original article

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ORIGINAL ARTICLE

Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes

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Aim: To assess the 104-week efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes and inadequate glycaemic control (HbA_{1C} 7.5–11%) on diet and exercise.

Methods: This study was a 50-week, double-blind extension of a 54-week, randomized, double-blind, factorial study of the initial combination of sitagliptin and metformin, metformin monotherapy and sitagliptin monotherapy (104 weeks total duration). Patients assigned to active therapy in the 54-week base study remained on those treatments in the extension study: sitagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d. (higher dose combination), sitagliptin 50 mg b.i.d. + metformin 500 mg b.i.d. (lower dose combination), metformin 1000 mg b.i.d. (higher dose), metformin 500 mg b.i.d. (lower dose) and sitagliptin 100 mg q.d. Patients randomized to receive the sequence of placebo/metformin were switched, in a blinded manner, from placebo to metformin monotherapy uptitrated to 1000 mg b.i.d. beginning at week 24 and remained on higher dose metformin through the extension.

Results: Amongst patients who entered the extension study without having initiated glycaemic rescue therapy, least-squares mean changes in HbA_{1C} from baseline at week 104 were −1.7% (higher dose combination), −1.4% (lower dose combination), −1.3% (higher dose), −1.1% (lower dose) and −1.2% (sitagliptin). The proportions of patients with an HbA_{1C} <7% at week 104 were 60% (higher dose combination), 45% (lower dose combination), 45% (higher dose), 28% (lower dose) and 32% (sitagliptin). Fasting and postmeal measures of glycaemic control and β-cell function improved in all groups, with glycaemic responses generally maintained over the 104-week treatment period. The incidence of hypoglycaemia was low across all groups. The incidences of gastrointestinal adverse experiences were generally lower in the sitagliptin group and similar between the metformin monotherapy and combination groups.

Conclusions: Initial combination therapy with sitagliptin and metformin and monotherapy with either drug alone provided substantial and sustained glycaemic improvements and were well tolerated over 104 weeks in patients with type 2 diabetes.

Keywords: biguanides, dipeptidyl peptidase-4, incretins

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Introduction

Sitagliptin, a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor, and initial combination therapy with sitagliptin and metformin, a biguanide, are incretin-based approaches for the treatment of patients with type 2 diabetes [1,2]. A recent pooled safety analysis of 6139 patients treated for up to 2 years showed that sitagliptin was well tolerated compared with non-sitagliptin therapy [3]. In patients with type 2 diabetes, sitagliptin and initial combination therapy with sitagliptin and metformin were shown to be effective and well tolerated for up to 54 weeks [4,5]. Moreover, the gastrointestinal tolerability profile of the initial combination of sitagliptin and metformin was similar to that of metformin monotherapy. To evaluate the longer term efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy, the aforementioned 54-week study [5] was extended for 50 weeks, and the 104-week study results are presented herein.

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Methods

The 104-week treatment period consisted of a 50-week, double-blind, extension study that followed a previously reported 54-week, multinational, randomized, double-blind, base study ([4,5]; Clinicaltrials.gov: NCT00103857) in patients with type 2 diabetes. The extension study was conducted at 117 clinical sites (out of 140 sites from base study) in 18 countries (see Appendix for extension study clinical sites; all 140 clinical sites are published elsewhere [4]). The protocol was reviewed and approved by the appropriate committees and authorities, and the study was performed in accordance with the principles of the Declaration of Helsinki.

Key inclusion and exclusion criteria for the base study have been previously published [4,5]. After a screening diet/exercise run-in period (including a drug wash-off period for patients

on oral antihyperglycaemic agents at screening) of 6–10 weeks (or 8–12 weeks for those on thiazolidinediones), patients with HbA_{1c} ≥7.5 to ≤11.0% entered a 2-week, single-blind, placebo run-in period. Patients then had baseline assessments and were randomized to one of six treatments using a computer-generated allocation schedule: placebo ($n = 176$), sitagliptin 100 mg q.d. ($n = 179$), metformin 500 mg b.i.d. (lower dose; $n = 182$), metformin 1000 mg b.i.d. (higher dose; $n = 182$), sitagliptin 50 mg b.i.d. + metformin 500 mg b.i.d. (lower dose combination; $n = 190$) and sitagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d. (higher dose combination; $n = 182$). At week 24, patients initially receiving placebo were switched, in a double-blind manner, to the higher dose metformin monotherapy with gradual uptitration of 500 mg/week to metformin 1000 mg b.i.d. Patients were eligible for the 50-week extension study if they completed the 54-week base study, were at least 75% compliant in taking study medication (as assessed by the investigator based on patient interview and tablet count), had not developed a contraindication to study medication or other medical condition that would make participation in the study not in their best interest, and had provided written informed consent. Blinded treatment assignment was not changed during the extension study. All patients received the same total number of tablets (active or placebo-matched) throughout the study. Patients received counselling on diet and exercise consistent with American Diabetes Association recommendations throughout the study.

Patients whose glycaemic parameters did not meet cut points that became increasingly strict over time were provided open-label rescue therapy with glyburide (glibenclamide) as previously described [4,5]. Throughout the 50-week extension study, the criterion for initiation of glycaemic rescue therapy was an HbA_{1c} value >7.5%. For patients requiring glycaemic rescue therapy during the study, therapy continued until patients discontinued from or completed the study.

Efficacy Endpoints

The primary efficacy endpoint for the extension study was change from baseline (i.e. week 0 randomization) in HbA_{1c} at week 104. Secondary endpoints included fasting plasma glucose (FPG), 2-h postmeal glucose (PMG) and body weight. The proportion of patients with an HbA_{1c} <7% at week 104 and the proportion of patients who had an HbA_{1c} <7% at both weeks 24 and 104 were calculated. Other endpoints included fasting serum insulin, fasting serum proinsulin, proinsulin/insulin ratio, homeostasis model assessment-β (HOMA-β) cell function, HOMA-insulin resistance (HOMA-IR) and lipid parameters, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C and triglycerides.

A standard meal-tolerance test was administered at baseline (prior to first dose of study medication), at weeks 24 and 54 (data previously described [4,5]), and at week 104. Patients took study medication 30 min prior to the standard meal, which was ingested within 15 min and consisted of one nutrition bar and one nutrition drink (~460 kcal; 75 g carbohydrate, 9 g fat and 18 g protein). Blood was collected at 0, 60, and 120 min from the meal start. Plasma glucose, serum insulin and serum C-peptide were measured and used to determine 2-h PMG, area under the glucose concentration-time curve (AUC), insulin AUC, C-peptide AUC and the insulin AUC/glucose AUC ratio.

Safety Endpoints

Data were collected on clinical and laboratory adverse experiences, physical examinations, vital signs and electrocardiograms (ECGs) throughout the 104-week treatment period. Patients were counselled with regard to the symptoms and treatment of hypoglycaemia as previously described [5]. All clinical adverse experiences were assessed by investigators for relationship to study drug. Laboratory evaluations included blood chemistry, haematology and urinalysis. Clinical adverse experiences of interest included hypoglycaemia and prespecified, select, gastrointestinal adverse experiences (abdominal pain/discomfort, nausea, vomiting and diarrhoea).

Laboratory measurements and ECGs were analysed at central laboratories (PPD Global Central Labs, LLC, Highland Heights, KY, USA and Zaventem, Belgium; and Covance Central Diagnostics, Inc., Reno, NV, USA, respectively) by technicians blinded to treatment group as previously described [4,5]. For data presented in conventional units, the following SI conversion factors may be used: to convert glucose values to mmol/l, multiply by 0.05551; to convert insulin values to pmol/l, multiply by 6; to convert C-peptide values to nmol/l, multiply by 0.331; to convert cholesterol values to mmol/l, multiply by 0.0259 and to convert triglycerides to mmol/l, multiply by 0.0113.

Statistical Analyses

The population for the efficacy analysis included all randomized patients who had a baseline measurement, had not initiated glycaemic rescue therapy during the initial 54-week study and had at least one efficacy measurement during the extension study. To avoid the confounding influence of glycaemic rescue therapy initiated during the extension study on efficacy comparisons, data collected after initiation of rescue therapy were treated as missing. An analysis of covariance was used to model the change from baseline at week 104 in continuous efficacy parameters, controlling for baseline values and prior diabetes pharmacotherapy status as covariates. Missing data were handled with the last-observation-carried-forward method. Within-group differences [least-squares (LS) mean changes from baseline at week 104] with 95% confidence intervals (CIs) and sample sizes were provided for the efficacy endpoints for the patients who were treated with active therapy throughout the study. Statistical analyses of the between-group differences were not performed in the extension study.

Efficacy results for the 104-week treatment period for patients randomized to receive active therapy are presented in this manuscript. Efficacy data from patients who were switched from placebo to metformin at week 24 are not presented because such an analysis would include patients who successfully completed 24 weeks of placebo treatment without requiring glycaemic rescue therapy (i.e. in contrast to the other treatment groups, such an analysis would contain only

those patients who were able to maintain glucose levels below glycaemic rescue criteria despite not receiving active therapy for the first 24 weeks of the base study). Moreover, because the active treatment (metformin) in this switch group and the continuous treatments in the other groups were not initiated simultaneously at randomization, the duration of the active-treatment period differed for this treatment group relative to the other treatment groups.

The population for the safety analysis included all randomized patients (including those from the placebo/metformin switch group) who received at least one dose of blinded study medication during the 104-week treatment period. The analysis of safety excluded adverse experiences occurring after initiation of glycaemic rescue therapy. All serious adverse experiences and reported deaths are summarized herein regardless of initiation of glycaemic rescue therapy.

Results

Of the 1091 patients who were randomized at baseline, 685 (47%) continued into the 50-week extension study. A total of 517 patients (75% of those entering the extension study) completed 104 weeks of treatment (Table 1). The baseline characteristics by treatment group for the randomized population were reported previously [4]. For the extension efficacy analysis population, the baseline demographics and efficacy characteristics were similar across the treatment groups (Table 2). Over the 104-week treatment period the glycaemic rescue criteria became stricter such that any patient with an HbA_{1C} >7.5% after week 54 required rescue. As a result, the proportions of patients requiring glycaemic rescue therapy were lower in the co-administration groups [44% (lower dose) and 32% (higher dose)] when compared with their respective monotherapy groups (73% on lower dose metformin, 53% on higher dose metformin and 78% on sitagliptin).

Efficacy

Given the design of the trial and declining group sizes from the base through the extension study, statistical testing was not performed on between-group differences. Over 104 weeks, substantial reductions from baseline were observed in all treatment groups (Figure 1). At each metformin dose studied, the reduction in HbA_{1C} was greater with the co-administration of sitagliptin and metformin than with the administration of metformin alone at the respective dose; for the higher dose co-administration group, glycaemic improvement was also greater than for sitagliptin alone (Table 3). Greater reductions in HbA_{1C} from baseline were observed in patients with higher baseline HbA_{1C} levels (Figure 2).

Table 1. Disposition of randomized patients over 104 weeks (patients screened, $N = 3544$; patients randomized, $n = 1091$*).

	Sitagliptin 100 mg q.d.	MF 500 mg b.i.d.	MF 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d.+ MF 500 mg b.i.d.	Sitagliptin 50 mg b.i.d.+ MF 1000 mg b.i.d.	Placebo/MF 1000 mg b.i.d.
Randomized, *n*	179	182	182	190	182	176
Discontinued during 54-week base study, *n*	57	56	46	42	41	61
Completed 54-week base study, *n*	122	126	136	148	141	115
Completed 54-week base study and did not enter 50-week extension study, *n*	19	19	15	14	19	17
Entered 50-week extension study, *n*	103	107	121	134	122	98
Discontinued during 50-week extension study, *n*	38	27	26	36	21	20
Reasons for discontinuations over 104 weeks (total of rows 3 and 7)						
Clinical AE, *n*	10	9	11	6	4	10
Laboratory AE, *n*	4	3	2	0	2	2
Lack of efficacy†, *n*	37	29	20	20	11	22
Lost to follow-up, *n*	9	4	8	9	13	12
Other, *n*	5	4	3	2	8	6
Moved, *n*	0	1	2	4	3	1
Withdrew consent, *n*	19	21	18	23	13	18
Met protocol-specific discontinuation criteria, *n*	4	7	5	8	8	6
Protocol deviation, *n*	7	5	3	6	0	4
Completed extension study, *n* (% of randomized)	65 (36)	80 (44)	95 (52)	98 (52)	101 (56)	78 (44)

MF, metformin.

*Disposition of patients not randomized published in Goldstein et al. [4].

†Includes patients not meeting the progressively stricter protocol-specified glycaemic criteria and/or not meeting the investigator's expectations of glycaemic improvement.

Table 2. Extension study: baseline characteristics of the efficacy analysis population.

Parameter	Sitagliptin 100 mg q.d. $N = 52$	MF 500 mg b.i.d. $N = 65$	MF 1000 mg b.i.d. $N = 88$	Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. $N = 100$	Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. $N = 107$	Placebo/MF 1000 mg b.i.d. $N = 42$
Age (years)	54.1 ± 9.1	55.9 ± 8.9	54.3 ± 9.9	54.5 ±9.5	53.9 ± 8.6	54.1 ± 11.0
Males, *n* (%)	30 (58)	30 (46)	39 (44)	50 (50)	40 (37)	21 (50)
BMI (kg/m^2)	30.3 ± 5.5	32.2 ± 6.9	31.9 ± 7.1	31.6 ± 7.3	31.4 ± 6.0	31.9 ± 5.5
HbA_{1C} (%) (range)	8.5 ± 0.9 (7.2–10.8)	8.6 ± 0.9 (7.4–10.4)	8.5 ± 0.8 (6.9–10.9)	8.7 ± 0.9 (6.8–11.0)	8.6 ± 1.0 (6.6–11.2)	8.1 ± 0.7 (7.0–9.7)
FPG (mg/dl)	178.3 ± 37.0	180.4 ± 40.8	185.7 ± 45.1	188.4 ± 44.8	192.1 ± 52.2	160.0 ± 30.6
Duration of T2DM (years)	3.7 ± 4.9	4.0 ± 3.9	3.9 ± 4.0	3.7 ± 4.3	4.4 ± 4.2	4.0 ± 5.9

Data are expressed as mean ± standard deviation or frequency [*n* (%)]. BMI, body mass index; FPG, fasting plasma glucose; MF, metformin; T2DM, type 2 diabetes mellitus.

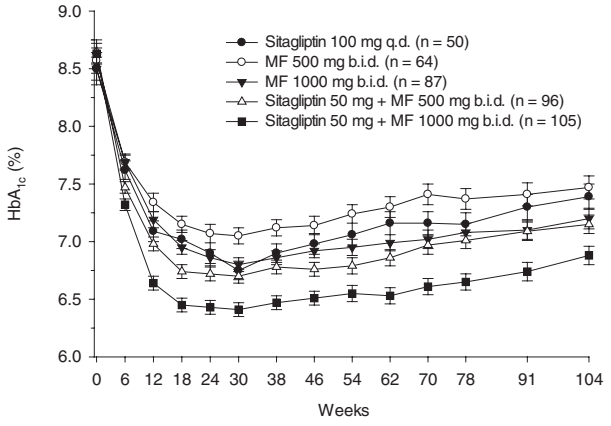

Figure 1. HbA_{1C} over time (mean ± s.e.).

The proportions of patients with an HbA_{1C} <7% at week 104 were 60, 45, 45, 28 and 32% for the higher dose co-administration, lower dose co-administration, higher dose metformin, lower dose metformin and sitagliptin groups, respectively. Of the patients with an HbA_{1C} <7% in the week 24 analysis, the proportions with an HbA_{1C} <7% in the week 104 analysis were 71% (*n*/*N*: 60/84), 67% (40/60), 64% (35/55), 38% (11/29) and 50% (15/30) for the higher dose co-administration, lower dose co-administration, higher dose metformin, lower dose metformin and sitagliptin groups, respectively.

The durability of the effects of the treatments on FPG is reflected in the plots over time (Figure 3). Reductions from baseline were observed in all treatment groups. At each metformin dose studied, the reduction in FPG was greater with the co-administration of sitagliptin and metformin than with the administration of either agent alone (Table 3).

Fasting measures of β-cell function, HOMA-β, fasting proinsulin and the proinsulin/insulin ratio, were improved relative to baseline at week 104 in all treatment groups, with larger improvements observed in the co-administration groups relative to their respective monotherapy groups (Table 3). HOMA-IR was reduced from baseline in all metformin-based treatment groups at week 104 (Table 3).

Following a standard meal at week 104, 2-h PMG, total glucose AUC and insulin AUC/glucose AUC ratio were improved with all active treatments relative to baseline (Table 4). The changes in the glucose parameters with co-administration were larger when compared with the sitagliptin and respective metformin monotherapy groups. Changes from baseline in total insulin or C-peptide AUC were variable across the treatment groups at week 104 (Table 4). The changes in glucose and insulin AUC led to improvements relative to baseline in the insulin/glucose AUC ratio, suggesting improved β-cell responsiveness to glucose, with all treatments (Table 4).

After 104 weeks of treatment, HDL-C was increased by 6–9% across treatment groups (Table 5). The changes in the other lipid parameters were small and unlikely to be clinically meaningful (Table 5).

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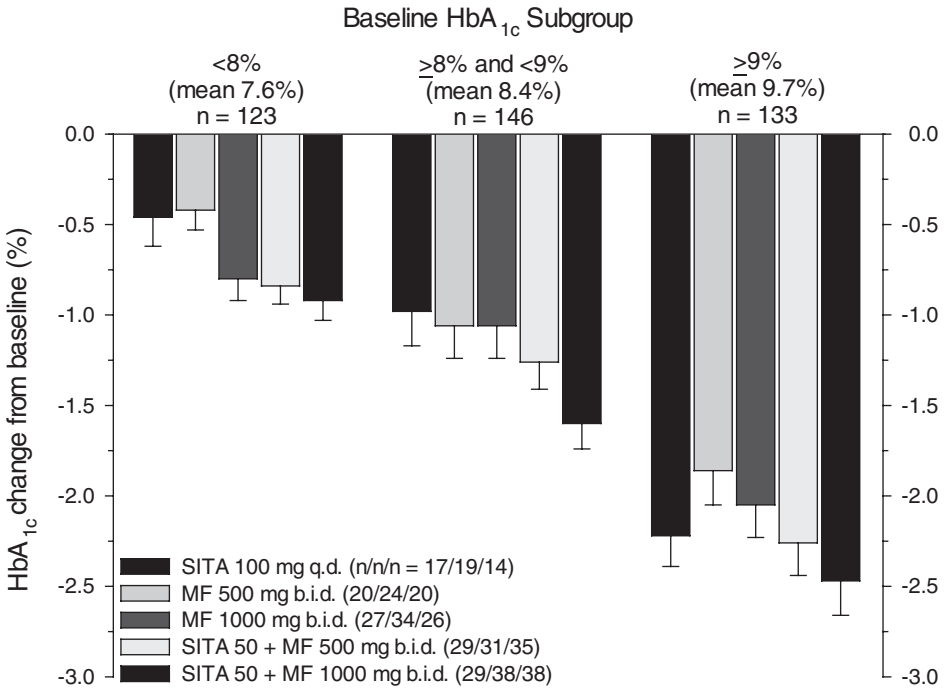

Figure 2. Mean change (s.e.) from baseline in HbA_{1C} by baseline HbA_{1C} subgroup. MF, metformin; SITA, sitagliptin.

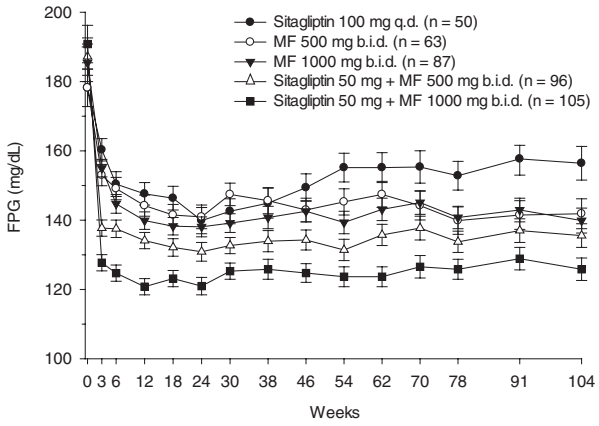

Figure 3. Fasting plasma glucose (FPG) over time (mean ± s.e.).

After 104 weeks, body weight was reduced relative to baseline in the higher dose co-administration group [LS mean change from baseline (95% CI): −1.2 kg (−2.0, −0.3); $n = 100$] and the higher dose metformin monotherapy group [−2.4 kg (−3.3, −1.5); $n = 81$]. There was no meaningful change in body weight from baseline for patients in the lower dose co-administration group [0.0 kg (95% CI; −0.8, 0.9); $n = 94$], the lower dose metformin monotherapy group [−0.8 kg (−1.9, 0.3); $n = 59$], and the sitagliptin group [0.5 kg (−0.7, 1.7); $n = 50$]. For waist circumference, there was a reduction relative to baseline in the higher dose co-administration group [LS mean change from baseline (95% CI): −2.3 cm (−4.1, −0.6); $n = 89$]. In the other treatment groups, there was no meaningful change in waist circumference from baseline: −1.3 cm (95% CI; −3.2, 0.6) in the lower dose co-administration group ($n = 78$), −1.9 cm (−3.9, 0.0) in the higher dose metformin monotherapy group ($n = 71$), −0.8 cm (−3.2, 1.6) in the lower dose metformin monotherapy group ($n = 47$), and 1.2 cm (−1.5, 3.9) in the sitagliptin group ($n = 37$).

Safety/Tolerability

After 104 weeks of treatment, the incidences of adverse experiences were generally similar in the co-administration groups and their respective metformin monotherapy groups (Table 6). Amongst the groups randomized to active therapy, the lowest incidence of drug-related adverse experiences was reported for the sitagliptin group; the incidences were generally similar for the dose-matched metformin-treated groups. The incidence of serious adverse experiences was highest in the placebo/metformin switch group. Five deaths were reported amongst randomized patients (including one death following initiation of rescue therapy in the placebo/metformin group): two in the initial 54-week study period (one patient in the placebo group died of sudden cardiac death; the other patient, in the higher dose co-administration group, died of an inadvertent electrical shock), two in the extension study (one patient in the lower dose co-administration group because of worsening coronary artery disease and one patient on metformin in the placebo/metformin group because of unknown causes) and one patient in the lower dose metformin monotherapy group (as an outcome, following discontinuation from the study, for the serious adverse event of oesophageal cancer). Treatment discontinuations because of an adverse experience or a drug-related adverse experience were low across all groups (Table 6).

Table 3. Fasting diabetes-related endpoints.

Parameter	Sitagliptin 100 mg q.d.	MF 500 mg b.i.d.	MF 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d.
HbA_{1C} (%), *n*	50	64	87	96	105
Baseline	8.5 ± 0.9	8.6 ± 0.9	8.5 ± 0.8	8.7 ± 0.9	8.6 ± 1.0
Week 104	7.4 ± 0.7	7.5 ± 0.7	7.2 ± 0.9	7.2 ± 0.9	6.9 ± 0.9
Change from baseline	− 1.2 (−1.4, −0.9)	− 1.1 (−1.3, −0.9)	− 1.3 (−1.5, −1.2)	− 1.4 (−1.6, −1.2)	− 1.7 (−1.8, −1.5)
FPG (mg/dl), *n*	50	63	87	96	105
Baseline	178.0 ± 37.2	178.1 ± 38.6	185.6 ± 45.4	187.7 ± 45.2	191.5 ± 51.9
Week 104	156.0 ± 36.4	141.3 ± 30.3	140.4 ± 40.0	137.0 ± 33.0	127.4 ± 32.7
Change from baseline	− 26.8 (− 36.2, −17.4)	− 41.4 (−49.8, −33.0)	− 43.2 (−50.3, −36.2)	− 47.5 (−54.3, −40.7)	− 57.3 (−63.7, −50.8)
Fasting insulin (μIU/ml), *n*	43	55	78	85	98
Baseline	11.9 ± 9.7	13.1 ± 10.7	14.2 ± 9.1	13.7 ± 12.6	14.3 ± 12.0
Week 104	14.0 ± 10.9	13.1 ± 9.6	12.5 ± 7.4	14.9 ± 10.2	15.1 ± 14.0
Change from baseline	1.6 (−0.8, 4.0)	− 0.1 (−2.2, 2.0)	− 1.6 (−3.3, 0.2)	1.2 (−0.5, 2.9)	1.0 (−0.6, 2.6)
Fasting proinsulin (pmol/l), *n*	24	29	61	65	79
Baseline	23.9 ± 14.5	31.3 ± 32.2	41.0 ± 38.7	35.3 ± 40.5	37.0 ± 32.2
Week 104	17.2 ± 10.7	23.0 ± 23.5	21.8 ± 25.6	22.8 ± 26.4	22.2 ± 26.1
Change from baseline	− 12.6 (−19.7, −5.6)	− 10.6 (−17.1, −4.2)	− 16.5 (−20.9, −12.1)	− 12.7 (−16.9, −8.4)	− 13.9 (−17.8, −10.0)
Proinsulin/insulin ratio, *n*	24	29	61	64	79
Baseline	0.36 ± 0.16	0.41 ± 0.31	0.44 ± 0.21	0.50 ± 0.33	0.45 ± 0.31
Week 104	0.25 ± 0.16	0.29 ± 0.20	0.29 ± 0.21	0.28 ± 0.20	0.27 ± 0.26
Change from baseline	− 0.17 (−0.25, −0.09)	− 0.16 (−0.23, −0.09)	− 0.15 (−0.20, −0.10)	− 0.20 (−0.24, −0.15)	− 0.17 (−0.21, −0.13)
HOMA-β, *n*	43	55	78	85	98
Baseline	43.6 ± 38.5	44.4 ± 38.8	47.5 ± 34.6	45.1 ± 40.4	46.0 ± 38.3
Week 104	67.5 ± 72.6	72.4 ± 72.9	71.6 ± 53.1	86.9 ± 75.3	98.3 ± 89.0
Change from baseline	27.8 (9.8, 45.9)	30.7 (14.8, 46.6)	23.5 (10.2, 36.8)	43.6 (30.8, 56.4)	51.3 (39.4, 63.1)
HOMA-IR, *n*	43	55	78	85	98
Baseline	5.1 ± 4.3	5.8 ± 4.9	6.6 ± 4.9	6.3 ± 6.3	6.8 ± 6.4
Week 104	5.3 ± 4.5	4.6 ± 3.4	4.4 ± 3.0	5.1 ± 3.9	5.1 ± 5.3
Change from baseline	− 0.4 (−1.5, 0.7)	− 1.5 (−2.4, −0.5)	− 2.0 (−2.9, −1.2)	− 1.2 (−1.9, -0.4)	− 1.4 (−2.2, −0.7)

n = number of patients with evaluable data included in the analysis. Baseline and week 104 data are expressed as mean ± standard deviation. Change from baseline data is expressed as LS mean change (95% CI). FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment-β; HOMA-IR, HOMA-insulin resistance; MF, metformin.

The incidences of hypoglycaemia and gastrointestinal-related adverse experiences were of clinical interest in this study. Over 104 weeks, the incidences of hypoglycaemia were low (1–5%), with the lowest incidence in the sitagliptin group and highest in the higher dose co-administration group (Table 6). No patient receiving sitagliptin as monotherapy or as part of combination therapy was reported to have an episode of hypoglycaemia that required assistance (including medical treatment) or exhibited marked severity (i.e. depressed level of consciousness, loss of consciousness or seizure). A total of two patients (both in the lower dose metformin monotherapy group) were reported to have hypoglycaemic events that required non-medical assistance. Following the initiation of glyburide rescue therapy, one patient (in the higher dose metformin monotherapy group) required assistance (non-medical intervention) to treat an event of hypoglycaemia.

The incidence of gastrointestinal-related adverse experiences overall and the incidences of the prespecified gastrointestinal adverse experiences of diarrhoea, nausea, vomiting and abdominal pain/discomfort were similar between the co-administration and the metformin monotherapy groups (Table 6). The incidences of diarrhoea and nausea were lower in the sitagliptin group relative to the metformin monotherapy and combination groups.

In an additional analysis comparing the sitagliptin monotherapy group with the pooled higher and lower dose metformin monotherapy groups over the 104-week period, the between-group differences (95% CI) showed a lower incidence of nausea [−4.8% (−7.8, −1.3)], vomiting [−2.9% (−5.4, −0.0)], and diarrhoea [−7.4% (−11.6, −2.3)] in patients taking sitagliptin relative to those taking metformin. There was no meaningful between-group difference in reported events of abdominal pain/discomfort between the sitagliptin and the pooled metformin monotherapy groups [0.7% (−2.8, 5.3)].

Discussion

In this extension study, treatment with sitagliptin and metformin as initial combination therapy or as monotherapy provided substantial and sustained improvements in glycaemic control over 2 years in patients with type 2 diabetes. As observed in shorter studies of other antihyperglycaemic agents [6], including sitagliptin [7,8], patients with more severe hyperglycaemia at baseline had the greatest improvements in glycaemic control with all treatments. The HbA_{1C}-lowering efficacy observed in the present study is generally consistent with 2-year results reported from randomized,

Table 4. Postprandial responses to a standard meal.

Parameter	Sitagliptin 100 mg q.d.	MF 500 mg b.i.d.	MF 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d.
2-h PMG (mg/dl), *n*	40	49	69	78	88
Baseline	247.9 ± 75.9	270.2 ± 65.8	269.2 ± 83.1	277.6 ± 81.4	274.9 ± 81.3
Week 104	189.6 ± 61.4	195.4 ± 56.6	180.7 ± 51.1	173.4 ± 46.6	158.1 ± 56.3
Change from baseline	− 74.1 (−90.3, −57.9)	− 72.7 (−87.4, −58.1)	− 86.7 (−99.0, −74.5)	− 96.2 (−107.8, −84.6)	− 110.0 (−120.9, −99.1)
Glucose AUC (mg h/dl), *n*	39	50	67	78	86
Baseline	469.7 ± 104.9	503.1 ± 94.6	509.4 ± 120.6	509.8 ± 130.4	512.1 ± 127.4
Week 104	389.5 ± 102.5	382.2 ± 88.5	362.9 ± 82.6	342.8 ± 79.5	310.7 ± 89.4
Change from baseline	− 105.7 (−132.4, −79.1)	− 120.0 (−143.5, −96.5)	− 138.8 (−159.0, −118.6)	− 160.3 (−179.1, −141.4)	− 190.5 (−208.4, −172.6)
Insulin AUC (μIU h/ml), *n*	35	44	66	68	81
Baseline	78.3 ± 43.3	86.4 ± 52.4	81.8 ± 42.0	81.4 ± 47.5	80.2 ± 50.1
Week 104	84.8 ± 45.1	104.3 ±75.6	89.4 ± 54.6	98.4 ± 58.5	83.2 ± 53.0
Change from baseline	7.1 (−6.3, 20.5)	19.4 (7.4, 31.4)	7.5 (−2.2, 17.3)	17.4 (7.8, 27.0)	2.1 (−6.7, 10.9)
C-peptide AUC (ng h/ml), *n*	41	51	66	76	88
Baseline	11.0 ± 4.5	10.6 ± 3.8	11.1 ± 4.1	9.8 ± 4.1	10.4 ± 4.3
Week 104	11.3 ± 3.7	11.0 ± 4.1	11.0 ± 4.8	10.4 ± 3.6	10.3 ± 4.3
Change from baseline	0.6 (−0.3, 1.6)	0.5 (−0.3, 1.4)	0.1 (−0.6, 0.8)	0.4 (−0.3, 1.1)	− 0.3 (−0.9, 0.4)
Insulin AUC/glucose AUC, *n*	34	43	63	67	76
Baseline	0.18 ± 0.12	0.19 ± 0.13	0.18 ± 0.13	0.18 ± 0.13	0.18 ± 0.14
Week 104	0.25 ± 0.18	0.30 ± 0.24	0.27 ± 0.19	0.30 ± 0.20	0.27 ± 0.17
Change from baseline	0.08 (0.03, 0.12)	0.12 (0.07, 0.16)	0.08 (0.05, 0.12)	0.12 (0.09, 0.16)	0.09 (0.06, 0.12)

n, number of patients with evaluable data included in the analysis. Baseline and week 104 data are expressed as mean ± standard deviation. Change from baseline data is expressed as LS mean change (95% CI). AUC, area under the concentration-time curve; MF, metformin; PMG, postmeal glucose.

Table 5. Fasting lipid profiles.

Parameter	Sitagliptin 100 mg q.d.	MF 500 mg b.i.d.	MF 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d.
TC (mg/dl), *n*	47	59	83	86	102
Baseline	190.4 ± 40.9	191.9 ± 46.0	188.6 ±42.0	198.6 ± 46.3	194.0 ± 44.2
Week 104	191.0 ± 45.9	185.8 ± 36.9	188.0 ± 45.9	191.8 ± 42.3	189.3 ± 41.7
% change from baseline	0.6 (−4.2, 5.5)	− 1.2 (−5.5, 3.0)	0.6 (−3.0, 4.2)	− 1.1 (−4.7, 2.4)	− 0.2 (−3.4, 3.1)
HDL-C (mg/dl), *n*	45	59	83	86	102
Baseline	41.4 ± 7.6	42.6 ± 8.6	44.8 ± 11.1	44.2 ± 9.5	43.6 ± 11.3
Week 104	44.2 ± 9.8	46.0 ± 11.1	48.3 ± 12.4	46.0 ± 9.4	46.7 ± 13.7
% change from baseline	6.5 (1.1, 11.8)	7.8 (3.1, 12.4)	9.4 (5.5, 13.3)	6.4 (2.5, 10.2)	8.3 (4.7, 11.8)
LDL-C (mg/dl), *n*	45	59	82	85	102
Baseline	114.8 ± 33.6	107.3 ±29.9	106.1 ± 35.5	118.9 ± 37.7	116.0 ± 37.0
Week 104	109.2 ± 36.9	101.4 ±31.3	102.3 ± 37.2	110.5 ± 36.0	108.9 ± 35.2
% change from baseline	− 2.1 (−11.2, 7.0)	− 4.8 (−12.8, 3.1)	1.0 (−5.8, 7.7)	− 2.9 (−9.5, 3.7)	− 0.9 (−6.9, 5.2)
Non-HDL-C (mg/dl), *n*	45	59	83	86	102
Baseline	147.1 ± 38.1	149.4 ± 45.7	143.8 ± 41.9	154.4 ± 45.6	150.3 ± 43.3
Week 104	144.7 ± 42.4	139.8 ± 36.3	139.8 ± 45.1	145.8 ± 41.4	142.6 ± 40.9
% change from baseline	− 0.8 (−7.3, 5.7)	− 3.2 (−8.9, 2.5)	− 1.6 (−6.4, 3.2)	− 2.5 (−7.2, 2.2)	− 1.7 (−6.0, 2.7)
Triglycerides (mg/dl), *n*	47	59	83	86	102
Baseline*	152.0 ± 48.4	189.0 ± 94.9	151.0 ± 106.0	152.0 ± 128.4	155.5 ± 94.9
Week 104*	155.0 ± 72.6	178.0 ± 100.5	169.0 ± 115.3	157.5 ± 77.2	157.0 ± 115.3
Median % change from baseline	1.1 (−14.3, 16.5)	2.6 (−7.4, 12.7)	− 2.6 (−13.7, 8.4)	− 5.0 (−16.1, 6.2)	− 1.8 (−10.4, 6.7)

n = number of patients with evaluable data included in the analysis. Baseline and week 104 are expressed as mean ± standard deviation (s.d.) or *median ± standard deviation for median. Percent change from baseline data is expressed as LS mean percent change (95% CI) or median percent change (95% CI). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MF, metformin; TC, total cholesterol.

Table 6. Summary of clinical adverse experiences through 104 weeks.

Number (%) of patients*	Sitagliptin 100 mg q.d. *N* = 179	MF 500 mg b.i.d. *N* = 182	MF 1000 mg b.i.d. *N* = 182	Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. *N* = 190	Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. *N* = 182	Placebo/MF 1000 mg b.i.d.† *N* = 176
One or more AEs	108 (60.3)	117 (64.3)	135 (74.2)	135 (71.1)	137 (75.3)	104 (59.1)
Drug-related AEs‡	17 (9.5)	27 (14.8)	35 (19.2)	33 (17.4)	37 (20.3)	22 (12.5)
Serious AEs (SAEs)	13 (7.3)	7 (3.8)	9 (4.9)	12 (6.3)	11 (6.0)	17 (9.7)
Drug-related SAEs‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Who died	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.1)§
Discontinued because of AEs	5 (2.8)	8 (4.4)	7 (3.8)	6 (3.2)	4 (2.2)	10 (5.7)
Discontinued because of drug-related AEs	0 (0.0)	2 (1.1)	5 (2.7)	3 (1.6)	2 (1.1)	2 (1.1)
Discontinued because of SAEs	4 (2.2)	5 (2.7)	1 (0.5)	1 (0.5)	0 (0.0)	8 (4.5)
Discontinued because of drug-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Adverse experiences of clinical interest						
Hypoglycaemia	2 (1.1)	3 (1.6)	4 (2.2)	5 (2.6)	9 (4.9)	5 (2.8)
All gastrointestinal AEs	37 (20.7)	38 (20.9)	60 (33.0)	56 (29.5)	60 (33.0)	32 (18.2)
Diarrhoea	8 (4.5)	14 (7.7)	23 (12.6)	19 (10.0)	25 (13.7)	12 (6.8)
Nausea	2 (1.1)	6 (3.3)	19 (10.4)	10 (5.3)	12 (6.6)	4 (2.3)
Abdominal pain‖	9 (5.0)	7 (3.8)	12 (6.6)	7 (3.7)	9 (4.9)	5 (2.8)
Vomiting	1 (0.6)	0 (0.0)	8 (4.4)	4 (2.1)	9 (4.9)	1 (0.6)

AE, adverse experiences; MF, metformin.
*Excludes data after initiation of glycaemic [glyburide/glibenclamide] rescue therapy.
†Patients were switched from placebo to metformin 1000 mg b.i.d. at week 24.
‡Considered by the investigator to be drug-related.
§All reported deaths included those that occurred after initiation of glycaemic rescue therapy (*n* = 1).
‖Including abdominal pain, abdominal discomfort, upper abdominal pain and stomach discomfort.

double-blind trials with other oral antihyperglycaemic agents as monotherapy [9] and as initial combination therapy [10].

Although no statistical comparisons were performed between groups in the extension study, the improvement in glycaemic control was generally better in the higher dose combination group. Specifically, for patients participating in the extension study, 60% of the patients in the higher dose combination therapy group had an HbA_{1C} of <7.0% at week 104. In addition, of the patients in this group with an HbA_{1C} <7% at 24 weeks, 71% had an HbA_{1C} <7% at 104 weeks. As patients treated with antihyperglycaemic agents often fail to maintain glycaemic goals long term because of the progressive nature of the disease [11], this durability of treatment effect is noteworthy in patients treated with initial combination therapy with sitagliptin and metformin for over 2 years.

In addition to the changes in HbA_{1C}, there were substantial reductions in FPG and 2-h PMG at 104 weeks for all groups, with larger reductions noted in the combination-therapy groups compared with their respective monotherapy groups. The 104-week results for FPG and 2-h PMG were generally similar to those observed at 54 weeks [5]. The improvements in measures of β-cell function (HOMA-β and ratio of postmeal insulin AUC/glucose AUC) and insulin resistance with the combination of sitagliptin and metformin at 104 weeks were also similar to those observed at 54 weeks [5], suggesting durable effects on β-cell responsiveness and insulin action with sitagliptin plus metformin.

Over the 104-week treatment period, all treatments were generally well tolerated. The incidence of hypoglycaemia remained low throughout the study. The gastrointestinal tolerability profile of initial combination therapy was similar to that of metformin alone. Treatment with metformin is commonly associated with gastrointestinal adverse experiences [11], and the present study shows that the combination of sitagliptin and metformin therapies does not exacerbate the gastrointestinal side effects. Further, sitagliptin monotherapy treatment appeared to have generally better gastrointestinal tolerability relative to treatment with metformin monotherapy or combination treatments.

Treatment with the higher dose combination resulted in modest weight loss that was less than that observed with higher dose metformin alone. The other treatments were generally weight neutral over the 104 weeks. Because improvement in glycaemic control can lead to weight gain, the modest reduction in body weight or lack of weight gain with the substantial improvement in glycaemic control observed for all of the active-treatment groups over 2 years is a clinically important finding, particularly given the high prevalence of obesity in patients with type 2 diabetes.

DPP-4 inhibitors such as sitagliptin and biguanides such as metformin have different mechanisms of action [11,12]. Sitagliptin inhibits the enzymatic degradation and inactivation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, which are involved in glucose homeostasis [12,13]. Through its effects on incretins, sitagliptin lowers blood glucose by increasing postprandial insulin release and reducing glucagon release in a glucose-dependent manner in patients with type 2 diabetes [14] and via improvement of α- and β-cell function [7,14–17]. The mechanism of action of metformin involves suppression of hepatic glucose output, reduction of insulin resistance [18], and possibly an increase in total (including active) GLP-1 release [19,20] via a mechanism independent of DPP-4 inhibition [21,22]. When taken together, the combination of sitagliptin and metformin leads to greater increases in active GLP-1 than either treatment alone [20]. Further, this combination improves the three key pathologic abnormalities associated with type 2 diabetes: diminished β-cell function with reduced insulin release, increased insulin resistance and increased hepatic glucose output [23,24]. As showed throughout this study [4,5], the complementary effects of sitagliptin and metformin lead to robust and long-term improvements in glycaemic control.

In conclusion, the initial combination therapy with sitagliptin and metformin and treatment with either therapy alone led to substantial and sustained improvements in glycaemic control and β-cell function over 2 years in patients with type 2 diabetes, with greater improvements generally observed in the higher dose combination group. Moreover, the overall safety profile of initial combination therapy with sitagliptin and metformin was favourable over the 2-year period, with incidences of hypoglycaemia and gastrointestinal-related side effects similar to those observed with metformin monotherapy.

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Conflict of Interest

All authors are current or prior employees of Merck & Co., Inc. and may own stock or have stock options in the company.

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Appendix

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