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ORIGINAL ARTICLE

Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes

J. Wainstein[1], L. Katz[2], S. S. Engel[2], L. Xu[2], G. T. Golm[2], S. Hussain[2], E. A. O'Neill[2], K. D. Kaufman[2] & B. J. Goldstein[2]

[1]*The E. Wolfson Medical Center, Diabetes Unit, Holon, Israel*
[2]*Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA*

Aims: To evaluate the efficacy and safety of initial therapy with a fixed-dose combination (FDC) of sitagliptin and metformin compared with pioglitazone in drug-naïve patients with type 2 diabetes.

Methods: After a 2-week single-blind placebo run-in period, patients with type 2 diabetes, HbA1c of 7.5–12% and not on antihyperglycaemic agent therapy were randomized in a double-blind manner to initial treatment with a FDC of sitagliptin/metformin 50/500 mg twice daily (N = 261) or pioglitazone 30 mg per day (N = 256). Sitagliptin/metformin and pioglitazone were up-titrated over 4 weeks to doses of 50/1000 mg twice daily and 45 mg per day, respectively. Both treatments were then continued for an additional 28 weeks.

Results: From a mean baseline HbA1c of 8.9% in both groups, least squares (LS) mean changes in HbA1c at week 32 were −1.9 and −1.4% for sitagliptin/metformin and pioglitazone, respectively (between-group difference = −0.5%; $p < 0.001$). A greater proportion of patients had an HbA1c of <7% at week 32 with sitagliptin/metformin vs. pioglitazone (57% vs. 43%, $p < 0.001$). Compared with pioglitazone, sitagliptin/metformin treatment resulted in greater LS mean reductions in fasting plasma glucose (FPG) [−56.0 mg/dl (−3.11 mmol/l) vs. −44.0 mg/dl (−2.45 mmol/l), $p < 0.001$] and in 2-h post-meal glucose [−102.2 mg/dl (−5.68 mmol/l) vs. −82.0 mg/dl (−4.56 mmol/l), $p < 0.001$] at week 32. A substantially greater reduction in FPG [−40.5 mg/dl (−2.25 mmol/l) vs. −13.0 mg/dl (−0.72 mmol/l), $p < 0.001$] was observed at week 1 with sitagliptin/metformin vs. pioglitazone. A greater reduction in the fasting proinsulin/insulin ratio and a greater increase in homeostasis model assessment of β-cell function (HOMA-β) were observed with sitagliptin/metformin than with pioglitazone, while greater decreases in fasting insulin and HOMA of insulin resistance (HOMA-IR), and a greater increase in quantitative insulin sensitivity check index (QUICKI) were observed with pioglitazone than with sitagliptin/metformin. Both sitagliptin/metformin and pioglitazone were generally well tolerated. Sitagliptin/metformin led to weight loss (−1.4 kg), while pioglitazone led to weight gain (3.0 kg) ($p < 0.001$ for the between-group difference). Higher incidences of diarrhoea (15.3% vs. 4.3%, $p < 0.001$), nausea (4.6% vs. 1.2%, $p = 0.02$) and vomiting (1.9% vs. 0.0%, $p = 0.026$), and a lower incidence of oedema (1.1% vs. 7.0%, $p < 0.001$), were observed with sitagliptin/metformin vs. pioglitazone. The between-group difference in the incidence of hypoglycaemia did not reach statistical significance (8.4 and 4.3% with sitagliptin/metformin and pioglitazone, respectively; $p = 0.055$).

Conclusion: Compared with pioglitazone, initial therapy with a FDC of sitagliptin and metformin led to significantly greater improvement in glycaemic control as well as a higher incidence of prespecified gastrointestinal adverse events, a lower incidence of oedema and weight loss vs. weight gain.

Keywords: dipeptidyl peptidase-4 inhibitors, incretins, MK-0431

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Introduction

Type 2 diabetes is a disease that affects a large and growing population [1]. The incidence of microvascular complications associated with diabetes (e.g. retinopathy, nephropathy and neuropathy) can be reduced with appropriate glycaemic control [2,3], but due to the chronic and progressive nature of the disease, affected patients may not achieve or maintain desired glycaemic control with monotherapy [4,5]. However, when patients do not achieve glycaemic goals with initial monotherapy treatment, physicians frequently do not intensify antihyperglycaemic therapy, despite the availability of other agents [6]. Furthermore, benefits of early achievement of glycaemic goals have been suggested by the long-term follow-up of studies evaluating intensive control of hyperglycaemia in patients with either type 1 [7] or type 2 [8] diabetes. In these studies, intensive glycaemic control resulted in

Correspondence to: Dr Samuel S. Engel, Merck Research Laboratories, RY34-A232, Rahway, NJ 07065, USA.
E-mail: samuel.engel@merck.com

persistent reductions in both microvascular and macrovascular complications long after the between-group differences in glycaemic control had disappeared. These data support the use of treatment paradigms that target the early achievement of glycaemic goals in patients with type 2 diabetes.

To address the need for rapid and effective treatment of type 2 diabetes, initial combination therapy may result in a larger proportion of patients achieving glycaemic goals. Both the American Association of Clinical Endocrinologists and the Canadian Diabetes Association include the use of initial combination therapy in their recommendations for treatment of patients with severe hyperglycaemia (HbA1c $\geq$ 9.0%) [9], (HbA1c $>$ 7.6%) [10], and both the American Diabetes Association and the European Association for the Study of Diabetes consider early initiation of combination therapy a treatment option in patients with high levels of glycaemia (e.g. HbA1c $>$ 8.5%) [11].

The most commonly used oral antihyperglycaemic agent (AHA) for the treatment of type 2 diabetes, both as monotherapy and in combination with other AHAs, is the biguanide metformin [12,13]. Metformin primarily acts by reducing hepatic glucose production, but it may also reduce insulin resistance in the periphery [12–16]. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, lowers plasma glucose by increasing glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide concentrations, thus enhancing insulin release and reducing glucagon secretion, in a glucose-dependent manner [17]. Either as add-on therapy or as initial co-administration therapy, sitagliptin in combination with metformin has been shown to be safe and effective for patients with type 2 diabetes [18–21]. Studies of up to 2 years duration have showed long-term efficacy of the combination of sitagliptin and metformin [22].

Thiazolidinediones (TZDs) are another class of commonly used oral AHAs. These compounds, including rosiglitazone and pioglitazone, are peroxisome proliferator-activated receptor-γ agonists which lower glucose concentrations by increasing peripheral insulin sensitivity [23]. Pioglitazone is currently recommended as the preferred TZD for treatment of type 2 diabetes [11].

To further evaluate the relative benefits of initial therapy with a fixed-dose combination (FDC) of sitagliptin and metformin to patients with type 2 diabetes, we assessed the efficacy and safety of this treatment compared with pioglitazone monotherapy.

Methods

This was a multicentre, randomized, double-blind, active-comparator (pioglitazone) controlled study. The duration of this study was up to 35 weeks, including a 1-week period between the screening visit and the beginning of a 2-week single-blind placebo run-in period, and a 32-week double-blind active treatment period.

Patients were to be $\geq$18 and $\leq$78 years of age with a diagnosis of type 2 diabetes and inadequate glycaemic control (defined as HbA1c $\geq$7.5 and $\leq$12.0% while on a diet/exercise regimen). Patients were not to have been on an AHA in the 3 months prior to the screening visit and were to have had less than 4 weeks of cumulative duration of treatment with an AHA over the 3 years prior to the screening visit.

Patients were to be excluded if they had a history of type 1 diabetes, a contraindication to biguanide or TZD medications, previous treatment with any DPP-4 inhibitor or incretin mimetic, required treatment with CYP2C8 inhibitors or inducers, had impaired renal function (creatinine clearance $<$60 ml/min), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than twofold the upper limit of normal, or a fasting glucose value $<$130 mg/dl (7.2 mmol/l) or $>$320 mg/dl (17.8 mmol/l) prior to randomization.

The starting dose of the sitagliptin/metformin FDC was 50/500 mg administered twice daily. The dose was increased to 50/500 mg in the morning and 50/1000 mg in the evening at week 2, and then increased to 50/1000 mg twice daily at week 4. The starting dose of pioglitazone was 30 mg per day, which was up-titrated to 45 mg per day at week 4.

The standard meal challenge consisted of one nutrition bar and one nutrition drink (about 460 kcal, including approximately 75 g of carbohydrate, 9 g of fat and 18 g of protein).

Patients were to be discontinued from the study if they experienced repeated episodes of unexplained hypoglycaemia as defined by FPG or fingerstick glucose $<$50 mg/dl (2.78 mmol/l) with or without symptoms of hypoglycaemia or $<$70 mg/dl ($<$3.89 mmol/l) with symptoms of hypoglycaemia. In addition, patients were to be discontinued from the study if they failed to meet prespecified, progressively stricter glycaemic control criteria. From study day 1 through week 8, patients were discontinued if FPG was consistently $>$300 mg/dl (16.65 mmol/l); after week 8 through week 14, patients were discontinued if their FPG was consistently $>$240 mg/dl (13.32 mmol/l); after week 14 through week 26, patients were discontinued if their FPG was consistently $>$220 mg/dl (12.21 mmol/l); and after week 26 through week 32, patients were discontinued if their FPG was consistently $>$200 mg/dl (11.10 mmol/l).

All patients provided written informed consent to participate. This study (Sitagliptin Protocol 066; ClinicalTrials.gov: NCT00532935) was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory authorities.

Study Evaluations

Primary Hypotheses

The primary hypotheses of this study were that 32 weeks of treatment with sitagliptin/metformin FDC 50/1000 mg twice daily would be well tolerated and would lower HbA1c (mean change from baseline) more than pioglitazone 45 mg daily. Secondary hypotheses were that after 1 week, treatment with sitagliptin/metformin FDC 50/500 twice daily would provide greater reduction in fasting plasma glucose (FPG) than treatment with pioglitazone 30 mg daily; that after 32 weeks, treatment with sitagliptin/metformin FDC 50/1000 mg twice daily would result in greater reduction from baseline in

2-h post-meal glucose (PMG) after a standard meal challenge, greater reduction from baseline in FPG and a greater percentage of patients achieving HbA1c <7.0%, than treatment with pioglitazone 45 mg once daily; and that after 32 weeks, treatment with pioglitazone 45 mg daily would result in an increase in body weight (mean change from baseline) relative to the effect of treatment with sitagliptin/metformin on body weight.

Efficacy Assessments

The primary efficacy outcome was change from baseline in HbA1c at week 32. Secondary efficacy endpoints included the percentages of patients with HbA1c values at goals of <7.0 and <6.5%. Change from baseline in FPG at weeks 1 and 32 was evaluated. Change from baseline in proinsulin/insulin ratio, homeostasis model assessment of β-cell function (HOMA-β), HOMA of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) and per cent change from baseline in serum lipids were assessed at week 32. Change from baseline in 2-h PMG and in indices assessing insulin secretion following a standard meal challenge, including glucose profiles, insulin and insulinogenic index [24], were evaluated at week 32. HbA1c and FPG were also measured periodically throughout the course of this study.

Safety Assessments

Safety and tolerability were assessed through the analysis of adverse events, and by laboratory evaluations, body weight measurements and vital signs. All adverse events were rated by the study site investigators for intensity and relationship to study drug. Laboratory safety evaluations included blood chemistry, haematology and urinalysis.

Patients were requested to perform a fingerstick glucose measurement immediately if symptoms of hypoglycaemia occurred (e.g. weakness, dizziness, shakiness, sweating, palpitations or confusion) but to avoid delay in treating these symptoms. Patients were provided with, and instructed in the use of, a hypoglycaemia assessment log to document potential hypoglycaemia episodes and collect information on the severity of the events (such as the requirement for the assistance of another person or medical treatment), thereby assisting the investigator in assessing the event.

All laboratory efficacy and safety measurements were performed at central laboratories (Global Central Labs at PPD, Highland Heights, KY, USA and PPD Global Central Labs, LLC, Zaventem, Belgium) by technicians who were blinded to treatment allocation.

Statistical Methods: Analyses

Efficacy analyses included all randomized patients who took at least one dose of study medication and had both a baseline measurement and at least one post-randomization measurement of the respective endpoint. All continuous efficacy endpoints were analysed at week 32 (FPG was also analysed at week 1) using analysis of covariance (ANCOVA), controlling for treatment and the relevant baseline measurement. To account for violation of the ANCOVA normality assumption, the outcome variable in the ANCOVA model for triglycerides was the normalized score [25] of per cent change from baseline. For all efficacy analyses at week 32, the last observed post-randomization measurement was used in lieu of the week 32 measurement if the week 32 measurement was missing. Between-group differences in the proportions of patients with HbA1c value <7.0 and 6.5% at week 32 were estimated using the method of Miettinen and Nurminen [26]. The insulinogenic index was analysed on the log scale to accommodate the presence of outliers. Results are presented after appropriate back-transformation.

The type 1 error rate was controlled at 0.05 for change from baseline HbA1c, 2-h PMG and FPG by testing the between-group difference for each endpoint at $\alpha = 0.05$ (two-sided) in a prespecified order, such that testing of a successive endpoint was performed only if the p value for the previous endpoint was <0.05. The testing for change from baseline in FPG at week 1 and goal of HbA1c at week 32 were assessed at $\alpha = 0.05$ (two-sided) only if the p value for HbA1c was <0.05. For all other efficacy endpoints, nominal statistical significance was declared if the p value was <0.05.

Safety and tolerability were assessed by a review of safety parameters including adverse events, laboratory safety parameters and vital signs. Analyses of adverse events included all randomized patients who received at least one dose of study medication. The analysis of body weight included all randomized patients who received at least one dose of study treatment and had a baseline and at least one post-baseline measurement. Imputation was not performed for missing body weight data.

Between-group differences in incidence for safety parameters were estimated, along with the associated 95% confidence intervals (CIs) (and where prespecified, p values), using the method of Miettinen and Nurminen [26] when at least four patients experienced the event in at least one treatment group.

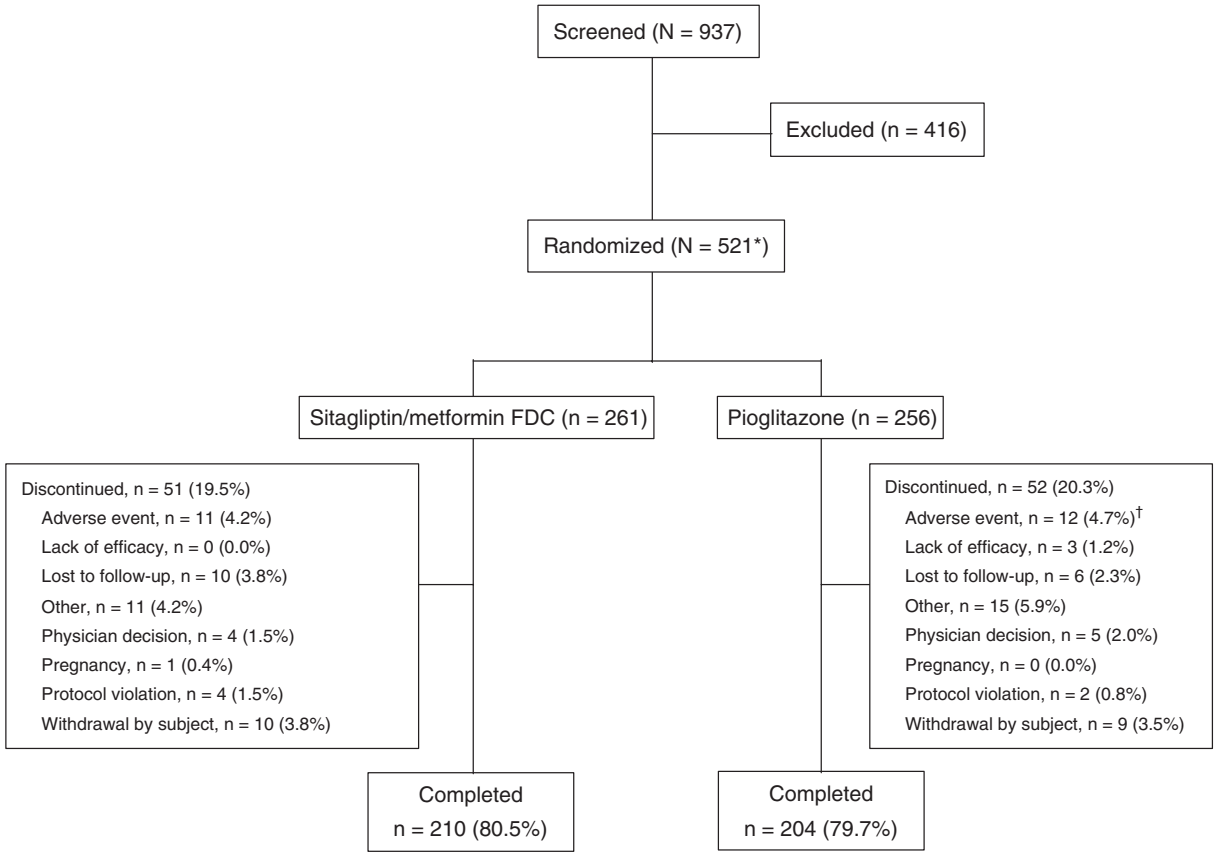
Calculations of p values were prespecified for between-group differences in the incidence of hypoglycaemia, selected gastrointestinal adverse events and oedema. Assessment of change from baseline in body weight used an ANCOVA model analogous to the primary analysis model. For continuous laboratory parameters and vital signs, summary tabulations of descriptive statistics over time were provided.

Prior to unblinding, it was found that two patients in this study enrolled at two different sites and were randomized twice. These patients were excluded from all analyses.

Results

Patient Disposition and Characteristics

A total of 937 patients were screened and 521 were randomized at 67 sites worldwide. This includes the two patients who were randomized twice (each at two different sites, thus four randomization numbers). Data for these two patients were excluded from all analyses (efficacy and safety), resulting in an elimination of four allocation numbers from the total number randomized. Of the 416 patients who were not randomized,



*Includes 2 patients who were each randomized twice at two different sites, but who were not included in any analyses.

†Includes 1 patient who discontinued due to an adverse event with onset prior to initiation of study medication.

Figure 1. Patient disposition.

the most common reason for exclusion was failure to meet the HbA1c inclusion criterion (65.1%).

Of the 517 randomized patients included in study analyses, 414 (79.5%) completed the study, 210 (80.5%) in the sitagliptin/metformin group and 204 (79.7%) in the pioglitazone group. Reasons for discontinuation were generally similar between treatment groups (figure 1). The treatment groups were generally similar with regard to demographics and efficacy parameters (Table 1).

Efficacy

At week 32, the least squares (LS) mean change from baseline in HbA1c was significantly ($p < 0.001$) lower in the sitagliptin/metformin group compared with the pioglitazone group (Table 2). In addition, the reduction in HbA1c in the sitagliptin/metformin combination group was more rapid than in the pioglitazone group (figure 2). Consistent with these results, the percentages of patients at each of the HbA1c goals were greater with sitagliptin/metformin than with pioglitazone (Table 3).

Meaningful decreases in HbA1c were observed in both treatment groups within all subgroups defined by baseline HbA1c (Table 4). In both treatment groups, there was a trend toward greater reduction of HbA1c at week 32 with increasing baseline HbA1c levels. In all HbA1c subgroups, this trend was greater with the sitagliptin/metformin FDC than with pioglitazone monotherapy. In the population of patients with HbA1c $\geq$10%, the difference in reduction from baseline between the combination treatment group and the pioglitazone monotherapy group was significant [−0.94 (95% CI: −1.37, −0.51), $p < 0.001$].

The between-group treatment differences were generally consistent across subgroups defined by race, ethnicity and body mass index. Meaningful reductions from baseline were observed in both treatment groups within all subgroups where the sample size was >10 patients per group (data not shown).

Treatment with the sitagliptin/metformin FDC resulted in rapid and sustained reduction in FPG, reaching near maximal effect by week 4, whereas treatment with pioglitazone resulted in a more gradual reduction in FPG (figure 3). The LS mean reductions from baseline in FPG were significantly greater ($p < 0.001$) in the sitagliptin/metformin treatment group compared with the pioglitazone monotherapy group (Table 2) at both weeks 1 and 32.

Both the LS mean reduction from baseline in the fasting proinsulin/insulin ratio and the LS mean increase from

Table 1. Baseline demographics and baseline efficacy endpoint data for all randomized patients.

Parameter	Sitagliptin /metformin (N = 261)	Pioglitazone (N = 256)
Age (years)	52.4 ± 10.7	52.2 ± 11.0
Gender, n (%)		
Male	143 (54.8)	134 (52.3)
Race, n (%)		
White	168 (64.4)	167 (65.2)
Asian	58 (22.2)	55 (21.5)
Multiracial	27 (10.3)	29 (11.3)
Black or African	6 (2.3)	5 (2.0)
American Indian	2 (0.8)	0 (0.0)
Other		
Ethnicity, n (%)		
Hispanic or Latino	82 (31.4)	83 (32.4)
Not Hispanic or Latino	179 (68.6)	173 (67.6)
Body weight (kg)	82.8 ± 21.1	81.4 ± 19.9
Body mass index (kg/m^2)	30.0 ± 6.1	29.6 ± 5.5
HbA1c, %	9.0 ± 1.3	8.9 ± 1.3
(range)	(6.4–12.0)	(6.5–13.2)
HbA1c distribution, n (%)		
<8%	63 (24.1)	72 (28.1)
≥8 and <9%	76 (29.1)	71 (27.7)
≥9 and <10%	59 (22.6)	65 (25.4)
≥10 and <11%	39 (14.9)	25 (9.8)
≥11	24 (9.2)	23 (9.0)
FPG, mg/dl (n)	190.6 ± 53.4 (261)	188.9 ± 57.1 (254)
2-h PMG, mg/dl (n)	273.7 ± 84.8 (239)	278.8 ± 86.4 (243)
Fasting Insulin, microIU/ml (n)	16.2 ± 15.4 (240)	14.7 ± 9.8 (244)
Duration of type 2 diabetes (years)	3.2 ± 4.0	3.3 ± 3.5

Data are expressed as mean ± standard deviation or frequency [n (%)] unless otherwise indicated. To convert FPG or PMG in mg/dl to mmol/l, divide by 18. FPG, fasting plasma glucose; PMG, post-meal glucose.

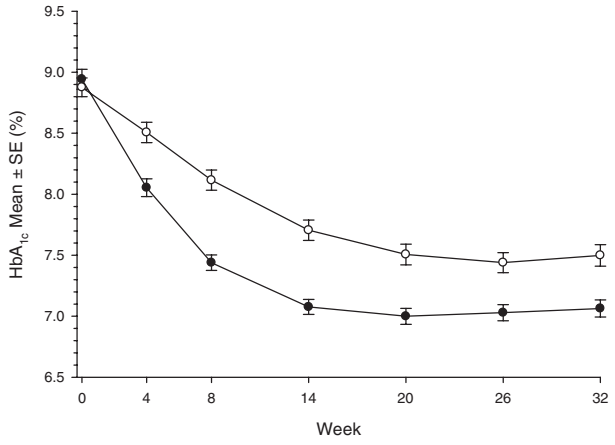


Figure 2. HbA1c: sitagliptin/metformin group (●); pioglitazone group (○).

baseline in HOMA-β were significantly greater in the sitagliptin/metformin treatment group than in the pioglitazone group (Table 2). The LS mean reduction from baseline

Table 2. Fasting efficacy endpoints.

Parameter	Sitagliptin/ metformin	Pioglitazone
HbA1c (%)		
n	253	246
Baseline	8.9 ± 1.3	8.9 ± 1.2
Week 32	7.1 ± 1.1	7.5 ± 1.4
Change from baseline	−1.9 (−2.0, −1.7)	−1.4 (−1.5, −1.3)
Change vs. pioglitazone	−0.5 (−0.7, −0.3)*	—
FPG (mg/dl)		
n	250	242
Baseline	190.0 ± 53.4	189.5 ± 57.5
Week 1	149.4 ± 38.4	176.7 ± 50.6
Change from baseline	−40.5 (−44.1, −36.9)	−13.0 (−16.6, −9.3)
Change vs. pioglitazone	−27.6 (−32.7, −22.4)*	—
FPG (mg/dl)		
n	258	250
Baseline	190.2 ± 53.3	188.9 ± 57.1
Week 32	133.8 ± 39.9	145.2 ± 51.6
Change from baseline	−56.0 (−60.9, −51.0)	−44.0 (−49.1, −39.0)
Change vs. pioglitazone	−11.9 (−19.0, −4.9)*	—
Fasting Insulin (μIU/ml)		
n	192	198
Baseline	15.7 ± 13.0	14.8 ± 9.6
Week 32	15.8 ± 14.3	11.4 ± 9.0
Change from baseline	0.3 (−1.2, 1.9)	−3.7 (−5.2, −2.1)
Change vs. pioglitazone	4.0 (1.8, 6.1)*	—
Fasting Proinsulin (pmol/l)		
n	191	200
Baseline	31.5 ± 25.7	31.2 ± 27.7
Week 32	20.5 ± 21.3	18.5 ± 15.9
Change from baseline	−11.0 (−13.2, −8.7)	−12.7 (−14.9, −10.6)
Change vs. pioglitazone	1.8 (−1.3, 4.9)	—
Fasting proinsulin/insulin ratio		
n	190	198
Baseline	0.397 ± 0.356	0.367 ± 0.245
Week 32	0.232 ± 0.168	0.298 ± 0.196
Change from baseline	−0.154 (−0.177, −0.132)	−0.079 (−0.101, −0.057)
Change vs. pioglitazone	−0.075 (−0.107, 0.044)*	—
HOMA-β (%)		
n	192	197
Baseline	56.1 ± 54.8	52.1 ± 39.3
Week 32	99.3 ± 101.9	74.1 ± 95.0
Change from baseline	43.7 (30.7, 56.7)	21.5 (8.7, 34.4)
Change vs. pioglitazone	22.2 (3.8, 40.5)†	—
HOMA-IR		
n	192	197
Baseline	7.1 ± 6.4	6.7 ± 4.5
Week 32	5.5 ± 6.7	3.8 ± 3.0
Change from baseline	−1.5 (−2.2, −0.8)	−3.0 (−3.7, −2.3)
Change vs. pioglitazone	1.5 (0.5, 2.5)†	—
QUICKI		
n	192	197
Baseline	0.302 ± 0.029	0.303 ± 0.029

Table 2. Continued.

Parameter	Sitagliptin/ metformin	Pioglitazone
Week 32	0.318 ± 0.035	0.326 ± 0.029
Change from baseline	0.016 (0.012, 0.019)	0.023 (0.020, 0.027)
Change vs. pioglitazone	−0.008 (−0.013, −0.002)†	—
Total cholesterol (mg/dl)		
n	227	227
Baseline	187.5 ± 40.7	188.0 ± 37.7
Week 32	182.7 ± 36.8	199.6 ± 42.4
Per cent change from baseline	−1.0 (−3.3, 1.3)	7.8 (5.5, 10.2)
Per cent change vs. pioglitazone	−8.8 (−12.1, −5.5)*	—
Triglycerides (mg/dl)		
n	227	227
Baseline	154.0 ± 115.3	140.0 ± 94.9
Week 32	145.0 ± 95.8	133.0 ± 86.5
Per cent change from baseline	0.5 (−5.7, 6.7)	−3.0 (−7.9, −1.9)
Per cent change vs. pioglitazone	4.6 (−1.9, 11.3)†	—
HDL-C (mg/dl)		
n	227	227
Baseline	44.4 ± 10.9	45.3 ± 11.1
Week 32	45.0 ± 11.0	50.1 ± 11.7
Per cent change from baseline	2.9 (0.4, 5.4)	13.0 (10.5, 15.5)
Per cent change vs. pioglitazone	−10.2 (−13.7, −6.6)*	—
LDL-C (mg/dl)		
n	226	226
Baseline	108.4 ± 36.0	110.2 ± 34.5
Week 32	103.1 ± 33.1	118.3 ± 38.6
Per cent change from baseline	−1.8 (−6.0, 2.4)	12.7 (8.5, 16.9)
Per cent change vs. pioglitazone	−14.6 (−20.5, −8.6)*	—

Baseline and week 32 data are expressed as mean (median for triglycerides) ± standard deviation; change or per cent change from baseline and change or per cent change vs. pioglitazone data are expressed as least squares mean (median for triglycerides) change (95% confidence interval). FPG, fasting plasma glucose.
*$p < 0.001$ for the between-group difference; †$p < 0.05$ for the between-group difference.

Table 3. Analysis of patients meeting HbA1c goals.

Parameter	Sitagliptin/ metformin (N = 253)	Pioglitazone (N = 246)
HbA1c < 7.0%, n (%)	145 (57.3)	107 (43.5)
Difference in % vs. pioglitazone (95% CI)	13.8 (5.0, 22.4)*	—
HbA1c < 6.5%, n (%)	79 (31.2)	44 (17.9)
Difference in % vs. pioglitazone (95% CI)	13.3 (5.8, 20.8)*	—

CI, confidence interval.
*$p < 0.001$ for the between-group difference.

Table 4. Change from baseline HbA1c at week 32 in patient subgroups defined by baseline HbA1c.

Baseline HbA1c	Sitagliptin/ metformin (N = 253)	Pioglitazone (N = 246)
<8.0%	−0.92 (−1.19, −0.64)* (n = 62)	−0.70 (−0.96, −0.45)* (n = 71)
≥8 and <9.0%	−1.52 (−1.77, −1.27)* (n = 74)	−1.21 (−1.47, −0.95)* (n = 68)
≥9 and <10.0%	−2.25 (−2.53, −1.97)* (n = 57)	−1.87 (−2.13, −1.60)* (n = 65)
≥10%	−2.97 (−3.25, −2.69)* (n = 60)	−2.03 (−2.36, −1.70)* (n = 42)

*$p < 0.001$ for change from baseline at week 32.

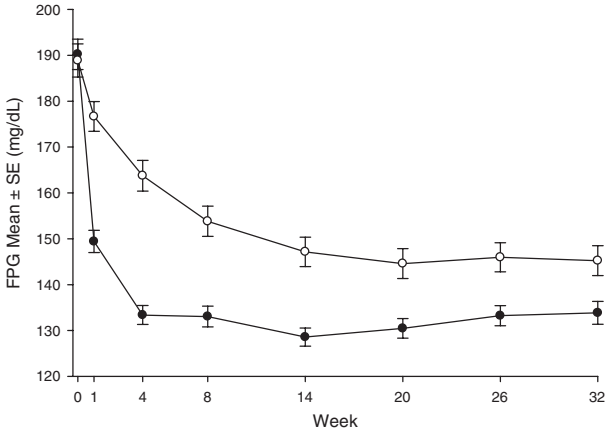


Figure 3. Fasting plasma glucose: sitagliptin/metformin group (●); pioglitazone group (○).

in HOMA-IR and increase from baseline in QUICKI were both significantly greater with pioglitazone than with sitagliptin/metformin therapy (Table 2).

Fasting total cholesterol, triglycerides and LDL-C were essentially unchanged from baseline with sitagliptin/metformin, while total cholesterol and LDL-C increased and triglycerides decreased after treatment with pioglitazone (Table 2). HDL-C increased with both treatments, with pioglitazone treatment resulting in a greater increase (Table 2).

Treatment with sitagliptin/metformin led to improvements in 2-h PMG, the 2-h post-meal proinsulin/insulin ratio and the insulinogenic index to a greater extent than pioglitazone (Table 5).

Safety and Tolerability

Over the 32-week treatment period, slightly higher incidences of overall and drug-related adverse events were reported in the sitagliptin/metformin group compared with the pioglitazone group, although the 95% CIs for the between-treatment group differences included 0 (Table 6). The between-group differences were primarily related to higher rates of specific gastrointestinal adverse events of diarrhoea, nausea and vomiting in the sitagliptin/metformin group compared

Table 5. Efficacy endpoints following a meal tolerance test.

Parameter	Sitagliptin + metformin fixed-dose combination	Pioglitazone (45 mg q.d.)
2-h post-meal glucose (mg/dl)		
n	192	198
Baseline	270.0 ± 83.0	271.1 ± 81.9
Week 32	168.1 ± 57.7	188.7 ± 71.8
Change from baseline	−102.2 (−110.7, −93.8)	−82.0 (−90.4, −73.7)
Change vs. pioglitazone	−20.2 (−32.1, −8.3)*	—
2-h Insulin (μIU/ml)		
n	190	196
Baseline	55.6 ± 44.4	59.3 ± 45.6
Week 32	59.0 ± 42.4	50.1 ± 32.2
Change from baseline	2.3 (−2.2, 6.9)	−8.1 (−12.7, −3.6)
Change vs. pioglitazone	10.5 (4.0, 16.9)‡	—
2-h Proinsulin (pmol/l)		
n	190	196
Baseline	77.7 ± 54.3	81.0 ± 65.8
Week 32	57.0 ± 45.9	59.5 ± 40.1
Change from baseline	−21.6 (−26.6, −16.7)	−20.5 (−25.4, −15.6)
Change vs. pioglitazone	−1.1 (−8.1, 5.8)	—
2-h Proinsulin/insulin ratio		
n	189	195
Baseline	0.323 ± 0.328	0.300 ± 0.292
Week 32	0.192 ± 0.141	0.248 ± 0.163
Change from baseline	−0.122 (−0.142, −0.102)	−0.062 (−0.081, 0.042)
Change vs. pioglitazone	−0.060 (−0.088, −0.033)*	—
Insulinogenic Index (μIU/ml per mg/dl)†		
n	158	174
Baseline	0.37 ± 0.89	0.40 ± 0.66
Week 32	0.63 ± 1.15	0.49 ± 0.83
Change from baseline (%)	67.7 (48.3, 89.6)	24.2 (10.5, 39.7)
Change vs. pioglitazone (%)	43.5 (18.8, 68.4)*	—

Baseline and week 32 data are expressed as mean ± standard deviation, except where indicated.
†Geometric mean; change and % change from baseline data are expressed as least squares mean change (95% confidence interval).
*$p < 0.001$ for the between-group difference; ‡$p < 0.05$ for the between-group difference.

Table 6. Clinical adverse event summary.

Number (%) of patients	Sitagliptin/metformin (N = 261)	Pioglitazone (N = 256)	Difference in per cent vs. pioglitazone (95% confidence interval)
With one or more			
AE	169 (64.8)	152 (59.4)	5.4 (−3.0, 13.7)
Drug-related AE†	59 (22.6)	50 (19.5)	3.1 (−4.0, 10.1)
Serious AE	11 (4.2)	8 (3.1)	1.1 (−2.4, 4.6)
Serious, drug-related AE	0 (0.0)	0 (0.0)	0.0
Patients discontinued due to AEs	11 (4.2)	11 (4.3)	−0.1 (−3.8, 3.6)
Prespecified AEs of interest‡			
Gastrointestinal			
Diarrhoea*	40 (15.3)	11 (4.3)	11.0 (6.1, 16.3)
Nausea*	12 (4.6)	3 (1.2)	3.4 (0.6, 6.8)
Vomiting*	5 (1.9)	0 (0.0)	1.9 (0.4, 4.4)
Abdominal pain/discomfort	10 (3.8)	7 (2.7)	1.1 (−2.2, 4.5)
Symptomatic hypoglycaemia	22 (8.4)	11 (4.3)	4.1 (−0.1, 8.6)
Severe hypoglycaemia**	0 (0.0)	0 (0.0)	0.0
Peripheral oedema*	3 (1.1)	18 (7.0)	−5.9 (−9.8, −2.7)

AE, adverse event. Data displayed are the number (%) of patients with one or more occurrence of the respective endpoint.
†Determined by the investigator to be related to the drug.
‡Inferential testing for between-group differences was performed for these endpoints.
**Protocol-specified definition of severe hypoglycaemia: hypoglycaemia requiring medical intervention or exhibiting markedly depressed level of consciousness, including loss of consciousness or seizure.
*$p < 0.05$.

with the pioglitazone group (Table 6). The incidence of hypoglycaemia was also numerically higher, but not statistically significant, in the sitagliptin/metformin group compared with the pioglitazone group (Table 6). There were no events of severe hypoglycaemia in either treatment group. Conversely, a significantly higher rate of peripheral oedema was reported in the pioglitazone group than in the sitagliptin/metformin group (Table 6). No deaths were reported in this study.

No meaningful changes from baseline in mean ALT or AST levels were observed in the sitagliptin/metformin group at weeks 14 or 32, while small mean decreases from baseline were observed in the pioglitazone group at both weeks 14 and 32 (mean changes from baseline ± standard deviation in IU/l at week 32: ALT, sitagliptin/metformin 0.7 ± 13.7, pioglitazone −6.3 ± 12.0; AST, sitagliptin/metformin 0.8 ± 8.9 and pioglitazone −2.4 ± 8.1).

The adverse event of increased ALT was reported for three (1.1%) patients in the sitagliptin/metformin group compared with none in the pioglitazone group. All of the adverse events of increased ALT were considered to be of mild intensity. In one patient, who was discontinued from this study due to meeting the protocol-specified discontinuation criterion of ALT >3 times the upper limit of normal, the event of increased ALT, which resolved within 7 days after discontinuing study drug, was considered by the investigator to be not drug-related and probably related to alcohol consumption. In a second patient, the adverse event was considered to be not drug-related and was resolving after the study concluded. In the third patient, adverse events of both increased ALT and increased AST were reported. Both adverse events were considered to be of mild intensity and considered drug-related, and were reported as continuing 35 days after the last dose of study drug. An adverse event of increased transaminases was reported for one (0.4%) patient in the sitagliptin/metformin group compared with none in the pioglitazone group. The adverse event was reported on

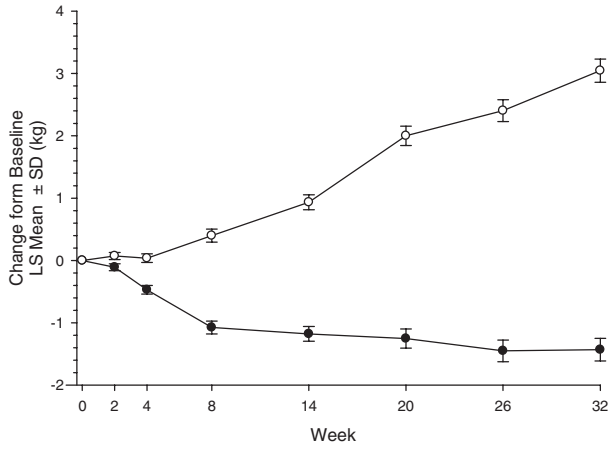


Figure 4. Change from baseline body weight: sitagliptin/metformin group (●); pioglitazone group (○).

day 94 of this study. It was considered to be of mild intensity and not drug-related and resolved by the end of this study while the patient continued on study drug.

There was a decrease from baseline in body weight in the sitagliptin/metformin group, occurring primarily during the first 8 weeks of treatment (the period during which the drug combination had been up-titrated), with a more gradual but continuing decline in body weight occurring over the remainder of the treatment period. In the pioglitazone group, there was a continuous increase in body weight after the first 4 weeks of treatment, when drug dose was increased from 30 to 45 mg per day (figure 4). At week 32, the LS mean change from baseline (95% CI) in body weight was −1.4 kg (−2.1 to −0.7) in the sitagliptin/metformin group and 3.0 kg (2.3 to 3.8) in the pioglitazone group. The between-group difference in change from baseline body weight between the sitagliptin/metformin group and the pioglitazone group was −4.5 kg (95% CI: −5.5 to −3.5; $p < 0.001$).

Discussion

This study compared the safety and efficacy of initial treatment with a FDC of sitagliptin and metformin with pioglitazone monotherapy in drug-naïve patients with type 2 diabetes mellitus and inadequate glycaemic control on diet and exercise. After 32 weeks, both treatments provided clinically meaningful reductions in all measures of efficacy (HbA1c, FPG and 2-h PMG) relative to baseline, with the FDC of sitagliptin and metformin providing a faster decline in HbA1c and FPG and, ultimately, greater improvements in all three glycaemic endpoints. Furthermore, each patient subgroup defined by baseline HbA1c exhibited numerically greater reduction in HbA1c after treatment with the sitagliptin/metformin FDC than with pioglitazone monotherapy, and the group with HbA1c ≥10% and treated with the combination had a significantly greater decrease in HbA1c than the group treated with pioglitazone monotherapy. In addition, after 32 weeks of treatment a significantly greater percentage of patients in the sitagliptin/metformin treatment group had HbA1c levels <7 and 6.5% than in the pioglitazone treatment group.

These observations indicate that greater glycaemic control can be achieved more quickly with initial treatment with the FDC of sitagliptin and metformin than with pioglitazone monotherapy. This conclusion is important for several reasons. First, there is a well-established correlation between decreased glycaemic levels and decreased risk of microvascular and macrovascular complications as well as mortality. In a prospective observational analysis of the UK Prospective Diabetes Study (UKPDS) study, each 1% reduction in HbA1c was associated with a 37% decrease in risk of microvascular complications and a 21% decrease in the risk of any endpoint including death related to diabetes [3]. Second, initial treatment with the FDC of sitagliptin/metformin may be useful for its potential to minimize the effects of clinical inertia [6], a term used to describe the reluctance of physicians to adjust therapeutic regimens in patients not meeting treatment goals despite the availability of other therapeutic options. Clinical inertia in the treatment of type 2 diabetes may occur because physicians are accustomed to initiating or adjusting therapeutic regimens in response to the presentation of symptoms, and patients with mild to moderate hyperglycaemia are likely to be asymptomatic in the short term. By the time they become symptomatic, however, patients may have lost years of potential improvement in glycaemic control because most patients with type 2 diabetes do not achieve or cannot maintain adequate glycaemic control with monotherapy [4,5]. A strategy of initial treatment with a FDC that uses an aggressive and well-tolerated treatment minimizes the possibility that clinical inertia will delay achievement of glycaemic goals. Avoidance of clinical inertia in type 2 diabetes may be especially crucial as there are long-term benefits of achieving maximal glycaemic control sooner, compared with later, due to a phenomenon referred to as metabolic memory [27,28] or legacy effects [29]. A 10-year observational follow-up to the UKPDS that compared the group receiving intensive therapy with the group receiving standard therapy during the prior interventional phase showed relative reductions in risk for any diabetes-related endpoint persisting at 10 years after the trial ended, despite the loss of between-group differences in HbA1c levels by the first year after the trial ended [8]. Similarly, in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, an observational follow-up to the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes, the group receiving intensive therapy throughout the DCCT trial compared with the group receiving standard therapy during the prior interventional phase showed a lower incidence of diabetes-related complications, despite similar glycaemic control between the two groups during the EDIC phase of the study [28,30–32].

Treatment with the sitagliptin/metformin FDC improved the measures of β-cell function more than treatment with pioglitazone, while the reverse was true for insulin resistance and sensitivity. Treatment with the FDC also improved the 2-h post-meal proinsulin/insulin ratio more than pioglitazone monotherapy. These differences are consistent with

the mechanisms of action of the individual therapies: metformin reduces hepatic glucose output, sitagliptin stimulates glucose-dependent insulin secretion and pioglitazone improves peripheral insulin response [14,33,34].

The changes in plasma lipids observed in the two treatment groups are consistent with previous reports. A prior study of the combination of sitagliptin and metformin as initial therapy in patients with type 2 diabetes revealed generally neutral effects on lipids, with a slight decrease in total and non-HDL-cholesterol and triglyceride and a slight increase in HDL-C compared with baseline [35]. Pioglitazone has been reported to increase both LDL-C and HDL-C compared with placebo [36]. The clinical impact of the between-group differences in plasma lipids observed in this study is unknown.

Both the FDC of sitagliptin/metformin and pioglitazone monotherapy were generally well tolerated. The incidence of adverse events overall was generally similar in both groups and the 95% CIs around the between-group differences included 0 for all summary measures. Statistically significant increases in the specific adverse events of diarrhoea, nausea and vomiting, which are typically associated with metformin use, were observed in the sitagliptin/metformin group compared with the pioglitazone group. A non-significant, numerically higher rate of the adverse event of hypoglycaemia was observed in the sitagliptin/metformin group compared with the pioglitazone group but no events of severe hypoglycaemia were seen in either treatment group. As has been previously reported with TZD therapy [37], a significantly higher rate of peripheral oedema was observed with pioglitazone monotherapy compared with sitagliptin/metformin combination therapy. No deaths were reported in this study.

The observed between-group difference in incidence of adverse events of increased liver enzymes associated with mean decreases in ALT and AST in the pioglitazone group in this study may be related to a decrease of hepatic steatosis associated with pioglitazone treatment and, consequently, a reduction in incidence of sporadic increases in liver enzymes in the pioglitazone group [38] rather than a sitagliptin/metformin-associated increase in liver enzymes. Consistent with this interpretation are data from a pooled analysis of 19 controlled clinical studies with sitagliptin including over 10 000 patients, in which the incidence of the adverse event of increased liver enzymes was similar in patients treated with sitagliptin alone or in combination with other AHAs including metformin, and those not exposed to sitagliptin (i.e. patients treated with placebo or an active comparator) [39].

The sitagliptin/metformin group experienced a mean reduction in body weight, while the pioglitazone treatment group experienced a mean increase in body weight over the course of 32 weeks of treatment. These observations are consistent with previous reports in which pioglitazone treatment was associated with weight gain [14], and other reports in which the combination of sitagliptin with metformin did not affect the weight loss observed during treatment with metformin alone despite further improvements in glycaemic control [35,40].

Conclusions

Initial treatment with a FDC of sitagliptin and metformin over 32 weeks produced greater reductions in HbA1c in a shorter time frame, resulting in more patients at glycaemic goal, compared with pioglitazone monotherapy. Compared to treatment with pioglitazone, treatment with the FDC resulted in a higher incidence of gastrointestinal adverse events, a lower incidence of oedema and weight loss vs. weight gain. Initiating dual therapy with the FDC of sitagliptin/metformin results in rapid and effective glycaemic control, and enhances the ability to achieve glycaemic targets in patients with type 2 diabetes.

Conflict of Interest

All authors except J. W. were employees of Merck Sharp & Dohme Corp. at the time this study was completed. J. W. has received honoraria for lecturing from MSD. J. W., L. K., S. S. E., L. X., G. T. G., K. D. K. and B. J. contributed to study design. All authors analysed the data reported here and all authors contributed to and reviewed the final article.

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