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ORIGINAL ARTICLE

A treatment strategy implementing combination therapy with sitagliptin and metformin results in superior glycaemic control versus metformin monotherapy due to a low rate of addition of antihyperglycaemic agents

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Aims: Combination therapy with sitagliptin and metformin has shown superior efficacy compared with metformin monotherapy. In this study, we compare two strategies: initial combination therapy with sitagliptin/metformin as a fixed-dose combination (FDC) and initial metformin monotherapy, with the option to add additional antihyperglycaemic agents (AHAs) in either treatment arm during the second phase of the study in order to reach adequate glycaemic control.

Methods: We evaluated the sitagliptin and metformin FDC compared with metformin monotherapy over 44 weeks in 1250 patients with type 2 diabetes mellitus in a two-part, double-blind, randomized, controlled clinical trial. The initial 18-week portion (Phase A) of this study in which additional AHAs were only allowed based on prespecified glycaemic criteria, has been previously reported. Here, we present results from the 26-week Phase B portion of the study during which double-blind study medication continued; however, unlike Phase A, during Phase B investigators were unmasked to results for haemoglobin A1C (HbA1c) and fasting plasma glucose (FPG) and directed to manage glycaemic control by adding incremental AHA(s) as deemed clinically appropriate.

Results: There were 1250 patients randomized in the study with 965 completing Phase A and continuing in Phase B. Among patients receiving sitagliptin/metformin FDC or metformin monotherapy, 8.8% and 16.7% received additional AHA therapy, respectively. Although glycaemic therapy in both groups was to have been managed to optimize HbA1c reductions with the option for investigators to supplement with additional AHAs during Phase B, patients randomized to initial therapy with sitagliptin/metformin FDC had larger reductions of HbA1c from baseline compared with patients randomized to initial metformin monotherapy [least squares (LS) mean change: −2.3% and −1.8% ($p < 0.001$ for difference) for sitagliptin/metformin FDC and metformin monotherapy groups, respectively]. A significantly larger reduction in FPG from baseline was observed in the sitagliptin/metformin FDC group compared with the metformin monotherapy group ($p = 0.001$). Significantly more patients in the sitagliptin/metformin FDC group had an HbA1c of less than 7.0% or less than 6.5% compared with those on metformin monotherapy. Both treatment strategies were generally well tolerated, with a low and similar incidence of hypoglycaemia in both groups and lower incidences of abdominal pain and diarrhoea in the sitagliptin/metformin FDC group compared with the metformin monotherapy group.

Conclusions: A strategy initially implementing combination therapy with sitagliptin/metformin FDC was superior to a strategy initially implementing metformin monotherapy, even when accounting for the later addition of supplemental AHAs. Sitagliptin/metformin FDC was generally well tolerated.

Keywords: antihyperglycaemic agents, incretins, metformin, sitagliptin, type 2 diabetes mellitus

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Introduction

The ultimate goal of caring for patients with type 2 diabetes mellitus (T2DM) is to prevent the chronic complications of the disease. The management of patients with T2DM requires the treatment of hyperglycaemia and the treatment of cardiovascular risk factors such as hypertension and dyslipidemia, which are frequently comorbidities in patients with T2DM [1–3]. Hyperglycaemia is due to the presence of insulin resistance, reduction in insulin secretion associated with deterioration of pancreatic β cell function, and overproduction of hepatic glucose production, which is primarily reflective of increased glucagon secretion [4,5]. The American Diabetes Association (ADA) recommends an haemoglobin A1C (HbA1c) level of <7.0% as the treatment target for most patients with T2DM although 6.5% is considered the diagnostic level for T2DM and <6.0% is considered normal [6].

Metformin, which suppresses hepatic gluconeogenesis, is generally accepted as a first-line pharmacologic therapy for treatment of hyperglycaemia [6]. Benefits of this agent include demonstrated glycaemic efficacy, weight loss and a

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potential benefit on mortality in overweight patients [7,8]. Initial monotherapy with metformin is typically recommended by guidelines from the ADA and the European Association for the Study of Diabetes (EASD). However, T2DM is a progressive disease leaving many patients unable to meet goals for adequate glycaemic control with metformin alone; the addition of other antihyperglycaemic agents (AHAs) is generally recommended if monotherapy does not result in adequate glycaemic control [9,10]. However, physicians often do not intensify antihyperglycaemic therapy despite the availability of other agents, an observation often described as clinical inertia [11]. In this context, initial combination therapy could offer important advantages in achieving glycaemic targets earlier and for a larger proportion of patients.

Incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), have been identified as important in maintaining glucose homeostasis. It has been shown that patients with T2DM have impaired incretin activity and that this probably accounts for failure of the mechanisms involved in insulin secretion to respond normally to meal-related glucose loads. Sitagliptin is an oral, selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with T2DM [12]. Sitagliptin delays the enzymatic degradation and GLP-1 and GIP through inhibition of DPP-4, thereby increasing insulin release and suppressing glucagon secretion, each in a glucose-dependent manner. Previous studies have shown that both sitagliptin 100 mg once daily and combination therapy with sitagliptin and metformin improve glycaemic control in patients with T2DM, including reductions in fasting and postprandial glucose concentrations [13,14].

We conducted a 2-part, 44-week, double-blind, randomised, controlled clinical trial comparing sitagliptin/metformin fixed-dose combination (FDC) and metformin monotherapy. Results from the initial Phase A portion of the study (weeks 0–18) have been previously reported and show that sitagliptin/metformin FDC resulted in significantly larger reductions of HbA1c and fasting plasma glucose (FPG) from baseline and resulted in a larger proportion of patients with an HbA1c <7.0% compared to metformin monotherapy [15]. In this study, we present data on the second, 26-week Phase B portion of this double-blind study, during which the two treatment strategies compared in Phase A (initial therapy with sitagliptin and metformin in a FDC or metformin monotherapy with the investigator's ability to add AHAs under limited circumstances with access to fingerstick glucose results but without access to laboratory measures of glycaemic control) were continued while unmasked laboratory measures of glycaemic control were available to the investigators, who were encouraged to use additional AHAs to attain glycaemic control. Additionally, we report data from patients after initiation of AHAs throughout the 44-week study period to show long-term duration of effect for the treatments that were assessed.

Patients and Methods

This study (Sponsor Protocol Number 079) was registered at clinicaltrials.gov (NCT00482729). Patients gave written informed consent upon enrollment in the study. The protocol and study were approved by site institutional review boards or independent ethics committees, and the study was conducted in accordance with principles of Good Clinical Practice.

Patients

The criteria for inclusion of patients in this study were described in the publication for Phase A of this study [15] but are also briefly summarized here. Patients included were 18–78 years old, had a diagnosis of type 2 diabetes with an HbA1c ≥7.5% while on a diet/exercise regimen, and were not to have been on AHA therapy ≥4 months prior to the screening visit.

Study Design

This was a randomised, double-blind, active-comparator controlled study consisting of an 18-week Phase A period and a 26-week Phase B period for a total of 44 weeks of treatment. There were seven clinic visits for each patient and two telephone calls.

Following a 1-week screening period, patients were randomised in a 1 : 1 ratio to one of two active treatment groups: sitagliptin/metformin FDC or metformin monotherapy. Patients remained on the double-blind active treatment during Phase A and Phase B. Treatment with sitagliptin/metformin FDC was initiated at a dose of 50/500 mg twice-daily and up-titrated over 4 weeks to 50/1000 mg b.i.d. In parallel, treatment with metformin was initiated at a dose of 500 mg twice-daily and was up-titrated over 4 weeks to 1000 mg b.i.d. Fingerstick blood glucose was monitored by patients throughout the study for safety purposes; results could trigger an unscheduled lab assessment throughout the study.

The objective of Phase A was to compare the treatment effect of sitagliptin/metformin FDC with metformin monotherapy. During Phase A, investigators were blinded to laboratory glycaemic efficacy measures, and initiation of additional AHAs was only allowed if protocol-specified criteria for FPG (as flagged by the central laboratory) were met.

The objective of Phase B was to compare a treatment strategy implementing initial combination therapy with sitagliptin/metformin FDC versus metformin monotherapy and the option to add other AHAs to either treatment as appropriate to achieve glycaemic control. Therefore, in contrast to Phase A, after the start of Phase B, investigators had routine access to glycaemic measures and were encouraged to initiate additional AHAs as they deemed appropriate to achieve glycaemic control, while patients continued to take double-blinded study medication. Additional AHAs allowed per protocol included sulfonylureas, meglitinides and thiazolidinediones.

Efficacy Measurements

The primary efficacy endpoint was change from baseline in HbA1c. Secondary endpoints included proportions of patients having HbA1c <7.0% and <6.5% at Week 44, change from baseline in FPG, lipid panel [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density

lipoprotein cholesterol (HDL-C), triglycerides (TG)], and body weight. All laboratory measurements were performed at a central laboratory (PPD Global Central Labs, LLC, Highland Heights, KY, USA) that was blinded to the patients' treatment assignments.

Safety Assessment

Safety assessments included collection of adverse experiences (AEs), physical examination and vital signs. Predefined safety endpoints included hypoglycaemia and selected gastrointestinal AEs [abdominal pain (including lower abdominal pain, upper abdominal pain, abdominal pain, abdominal discomfort and epigastric pain), nausea, vomiting, diarrhoea]. Patients were counselled to self-monitor their blood glucose levels and immediately notify investigators if they experienced symptoms of hypoglycaemia. Hypoglycaemia was assessed by the investigators through reviewing patient self-reports; a fingerstick blood glucose determination concurrent with the episode was not required.

Laboratory safety studies included blood chemistry [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase), haematology [including complete blood count (CBC), differential and absolute neutrophil count], urinalysis, and urine pregnancy testing (performed in women of childbearing potential).

Statistical Analysis

The primary approach for the efficacy and safety analysis at Week 44 included data after the initiation of additional AHAs. All efficacy analyses were performed in the full analysis set (FAS) defined as all randomised patients who received at least one dose of study drug and who had valid measurements both at baseline and at least one postbaseline measurement. It should be noted that data from all four patients (one patient in the sitagliptin/metformin FDC group and three patients in the metformin monotherapy group) enrolled at one site that did not follow Good Clinical practice were not included in safety and efficacy analyses.

The change from baseline in HbA1c at Week 44 was analysed using an analysis of covariance (ANCOVA) model controlling for treatment and baseline HbA1c. Differences in least squares (LS) mean changes from baseline and 95% confidence intervals (CI) were calculated to estimate the between-group differences. A p-value of <0.050 was considered statistically significant. The last-observation-carried-forward method was used to impute missing data. Data from Phase A were carried forward to Phase B, if data were missing during Phase B.

A logistic regression model controlling for treatment and baseline HbA1c was used to analyse the proportions of patients with HbA1c values $<7.0\%$ and $<6.5\%$ at Week 44. In addition, the difference in proportions and its 95% CI were calculated using the method of Miettinen and Nurminen [16]. Changes from baseline (or percent change, as appropriate) in other secondary efficacy endpoints were analysed using the ANCOVA model as specified for HbA1c but with the corresponding baseline value as a covariate. Percent changes from baseline in TG were analysed using a non-parametric ANCOVA model using ranks based upon Tukey's normalized scores controlling for treatment and baseline value.

The proportion of patients who initiated AHAs was compared between the two treatment groups using logistic regression with model terms for treatment and baseline HbA1c. An analysis of the time-to-first additional AHA was performed using the Kaplan–Meier estimate and plot and the log-rank test for the entire study.

Safety analyses were performed in the population consisting of all patients who took at least one dose of study drug. Between-group differences in AEs of hypoglycaemia and prespecified selected gastrointestinal AEs (i.e. abdominal pain, nausea, vomiting, diarrhoea) were tested for statistical significance. Tests and CIs comparing differences in proportions of events used the method of Miettinen and Nurminen [16].

Results

Patients

Patient demographics at baseline are detailed in the Phase A publication of this study but are summarized here [15]. There were 1250 patients randomised to study treatment with data from 1246 patients analysed; 625 were assigned to sitagliptin/metformin FDC and 621 were assigned to metformin monotherapy. Baseline demographics were generally similar among the sitagliptin/metformin FDC and metformin monotherapy treatment groups with regard to mean age (49.4 and 50.0 years, respectively), gender (56% and 57% male, respectively), body mass index (33.0 and 33.7, respectively), baseline HbA1c levels (9.9% and 9.8%, respectively), and duration of T2DM (3.5 and 3.2 years, respectively) [15].

Patient disposition and reasons for discontinuation during the study are in figure 1. The most common reasons for discontinuation during Phase B were (i) withdrawal by subject; (ii) patient lost to follow-up; and (iii) AEs. The reasons for discontinuation were generally similar in both treatment groups (figure 1).

Use of Additional AHAs

The proportion of patients receiving additional AHAs during the study was low. In the sitagliptin/metformin FDC group, 8.8% of patients were given additional AHAs compared with 16.7% of patients in the metformin monotherapy group. Figure 2 shows graphically this imbalance between groups in the use of additional AHAs and that more AHAs were added during Phase B compared with Phase A. Among patients who received additional AHAs, four patients in the sitagliptin/metformin FDC group and nine patients in the metformin monotherapy group received more than one additional AHA.

Additional AHAs given included sulfonylureas (glimepiride, glipizide, glyburide), thiazolidinediones (pioglitazone, rosiglitazone), meglitinides (repaglinide), sulfonylurea/thiazolidinedione combinations (glimepiride/pioglitazone, glimepiride/rosiglitazone), and insulin (although per protocol, only sulfonylureas, thiazolidinediones, and meglitinides were permitted as additional AHAs, one investigator initiated insulin in one patient in addition to pioglitazone in the sitagliptin/metformin

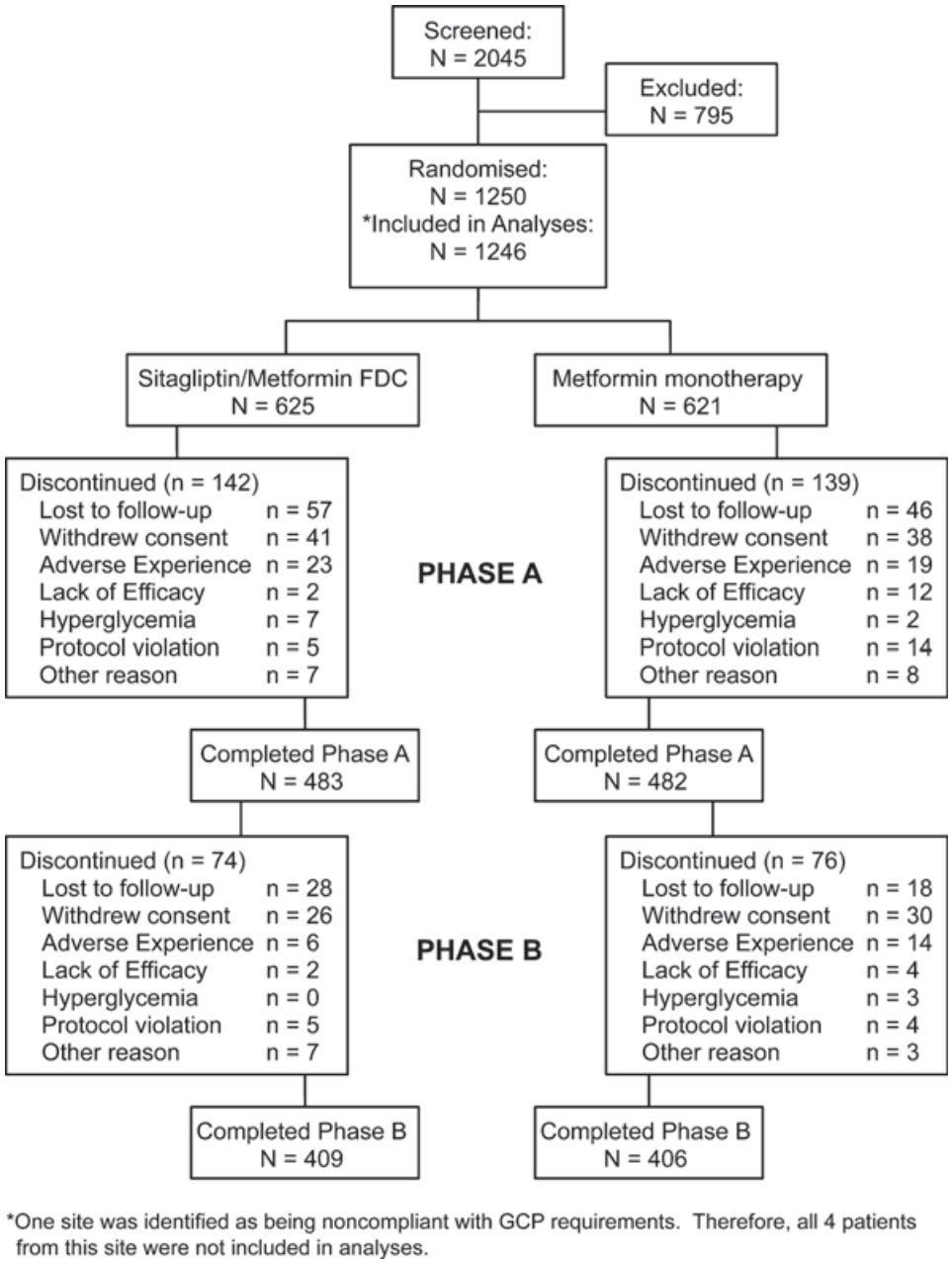

Figure 1. Patient disposition, including reasons for discontinuation are shown for both Phase A and Phase B of the study by treatment group.

FDC group). The most common additional AHAs administered were sulfonylureas (7.5% and 13.7% of patients on sitagliptin/metformin FDC and metformin monotherapy, respectively).

Figure 3 shows results of a post-hoc analysis assessing the proportion of patients who received additional AHAs during Phase B (i.e. with laboratory glycaemic values unmasked to investigators) based on HbA1c levels at the beginning of Phase B in the study. This shows that a relatively low percentage of patients requiring additional antihyperglycaemic therapy to achieve glycaemic goals actually received additional AHA therapy. Among patients who entered Phase B, 51% had an HbA1c level that was $\geq$7.0%; among these patients 79% did not receive additional AHAs. Even among patients who had an HbA1c level $\geq$10.0% at Week 18, 66% did not receive additional AHAs (figure 3).

Efficacy

In this analysis including data after initiation of additional AHAs in both groups (including protocol-specified rescue therapy in Phase A and additional supplemental AHAs as clinically indicated in Phase B), a significantly greater ($p \leq 0.001$) reduction from baseline in HbA1c and FPG was observed at Week 44 with the initial combination therapy with sitagliptin/metformin FDC compared with initial therapy

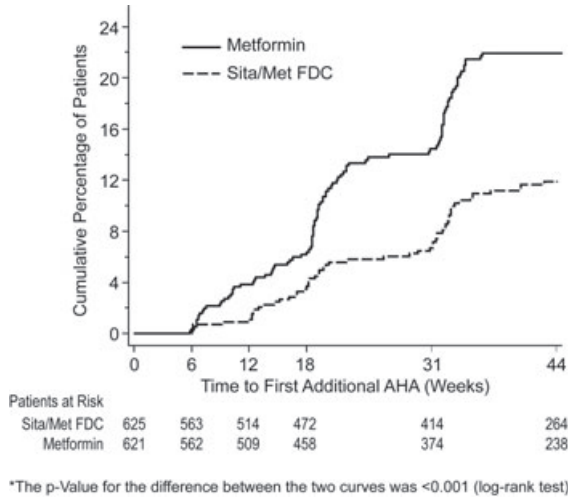

Figure 2. Kaplan–Meier curves for the addition of antihyperglycaemic agents (AHAs) over time by treatment group.

with metformin (Table 1). The LS mean changes in A1C from baseline over time through Week 44 show progressive reductions in A1C levels through Week 18, with a slight increase after Week 18 until Week 44, in both treatment groups (figure 4). Higher proportions of patients in the sitagliptin/metformin FDC group had HbA1c levels either <7.0% or <6.5% compared with the metformin monotherapy group (Table 1).

Baseline mean (s.d.) body weight was 95.4 (22.9) kg and 97.6 (25.3) kg for the sitagliptin/metformin FDC and metformin groups, respectively, and LS mean change from baseline was −1.1 kg (95% CI: −1.7, −0.6) and −1.2 kg (95% CI: −1.7, −0.6), respectively. For blood lipids, a significant between-group difference was observed in TG change from baseline: median change from baseline (s.d.) was −6.1 (48.6) and 0.0 (46.5) mg/dl for the sitagliptin/metformin FDC and metformin groups, respectively ($p = 0.040$).

Safety and Tolerability

The overall incidences of AEs, including serious AEs, drug-related AEs and discontinuations as a result of AEs were similar in both treatment groups (Table 2). Over the 44-week treatment period, three patients died; one patient in the sitagliptin/metformin FDC group (acute myocardial infarction) and two patients in the metformin group (cardio-respiratory arrest and electrocution); none of these fatal AEs were considered to be drug-related by the investigators. The most common AE was diarrhoea, which occurred in a significantly lower proportion of patients in the sitagliptin/metformin FDC group compared with the metformin monotherapy group. Other common AEs (i.e. occurring in ≥3.0% of patients in either treatment group) included nausea, vomiting, fatigue, nasopharyngitis, sinusitis, upper respiratory tract infection, hypoglycaemia and headache. These AEs each occurred at a relatively similar incidence among the treatment groups.

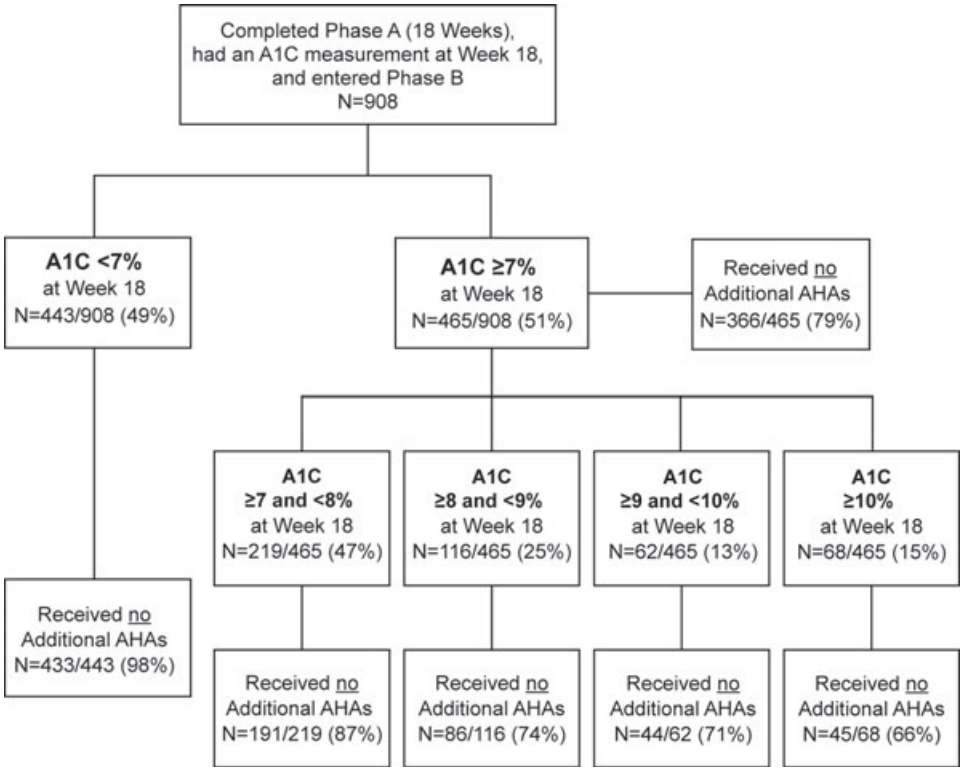

Figure 3. Addition of antihyperglycaemic agent (AHA) during Phase B by haemoglobin A1C (HbA1c) levels at the beginning of Phase B and by treatment group.

Table 1. Baseline and change from baseline in fasting glycaemic endpoints at Week 44 for the FAS population (including data after initiation of additional AHAs).

Parameter*	Sitagliptin/ metformin FDC	Metformin monotherapy
HbA1c (%)		
N	560	569
Baseline ± s.d.	9.9 ± 1.8	9.8 ± 1.8
LS mean change from baseline	−2.3 (−2.4, −2.1)	−1.8 (−1.9, −1.6)
Difference versus MET alone	−0.5 (−0.7, −0.3)†	—
Patients with HbA1c <7.0%		
N	560	569
n (%)	258 (46.1)†	173 (30.4)
Difference in percent (95% CI)	15.7 (10.0, 21.2)	—
Relative risk (95% CI)	1.52 (1.30, 1.77)	—
Patients with HbA1c <6.5%		
N	560	569
n (%)	157 (28.0)†	94 (16.5)
Difference in percent (95% CI)	11.5 (6.7, 16.3)	—
Relative risk (95% CI)	1.70 (1.35, 2.13)	—
Fasting plasma glucose (mg/dl)		
N	560	567
Baseline ± s.d.	222.7 ± 67.3	220.7 ± 71.1
LS mean change from baseline	−65.0 (−70.0, −60.0)	−53.4 (−58.3, −48.4)
Difference versus MET alone	−11.7 (−18.7, −4.6)†	—

AHAs, antihyperglycaemic agents; FAS, full analysis set; FDC, fixed-dose combination; HbA1c, haemoglobin A1C; MET, metformin; LS, least squares.
*Changes from baseline and differences versus metformin monotherapy are expressed as least squares mean (95% CI).
†$p \leq 0.001$ versus metformin monotherapy.

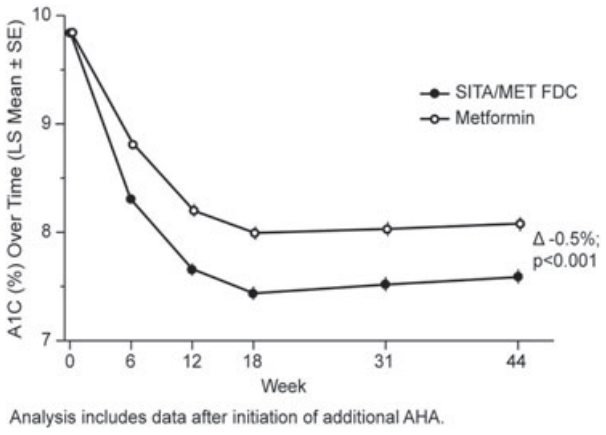

Figure 4. Haemoglobin A1C (HbA1c) (LS mean (±s.e.) over 44 weeks). The analysis includes data after initiation of additional antihyperglycaemic agent (AHA) therapy.

The incidence of hypoglycaemia was low and similar in both treatment groups (Table 3). No episode of hypoglycaemia required medical or non-medical assistance, and no episode exhibited marked severity (defined as markedly depressed level of consciousness, loss of consciousness or seizure). A significantly lower proportion of patients in the sitagliptin/metformin FDC group had the prespecified gastrointestinal AEs of abdominal pain and diarrhoea compared with patients in the metformin monotherapy group ($p < 0.050$; Table 3).

Table 2. Summary of AEs for weeks 0–44 including data after initiation of additional AHAs.

Parameter	Sitagliptin/ metformin FDC (N = 625)	Metformin monotherapy (N = 621)
One or more AEs	358 (57.3)	380 (61.2)
Drug-related* AEs	127 (20.3)	136 (21.9)
Serious AEs (SAEs)	28 (4.5)	38 (6.1)
Drug-related* SAEs	3 (0.5)	1 (0.2)
Deaths	1 (0.2)	2 (0.3)
Discontinued as a result of AEs	27 (4.3)	32 (5.2)
Discontinued as a result of drug-related* AEs	19 (3.0)	19 (3.1)
Discontinued as a result of SAEs	6 (1.0)	5 (0.8)
Discontinued as a result of drug-related* SAEs	2 (0.3)	1 (0.2)
Most common AEs (incidence ≥3% in one or more treatment groups)		
Diarrhoea	86 (13.8)	112 (18.0)
Nausea	37 (5.9)	44 (7.1)
Nasopharyngitis	33 (5.3)	26 (4.2)
Headache	35 (5.6)	23 (3.7)
Upper respiratory tract infection	30 (4.8)	31 (5.0)
Sinusitis	23 (3.7)	22 (3.5)
Vomiting	19 (3.0)	18 (2.9)
Hypoglycaemia	19 (3.0)	23 (3.7)
Fatigue	10 (1.6)	20 (3.2)

AEs, adverse experiences; AHAs, antihyperglycaemic agents; FDC, fixed-dose combination.
*Determined by the investigator to be related to study medication.

Table 3. Prespecified AEs of interest including data after initiation of additional AHAs.

Parameter	Sitagliptin/ metformin FDC (N = 625)	Metformin monotherapy (N = 621)
Hypoglycaemia	19 (3.0)	23 (3.7)
Prespecified gastrointestinal AEs		
Abdominal pain*	19 (3.0)†	33 (5.3)
Diarrhoea	86 (13.8)†	112 (18.0)
Nausea	37 (5.9)	44 (7.1)
Vomiting	19 (3.0)	18 (2.9)

AEs, adverse experiences; AHAs, antihyperglycaemic agents; FDC, fixed-dose combination.
*Includes abdominal pain lower, abdominal pain upper, abdominal pain, abdominal discomfort and epigastric pain.
†$p < 0.050$ versus metformin monotherapy.

Discussion

While metformin is a generally well-tolerated medication with proven effects on lowering glycaemic levels, patients often do

not achieve adequate reduction of hyperglycaemia to levels that are recommended by treatment guidelines [6]. This study was conducted to evaluate two different treatment paradigms: (i) initial combination therapy with sitagliptin/metformin in an FDC with additional AHA therapy added as clinically indicated; (ii) initial therapy with metformin monotherapy with additional AHA therapy added as clinically indicated. The results of this study show that patients randomized to sitagliptin/metformin FDC had better glycaemic control at the end of the study and more frequently achieved glycaemic targets compared with patients who initiated metformin monotherapy. The 26-week Phase B portion of this study was designed to resemble real-world clinical settings where physicians have the opportunity to monitor their patients' glycaemic levels and adjust their therapeutic regimens to meet evidence-based goals for glycaemic control. Therefore, the observation that the difference between treatment groups in glycaemic control remained stable over 44 weeks including the Phase B period is in contrast to what would be expected if patients with inadequate glycaemic control were given additional AHA in order to achieve guideline-defined targets. In order to better understand this observation, we more closely evaluated the utilization of AHAs in this study. During Phase A, the use of supplemental AHAs was low in both groups (although higher in the metformin monotherapy group), probably because of the masking of glycaemic levels unless flagged by the central laboratory. However, it should be noted that blood glucose was continuously monitored with fingerstick testing during this portion of the study as well. During Phase B, the use of additional AHAs increased and a greater proportion of patients on initial metformin monotherapy received additional AHAs compared with those treated initially with the sitagliptin/metformin FDC, which was probably because of better glycaemic control with the latter during Phase A of the study [15].

While greater use of additional AHA therapy was expected in the metformin monotherapy group, the utilization of add-on therapy was relatively low, even among patients whose HbA1c levels were well above 7.0% (e.g. HbA1c > 10%). The underutilization of additional AHAs is an explanation for the maintenance of the difference between the treatment groups in glycaemic efficacy at the end of the study. A potential limitation, which may have played a role in lowering the rate of intensification of the AHA regimen, is that the sponsor did not provide or pay for additional AHAs. However, this approach is not different from general clinical practice. Another limitation is that the study did not capture potential reasons for this underutilization. However, the utilization of additional AHAs in this study is consistent with previous evaluations of clinical decision making that show a reluctance to intensify therapy when patients meet criteria for advancement of therapy [11,17]. This phenomenon has been previously described as clinical inertia [11].

Several factors have been hypothesized to contribute to clinical inertia. In patients with T2DM, monitoring markers indicating hyperglycaemia and adjusting therapy accordingly to meet guidelines are widely accepted clinical treatment goals [1]. Despite this, physicians are motivated to initiate or adjust therapeutic regimens in response to the presentation of symptoms [11]. Patients with mild to moderate hyperglycaemia are likely to be asymptomatic in the short term and a lack of symptoms may lead to a false perception of improvement [11]. Other factors such as dietary non-adherence on the part of the patient can also be blamed for worsening glycaemic levels leading to a reluctance to adjust therapy despite this being the aspect of a patient's treatment strategy over which the physician has most control compared with enforcing a diet regimen [11].

It should be acknowledged that the determination of treatment strategies is based on a relationship between a doctor and a patient; thus, patient attitudes toward pharmacologic therapy for the management of markers rather than symptoms probably influence prescribing behaviours of physicians; acceptance of additional medications in a patient population who are already receiving multiple drugs for other disorders (i.e. hypertension and dyslipidemia) may be difficult and viewed as burdensome. Initial combination therapy is a treatment strategy that can provide early adherence to guidelines and avoid factors leading to clinical inertia. It is important to note that the use of initial combination therapy with sitagliptin and metformin in this study resulted in a greater proportion of patients with HbA1c levels <7.0% compared with initial monotherapy with metformin.

Another factor that influences physician decisions on whether to add medications to treatment regimens is the desire to limit potential adverse effects that can result from the use of additional medications in patients with T2DM. The most common tolerability issue with metformin is gastrointestinal disturbance, particularly diarrhoea and abdominal pain [18]; this is consistent with what was observed in this study. Interestingly, the combination of sitagliptin and metformin was associated with a lower incidence of diarrhoea and abdominal pain. A possible explanation for this may be due to increased levels of GLP-1 that may have an effect on gut motility, which can explain data from clinical trials of sitagliptin that have shown a slightly greater incidence of mild constipation while patients not exposed to sitagliptin in the same trials were more likely to develop diarrhoea as a result of their use of metformin [19,20]. Metformin is also associated with a reduction in body weight, which was also observed in this study; the addition of sitagliptin to metformin did not alter the effect of metformin on body weight. Additionally, the addition of sitagliptin did not increase the incidence of hypoglycaemia. These data support previous studies that show that sitagliptin, alone and in combination with metformin, is generally well tolerated [21,22].

In summary, compared with the strategy of metformin monotherapy with the option to add additional AHAs, the strategy of initial sitagliptin/metformin FDC with the option to add additional AHAs was superior in lowering HbA1c levels and FPG and resulted in a higher proportion of patients with A1C values meeting the ADA recommended treatment goals of glycaemic control of HbA1c <7.0%. Efficacy for this treatment approach was shown over a 44-week time period. The results of this study illustrate that 'clinical inertia' may delay attainment of target glycaemic goals in patients and that the use of initial combination therapy may be appropriate in certain patients to

achieve desired glycaemic control. The treatment strategy with initial combination therapy with sitagliptin and metformin was generally well tolerated.

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Conflict of Interest

L. O. has received honoraria for teaching and speaking from Merck & Co., Inc. C. R. has no conflicts of interest to disclose. T. L. S., D. E. W.-H., M. C., L. T., A. M., K. D. K. and B. J. G. are employees of Merck Sharp & Dohme Corp. and may own stock/stock options in Merck.

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