	116 (18.7)
Serious AEs (SAEs)	13 (2.1)	20 (3.2)
Drug-related† SAEs	1 (0.2)	1 (0.2)
Deaths	1 (0.2)	1 (0.2)
Discontinued due to AEs	25 (4.0)	25 (4.0)
Discontinued due to drug-related† AEs	18 (2.9)	16 (2.6)
Discontinued due to SAEs	6 (1.0)	5 (0.8)
Discontinued due to drug-related† SAEs	1 (0.2)	1 (0.2)

AE, adverse experience; AHA, antihyperglycaemic agents; APaT, all-patients-as-treated; FDC, fixed-dose combination; SAE, serious adverse experience.

*Excludes data obtained after the initiation of additional AHA.

†Drug-related, considered by the study investigator to be possibly, probably or definitely drug-related.

The incidences of adverse experiences classified by body system, including cardiac-related adverse experiences, infections and musculoskeletal adverse experiences, were generally similar in both treatment groups. For specific adverse experiences, the incidences were also generally similar in both treatment groups. Only a few adverse experiences occurred at a higher incidence in the sitagliptin/metformin FDC group compared with the metformin monotherapy group and vice versa (Table S1, Supporting information). Two deaths were reported during the 18-week treatment period (Table 3). One patient in the sitagliptin/metformin FDC group died due to an acute myocardial infarction and one patient in the metformin group died due to accidental electrocution; both deaths were considered to be not related to study drug by the investigators.

The incidence of laboratory adverse experiences throughout the 18 weeks was low and similar in the sitagliptin/metformin FDC and metformin groups. Small decreases from baseline in ALT (−1.81 and −1.38 IU/l), AST (−1.50 and −0.92 IU/l) and alkaline phosphatase (−11.34 and −9.71 IU/l) were observed in the sitagliptin/metformin FDC and metformin monotherapy groups, respectively. Changes from baseline in mean serum creatinine values were not observed in either treatment group; however, small and similar decreases in estimated creatinine clearance of −3.38 and −1.92 ml/min were observed in the sitagliptin/metformin FDC and metformin monotherapy groups, respectively.

Hypoglycaemia and selected gastrointestinal adverse experiences (i.e. abdominal pain, diarrhoea, nausea and vomiting) were prespecified as tier 1 adverse experiences in this study. The incidences of hypoglycaemia were low and similar in the sitagliptin/metformin FDC and the metformin monotherapy groups (2.1 vs. 1.8%, respectively; Table 4). No episodes required medical or non-medical assistance. The incidences of overall gastrointestinal adverse experiences were 20.6% in the sitagliptin/metformin FDC group and 24.6% in the metformin monotherapy group. The most frequently reported gastrointestinal adverse experience was diarrhoea in both the sitagliptin/metformin FDC and metformin groups (12.0 vs. 16.6%), with the incidence of diarrhoea being significantly lower in the sitagliptin/metformin FDC group than in the metformin group ($p = 0.021$; Table 4). In addition, abdominal pain was reported significantly less frequently in the sitagliptin/metformin FDC group than in the metformin group (1.1 vs. 3.9%; $p = 0.002$). The incidences of nausea (5.6 vs. 6.3%, respectively; $p = 0.612$) and vomiting (2.9 vs. 2.6%, respectively; $p = 0.742$) were similar in the sitagliptin/metformin FDC and the metformin groups.

Table 4. Analysis of prespecified adverse experiences of clinical interest for the APaT population over 18 weeks of metformin monotherapy or treatment with sitagliptin/metformin FDC.†

Adverse experiences	Sitagliptin/ metformin FDC N = 625	Metformin monotherapy N = 621	Difference in % vs. Metformin (95% CI)
Hypoglycaemia	13 (2.1)	11 (1.8)	0.3 (−1.3, 2.0)
All gastrointestinal AEs	129 (20.6)	153 (24.6)	−4.0 (−8.7, 0.7)
Prespecified gastrointestinal AEs			
Abdominal pain‡	7 (1.1)*	24 (3.9)	−2.7 (−4.7, −1.1)
Diarrhoea	75 (12.0)*	103 (16.6)	−4.6 (−8.5, −0.7)
Nausea	35 (5.6)	39 (6.3)	−0.7 (−3.4, 2.0)
Vomiting	18 (2.9)	16 (2.6)	0.3 (−1.6, 2.2)

AE, adverse experience; AHA, antihyperglycaemic agents; APaT, all-patients-as-treated; FDC, fixed-dose combination.

*$p < 0.050$ versus metformin monotherapy.

†Excludes data obtained after the initiation of additional AHAs.

‡Includes abdominal pain lower, abdominal pain upper, abdominal pain, abdominal discomfort and epigastric pain.

Discussion

This study evaluated the efficacy and safety of initial treatment with sitagliptin/metformin FDC compared with metformin monotherapy in drug-naïve patients with T2DM and moderate-to-severe hyperglycaemia. After 18 weeks, both treatments produced clinically meaningful reductions in HbA1c and FPG relative to baseline, with sitagliptin/metformin FDC providing significantly greater improvements compared with metformin monotherapy. The mean HbA1c change from baseline was −2.4% for the sitagliptin/metformin FDC group. Greater reductions from baseline in HbA1c were observed with both treatments among patients with higher baseline HbA1c values compared with those with lower baseline HbA1c values. Considering the high mean baseline HbA1c of 9.9% in the population included in this study, a substantial percentage of patients (49%) in the sitagliptin/metformin FDC group had an HbA1c <7% at week 18 compared with the percentage (34%) in the metformin monotherapy group.

Metformin is widely recommended as first-line therapy in patients with T2DM [9]. This recommendation is based on its beneficial clinical properties, including good glycaemic efficacy, a low risk of hypoglycaemia and a small reduction in body weight [9]. In addition, metformin monotherapy showed beneficial effects on cardiovascular events in the UKPDS substudy of overweight patients with T2DM [23]. Despite the proven benefits of metformin, a large proportion of patients do not achieve glycaemic targets with metformin monotherapy. This is confirmed by the finding in this study that only approximately one third of the patients had an HbA1c <7% with metformin monotherapy at week 18. The greater glycaemic efficacy of the combination of sitagliptin and metformin has been showed in a previous report [18] and can be explained by partly complementary mechanisms of action by which sitagliptin and metformin improve glucose control. Metformin reduces insulin resistance and hepatic glucose production while sitagliptin delays the inactivation of GLP-1 and GIP, thereby increasing insulin release and lowering glucagon secretion [11,12]. In addition, the efficacy of the combination of sitagliptin and metformin could be attributed to findings from a previous study that showed a complementary increase in total (active plus inactive) GLP-1 induced by metformin treatment, potentially enhancing the effects of the DPP-4 inhibitor sitagliptin [24]. This is further supported by the fact that the earlier study also showed that the combination of metformin and sitagliptin led to larger increases in active levels of GLP-1 compared with either sitagliptin or metformin monotherapy [24].

In addition to beneficial effects on glycaemic control, sitagliptin/metformin FDC showed significantly greater improvements in measures of fasting β-cell function (i.e. HOMA-β and proinsulin/insulin ratio) compared with metformin monotherapy. HOMA-β is a surrogate endpoint that is used to assess the ability of pancreatic β-cells to secrete insulin under fasting conditions, whereas the proinsulin/insulin ratio is a marker that is believed to increase as a result of less efficient insulin processing by dysfunctional pancreatic β-cells [25,26]. These markers of β-cell function show favourable results for sitagliptin/metformin FDC compared with metformin monotherapy. The clinical impact of these improvements will require the assessment of longer term data.

Patients in the sitagliptin/metformin FDC and metformin monotherapy groups experienced similar reductions from baseline in body weight. A positive correlation between weight gain and intensive glycaemic control has been showed in patients receiving AHA therapy [27]. The superior glycaemic improvement seen with sitagliptin/metformin FDC in this study did not lessen the weight loss observed with metformin monotherapy. This finding suggests that sitagliptin does not interfere with the weight loss typically associated with metformin therapy [28], despite the incremental improvement in glycaemic control.

An important concern with the use of combination therapies compared to monotherapy is the potential risk for increased incidences of adverse experiences. However, this study showed that both sitagliptin/metformin FDC and metformin monotherapy are generally well tolerated. The overall incidences of adverse experiences were similar in both treatment groups, including the incidence of hypoglycaemia. The low incidence of hypoglycaemia seen in this study with sitagliptin/metformin FDC despite the marked improvement in glycaemic control is consistent with the glucose-dependent mechanism of action of DPP-4 inhibition [29], as has been noted in other studies in which sitagliptin was used as monotherapy or in combination with AHAs that by themselves are not associated with hypoglycaemia [16–18,30,31]. As seen with other classes of antihyperglycaemic therapies, when sitagliptin was used in combination with insulin or sulfonylureas, medicines whose mechanism of action is not glucose-dependent, it has been associated with an increased rate of hypoglycaemia compared with placebo [32,33].

The incidences of overall gastrointestinal adverse experiences and the specific adverse experiences of nausea and vomiting were similar for the sitagliptin/metformin FDC and

metformin monotherapy groups. However, significantly lower incidences of abdominal pain and diarrhoea were observed with the sitagliptin/metformin FDC compared with metformin monotherapy. This finding is similar to findings in a prior study, in which numerically lower rates of abdominal pain and diarrhoea in T2DM patients receiving initial combination therapy with sitagliptin and metformin (administered as individual tablets taken concomitantly) relative to metformin monotherapy were observed [18]. The mechanism of the decrease in abdominal pain and diarrhoea with sitagliptin and metformin combination therapy relative to metformin monotherapy observed in these studies is not known; however, results from another study with a different DPP-4 inhibitor used in combination with metformin showed similar findings [34]. Additional research is needed regarding these observations.

In conclusion, treatment with sitagliptin/metformin FDC over 18 weeks produced significantly greater reductions in HbA1c, resulting in more patients at glycaemic goal, compared with metformin monotherapy. Treatment with the sitagliptin/metformin FDC also resulted in similar weight loss, similar incidences of hypoglycaemia and lower incidences of abdominal pain and diarrhoea compared with metformin monotherapy.

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Conflict of Interest

T. L. S., D. E. W.-H., M. C., L. T., A. O. J.-L., K. D. K. and B. J. G. are employees of Merck & Co., Inc. and may hold stock in the company. C. R. reports no conflicts of interest. L. O. has received honoraria (personal compensation), speaker fees and/or consultancy payments from Merck & Co., Inc. and other pharmaceutical companies.

C. Reasner, L. Olansky, T. Seck, D. E. Williams-Herman, K. D. Kaufman and L. Terranella all participated in the conception and/or design of the study. B. J. Goldstein supervised analyses. M. Chen provided the statistical analyses. C. Reasner, L. Olansky and T. Seck were involved in acquisition of data. All authors contributed to the interpretation of results and participated in the drafting and/or revision of the manuscript.

Supporting Information

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

Table S1. Summary of adverse experiences with an incidence ≥1% in one or both treatment groups for the APaT population over 18 weeks of treatment.

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