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ORIGINAL ARTICLE

Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes

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Aim: To compare the efficacy and safety of monotherapy with sitagliptin and metformin in treatment-naïve patients with type 2 diabetes.
Methods: In a double-blind study, 1050 treatment-naïve patients (i.e. not taking an antihyperglycaemic agent for ≥16 weeks prior to study entry) with type 2 diabetes and an HbA_{1c} 6.5–9% were randomized (1:1) to treatment with once-daily sitagliptin 100 mg (N = 528) or twice-daily metformin 1000 mg (N = 522) for 24 weeks. Metformin was up-titrated from 500 to 2000 mg per day (or maximum tolerated daily dose ≥1000 mg) over a period of 5 weeks. The primary analysis used a per-protocol (PP) approach to assess whether sitagliptin was non-inferior to metformin based on HbA_{1c} change from baseline at week 24. Non-inferiority was to be declared if the upper boundary of the 95% confidence interval (CI) for the between-group difference in this endpoint was <0.40%.
Results: From a mean baseline HbA_{1c} of 7.2% in the PP population, HbA_{1c} change from baseline was −0.43% with sitagliptin (n = 455) and −0.57% with metformin (n = 439). The between-group difference (95% CI) was 0.14% (0.06, 0.21), thus confirming non-inferiority. Baseline HbA_{1c} influenced treatment response, with larger reductions in HbA_{1c} observed in patients with baseline HbA_{1c} ≥8% in the sitagliptin (−1.13%; n = 74) and metformin (−1.24%; n = 73) groups. The proportions of patients at week 24 with HbA_{1c} values at the goals of <7 or <6.5% were 69 and 34% with sitagliptin and 76 and 39% with metformin, respectively. Fasting plasma glucose changes from baseline were −11.5 mg/dL (−0.6 mmol/l) and −19.4 mg/dl (−1.1 mmol/l) with sitagliptin and metformin, respectively (difference in LS mean change from baseline [95% CI] = 8.0 mg/dl [4.5, 11.4]). Both treatments led to similar improvements from baseline in measures of homeostasis model assessment-β cell function (HOMA-β) and insulin resistance (HOMA-IR). The incidence of hypoglycaemia was 1.7% with sitagliptin and 3.3% with metformin (p = 0.116). The incidence of gastrointestinal-related adverse experiences was substantially lower with sitagliptin (11.6%) compared with metformin (20.7%) (difference in incidence [95% CI] = −9.1% [−13.6, −4.7]), primarily because of significantly decreased incidences of diarrhoea (3.6 vs. 10.9%; p < 0.001) and nausea (1.1 vs. 3.1%; p = 0.032). Body weight was reduced from baseline with both sitagliptin (LS mean change [95% CI] = −0.6 kg [−0.9, −0.4]) and metformin (−1.9 kg [−2.2, −1.7]) (p < 0.001 for sitagliptin vs. metformin).
Conclusions: In this 24-week monotherapy study, sitagliptin was non-inferior to metformin in improving HbA_{1c} in treatment-naïve patients with type 2 diabetes. Although both treatments were generally well tolerated, a lower incidence of gastrointestinal-related adverse experiences was observed with sitagliptin.
Keywords: biguanides, dipeptidyl peptidase-4, incretins

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Introduction

Metformin has become the recommended monotherapy for treatment of type 2 diabetes because of its combination of efficacy, long-term experience and well-described safety profile [1]. However, gastrointestinal intolerance and the risk of lactic acidosis in low perfusion states and renal insufficiency limit its usefulness [2,3]. Sitagliptin, a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor, is an oral antihyperglycaemic agent for the treatment of type 2 diabetes. In clinical trials, sitagliptin monotherapy has been demonstrated to improve glycaemic control and β-cell function and to have a safety profile similar to placebo, with a low risk of hypoglycaemia or gastrointestinal side effects and no weight gain [4–6]. In particular, in previous registration trials, treatment with once-daily sitagliptin 100 mg significantly reduced HbA_{1c} by approximately 0.7% compared with placebo in patients with mild-to-moderate hyperglycaemia (mean baseline HbA_{1c} ~8%) [4,5]. The proportion of patients with HbA_{1c} <7% was approximately 40% in the sitagliptin groups compared with approximately 16% in the placebo groups in these studies [4,5]. Both sitagliptin and metformin may be considered by physicians for use as initial monotherapy in patients with type 2 diabetes in a variety of clinical situations [3,7]. This 24-week study compared the HbA_{1c}-lowering efficacy and safety between sitagliptin monotherapy and metformin

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monotherapy, using a non-inferiority trial design, in treatment-naïve patients with type 2 diabetes.

Methods

Patients

Inclusion/Exclusion Criteria. Men and women with type 2 diabetes (18–78 years of age) who were treatment naïve (i.e. not taking an antihyperglycaemic agent for at least 16 weeks prior to study entry) with HbA_{1c} 6.5–9.0% were potentially eligible to participate in the study if they met all screening criteria. Patients with type 1 diabetes, fasting plasma glucose (FPG) <120 mg/dl (6.7 mmol/l) or >250 mg/dl (13.9 mmol/l), unstable cardiac disease, significant renal impairment (creatinine ≥1.4 mg/dl for males or ≥1.3 mg/dl for females or creatinine clearance <60 ml/min), elevated alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase (more than 2 times upper limit of normal) or triglycerides >600 mg/dl were excluded. Patients were expected to follow a recommended regimen of diet and exercise for the duration of the study [8].

All patients provided written informed consent to participate, and the study protocol was reviewed and approved by the appropriate committees and authorities for each study site. The study was performed in accordance with the Declaration of Helsinki.

Study Design

This multinational, double-blind, randomized, active-controlled, non-inferiority study was conducted at 113 sites in 23 countries (see Appendix for list of study investigators and countries). The non-inferiority design was chosen as a standard approach to assess similarity of efficacy of a new agent to a standard treatment. After a 2-week placebo run-in period, eligible patients were randomized, using a computer-generated allocation schedule, in a 1:1 ratio to either once-daily sitagliptin 100 mg or twice-daily metformin 1000 mg for 24 weeks (Sitagliptin Protocol 049; Clinical Trials.gov NCT00449930). Metformin 500 mg (or matching placebo) was initiated at a dose of one tablet daily and up-titrated to two 500 mg tablets twice daily (i.e. 1000 mg b.i.d.) over a maximum 5-week period. Down-titration of metformin was permitted for intolerance to a minimum allowed dose of 1000 mg/day. Metformin-treated patients were analysed as a single group, regardless of final dose.

Patients were to be discontinued for lack of efficacy based on progressively stricter glycaemic criteria: from randomization to week 6, FPG >270 mg/dl (15 mmol/l); from >week 6 to week 12, FPG >240 mg/dl (13.3 mmol/l); and from >week 12 to week 24, FPG >210 mg/dl (11.7 mmol/l).

Study Evaluations

Efficacy Assessments. After an overnight fast of ≥12 h in duration, blood was collected for the assessment of HbA_{1c} (primary endpoint). Other endpoints included the proportions of patients with HbA_{1c} <7 or <6.5%, FPG, 1,5-anhydroglucitol [9,10], fasting serum insulin, fasting serum proinsulin and lipid parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and non-HDL-C. Homeostasis model assessment-β cell function (HOMA-β), HOMA-insulin resistance (HOMA-IR) and proinsulin/insulin ratio were calculated.

Safety Assessments. Data were collected on clinical and laboratory adverse experiences (AEs), physical examinations, body weight, vital signs and electrocardiograms (ECGs) at predefined time points. All AEs were rated by investigators for intensity and relationship to study drug. Laboratory evaluations included complete blood counts, chemistry panels and urinalysis. Patients were counselled with regard to the symptoms, fingerstick evaluation and treatment of hypoglycaemia; those experiencing symptoms consistent with hypoglycaemia were to obtain a fingerstick glucose, record the value in a log book and contact their study site. Clinical AEs of interest included symptomatic hypoglycaemia and the prespecified gastrointestinal AEs of diarrhoea, nausea, abdominal pain and vomiting. The analysis of abdominal pain included AEs reported as abdominal pain lower, abdominal pain upper, abdominal pain, abdominal discomfort and epigastric pain.

All laboratory efficacy and safety measurements were performed at central laboratories (PPD, Inc., Highland Heights, KY, USA, and Zaventem, Belgium); ECGs were collected and read locally at each study site by technicians blinded to treatment assignment.

Statistical Analyses

The primary efficacy analysis assessed whether the study treatments were non-inferior with regard to the HbA_{1c} change from baseline at week 24 using the per-protocol (PP) population. The PP population consisted of patients who completed the study and did not have any reasons for exclusion from this population, including absence of baseline or on-treatment data at the week 24 visit or major protocol violations (e.g. drug compliance <75%, addition of non-study antihyperglycaemic agent or incorrect double-blind study medication). Approximately 400 patients from each treatment group were planned for inclusion in the PP population.

To address the primary hypothesis, the change from baseline in HbA_{1c} at week 24 in the sitagliptin group was compared with that in the metformin group using the least-squares (LS) mean change and the 95% confidence interval (CI) as estimated via analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment and baseline HbA_{1c} value. Non-inferiority was to be declared if the upper boundary of the 95% CI of the treatment effect (sitagliptin minus metformin) was less than the margin, $\delta = 0.40\%$. To support the findings in the analysis of the PP population, additional efficacy analyses were performed for HbA_{1c} on the full analysis set (FAS) cohort that consisted of all randomized patients who received at least one dose of study treatment and who had both a baseline and at least one postbaseline efficacy measurement. Missing values in the FAS analysis were imputed by the last observation carried forward approach.

Other efficacy endpoints were also analysed for the PP population using the same ANCOVA model. A non-parametric approach was used for the analyses of triglycerides and 1,5-anhydroglucitol because of the violation of ANCOVA normality assumption; within-treatment effects were estimated using medians, and between-treatment effects were estimated using the Hodges–Lehmann estimate with a corresponding distribution-free 95% CI based on Wilcoxon's rank sum test. An analysis of the proportion of individuals whose HbA_{1c} values were <7 or <6.5% at week 24 was conducted using a logistic regression model to compare the sitagliptin and metformin groups. Prespecified subgroup analyses for HbA_{1c} change from baseline was performed to explore whether treatment effects were consistent within subgroups, which included baseline HbA_{1c}, gender, age, ethnicity, baseline BMI, duration of diabetes and geographical region (Asia, Latin America, USA and Europe).

The safety analysis was based on the 24-week results for the all-patients-as-treated (APaT) population, which consisted of all randomized patients who received at least one dose of study medication. In addition, for assessments based on laboratory measurements, both baseline and at least one postbaseline laboratory test were required for inclusion in the APaT population. Between-treatment differences in clinical AEs of interest [hypoglycaemia and selected gastrointestinal AEs (diarrhoea, nausea, abdominal pain and vomiting)] were evaluated statistically by calculating *p* values and 95% CIs using Fisher's exact test and the Wilson score method, respectively. To limit the potential for false positive results, testing of the selected gastrointestinal AEs was performed as follows. Diarrhoea was tested first, conditionally followed by nausea, abdominal pain and vomiting, such that each subsequent AE was tested only if a significant difference ($p < 0.05$, 2-sided) was found for the previous AE. In addition, AEs with an incidence of at least 1% in any treatment group were reported and the between-treatment differences were estimated with 95% CIs computed using the Wilson score method. In a post hoc analysis, body weight was compared in the APaT population using an ANCOVA model similar to the one described above.

For data presented in conventional units, the following SI conversion factors may be used: to convert glucose values to mmol/l, multiply by 0.0551; 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 triglyceride values to mmol/l, multiply by 0.0113.

Results

Patient Disposition and Characteristics

Data from one site (n = 8 patients) was excluded because of non-compliance with requirements for Good Clinical Practice. Analyses with or without these data did not affect any of the efficacy or safety conclusions. Of the 1050 randomized patients from compliant sites, 894 were included in the PP analysis (sitagliptin, n = 455 and metformin, n = 439). Of the 156 patients excluded from the PP analysis, 11 patients were protocol violators and the rest were missing on-treatment data at week 24. The disposition of screened and randomized patients is summarized in figure 1. More patients in the metformin group discontinued treatment compared with the sitagliptin group (figure 1); this difference primarily reflected the higher number of metformin-treated patients discontinuing because of AEs or because of withdrawal of informed consent (figure 1). More patients discontinued for lack of efficacy (i.e. patients not meeting the progressively stricter protocol-specified glycaemic criteria and/or not meeting the investigator's expectations of glycaemic improvement) in the sitagliptin group.

The treatment groups were generally balanced with respect to baseline demographics and efficacy variables for patients included in the PP population (table 1). Overall, these patients had mild-to-moderate hyperglycaemia at baseline, with a mean HbA_{1c} of 7.2% (~84% with an HbA_{1c} <8%), mean FPG of 142 mg/dl (7.9 mmol/l) and mean duration of type 2 diabetes of 2.4 years. The baseline characteristics of the PP population were similar to the entire randomized population (data not shown). At baseline, the most common concomitant medications were agents acting on the renin–angiotensin system (taken by 41.7 and 39.8% of patients in the sitagliptin and metformin groups, respectively), lipid-modifying agents (33.9 and 32.8%, respectively) and analgaesics (25.4 and 23.9%, respectively).

Titration of metformin up to a dose of 2000 mg/day (1000 mg b.i.d.) was required by the protocol over the first 5 weeks unless a patient could not tolerate uptitration. The mean dose of metformin after week 6 in the PP population was 1903 mg/day. During the course of the study, 96.4% of patients in the PP population reached a maximum dose of metformin of 2000 mg, and 88% of patients in the PP population were on the maximum dose of 2000 mg at week 24. For all patients, the mean duration of exposure to study drug was similar in the sitagliptin (155.7 days) and metformin (151.6 days) groups, and the mean (median) compliance was 98.6% (100%) in both treatment groups.

Efficacy

In the PP population, the LS mean HbA_{1c} change from baseline at week 24 was −0.43% in the sitagliptin group and −0.57% in the metformin group. The estimated difference in LS means for sitagliptin vs. metformin was 0.14% (95% CI: 0.06, 0.21). The upper limit of the two-sided 95% CI (0.21%) for the LS mean difference between sitagliptin and metformin was less than the prespecified non-inferiority margin of 0.40%, thus confirming non-inferiority of sitagliptin to metformin in the reduction of HbA_{1c} (table 2). Maximal HbA_{1c} efficacy appeared to have been achieved by week 18 for each treatment (figure 2A). The primary PP analysis is supported by an analysis based on the FAS population. From a baseline HbA_{1c} of 7.25% in both groups in the FAS population, the LS mean HbA_{1c} change from baseline at week 24 was −0.38% (95% CI: −0.43, −0.32) in the sitagliptin group (n = 512) and −0.55% (−0.61, −0.50) in the metformin group (n = 498). The estimated difference in LS means for sitagliptin vs. metformin in this supportive analysis was 0.18% (95% CI: 0.10, 0.25), within the non-inferiority parameter selected.

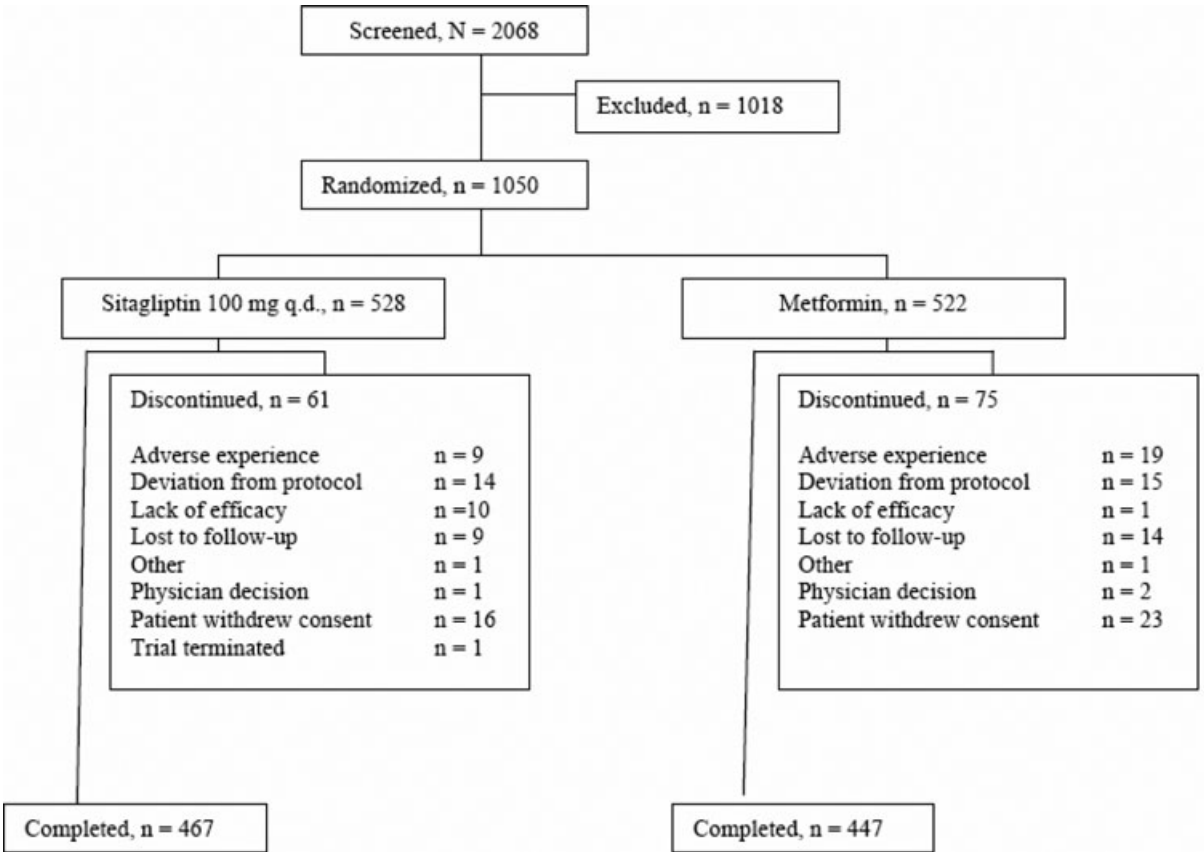

Figure 1. Disposition of randomized patients over 24 weeks.

Table 1. Patient demographics and baseline characteristics (PP population).

Parameter	Sitagliptin 100 mg q.d. N = 455	Metformin N = 439
Age, years	56.3 ± 10.7	55.7 ± 10.3
Males, n (%)	217 (48)	194 (44)
Body mass index, kg/m^2	30.7 ± 4.7	30.9 ± 4.9
HbA_{1c}, % (range)*	7.2 ± 0.7 (5.7–10.4)	7.2 ± 0.7 (5.6–10.1)
HbA_{1c} distribution at baseline, n (%)		
HbA_{1c} <7%	199 (44)	182 (41)
HbA_{1c} ≥7 to <8%	182 (40)	184 (42)
HbA_{1c} ≥8%	74 (16)	73 (17)
Fasting plasma glucose, mg/dl	142.4 ± 31.9	141.9 ± 33.1
1,5-anhydroglucitol, µg/ml	11.5 ± 7.1	10.9 ± 6.8
Duration of type 2 diabetes, years	2.6 ± 3.9	2.1 ± 3.5

Data are expressed as mean ± standard deviation or frequency (n [%]).
*Patients were eligible for the 2-week placebo run-in period prior to randomization if HbA_{1c} was in the range of 6.5–9.0%. Baseline measurements were obtained after this run-in period (at the randomization visit), and thus HbA_{1c} may be outside the range specified in eligibility criteria.

Sitagliptin and metformin were similarly effective in lowering HbA_{1c} across subgroups defined by gender, race, ethnicity, age, BMI, duration of diabetes and geographical region. HbA_{1c} responses in both treatment groups were influenced by baseline HbA_{1c}, with mean reductions up to 1.2% observed in patients with baseline HbA_{1c} >8% (figure 2B). The proportion of patients with an HbA_{1c} <7% at week 24 was greater with metformin (76%) compared with sitagliptin (69%) [between-treatment difference in proportions (95% CI) −7.1% (−12.9, −1.2)], whereas the proportion of patients with an HbA_{1c} <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups [between-treatment difference in proportions (95% CI) −5.6% (−11.8, 0.8)].

LS mean change from baseline in FPG was greater with metformin (−19.4 mg/dl [−1.1 mmol/l]) compared with sitagliptin (−11.5 mg/dl [−0.6 mmol/l]) (table 2). The profiles of mean change from baseline in FPG over time showed that both treatment groups exhibited similar trends, beginning with a decrease in the first 6 weeks followed by stable levels for the remainder of the study (figure 3). Increases in 1,5-anhydroglucitol levels after 24 weeks were consistent with the HbA_{1c} and FPG findings in the two treatment groups (table 2).

Reductions in fasting insulin, fasting proinsulin and the proinsulin/insulin ratio were observed in both the sitagliptin and metformin treatment groups at week 24. The reduction in fasting proinsulin was greater in the metformin group,

Table 2. Glycaemic and insulin-related endpoints at baseline and week 24 (PP population).

	n	Week 0 (Baseline) Mean ± s.d.	Week 24 Mean ± s.d.	LS Mean Change from Baseline (95% CI)	Difference in LS Mean Change (95% CI)
HbA_{1c} (%)					
Sitagliptin 100 mg q.d.	455	7.2 ± 0.7	6.8 ± 0.7	−0.43 (−0.48, − 0.38)	0.14 (0.06, 0.21)
Metformin	439	7.2 ± 0.7	6.7 ± 0.6	−0.57 (−0.62, − 0.51)	
Fasting plasma glucose (mg/dl)					
Sitagliptin 100 mg q.d.	446	142.5 ± 31.9	130.9 ± 31.5	−11.5 (−13.9, − 9.1)	8.0 (4.5, 11.4)
Metformin	435	142.1 ± 33.5	122.8 ± 27.7	−19.4 (−21.9, − 17.0)	
1,5-anhydroglucitol (μg/ml)*					
Sitagliptin 100 mg q.d.	393	10.4	14.9	2.8 (2.3, 3.3)	−0.9 (−1.5, − 0.3)
Metformin	395	9.6	15.1	4.0 (3.4, 4.6)	
Fasting serum insulin (μIU/ml)					
Sitagliptin 100 mg q.d.	395	16.5 ± 16.1	15.6 ± 11.1	−1.4 (−2.8, − 0.0)	1.1 (−0.8, 3.1)
Metformin	397	18.0 ± 19.3	14.9 ± 17.9	−2.5 (−3.9, − 1.1)	
Fasting serum proinsulin (pmol/l)					
Sitagliptin 100 mg q.d.	372	25.4 ± 24.5	23.2 ± 22.6	−2.6 (−4.6, − 0.7)	6.0 (3.2, 8.7)
Metformin	374	27.2 ± 30.0	18.2 ± 25.2	−8.6 (−10.6, − 6.7)	
Proinsulin/insulin ratio					
Sitagliptin 100 mg q.d.	362	0.313 ± 0.240	0.276 ± 0.196	−0.032 (−0.049, − 0.016)	0.050 (0.027, 0.074)
Metformin	368	0.298 ± 0.242	0.221 ± 0.168	−0.083 (−0.099, − 0.066)	
HOMA-β					
Sitagliptin 100 mg q.d.	379	80.2 ± 77.0	90.9 ± 71.4	8.2 (1.0, 15.4)	−4.5 (−14.6, 5.7)
Metformin	383	90.5 ± 94.4	100.8 ± 95.5	12.7 (5.6, 19.9)	
HOMA-IR					
Sitagliptin 100 mg q.d.	379	5.8 ± 6.3	5.2 ± 4.3	−0.9 (−1.7, − 0.1)	0.3 (−0.9, 1.4)
Metformin	384	6.5 ± 8.2	5.1 ± 10.8	−1.2 (−2.0, − 0.4)	

HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.
n, number of patients with evaluable data included in the analysis; Baseline and week 24 data are expressed as mean ± standard deviation; change from baseline data are expressed as LS mean change (95% CI) unless otherwise noted.
*Median and median change from baseline (95% CI).

which resulted in a larger reduction in the proinsulin/insulin ratio at week 24 (table 2). Both treatments produced similar increases in HOMA-β and reductions in HOMA-IR over 24 weeks (table 2).

HDL-C was similarly improved with both treatments (table 3). Triglycerides were slightly reduced from baseline with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin; modest increases in LDL-C and non-HDL-C were also observed with sitagliptin, but not metformin over 24 weeks (table 3).

Safety

Both treatments were generally well tolerated over 24 weeks. One or more AEs were reported for 198 (37.5%) patients in the sitagliptin group and 215 (41.2%) patients in the metformin group. Discontinuations because of AEs were 1.7% in the sitagliptin group and 3.6% in the metformin group. The incidence of drug-related AEs was lower in the sitagliptin group than in the metformin group (table 4), primarily because of the higher incidence of gastrointestinal-related AEs in the metformin group (see below). There was one reported death in the study (because of metastatic lung cancer; not considered related to treatment) in the sitagliptin group.

The incidence of gastrointestinal AEs overall was lower in the sitagliptin group compared with the metformin group [11.6 vs. 20.7%, respectively; difference in incidence (95% CI) = −9.1% (−13.6, −4.7%)]. In a prespecified analysis on selected gastrointestinal AEs, there were statistically significantly lower incidences of diarrhoea and nausea in the sitagliptin group relative to the metformin group [diarrhoea 3.6 vs. 10.9% ($p < 0.001$); nausea 1.1 vs. 3.1% ($p = 0.032$)] and numerically, but not significantly, lower incidences of abdominal pain [2.1 vs. 3.8% ($p = 0.103$)] and vomiting [0.4 vs. 1.3% ($p = 0.106$)] (table 5).

AEs of hypoglycaemia, generally rated as mild, occurred at low incidences in both groups. Nine patients (1.7%) in the sitagliptin group were reported to have 17 episodes of hypoglycaemia compared with 17 patients (3.3%) in the metformin group, who were reported to have 23 episodes ($p = 0.116$ for the between-treatment difference in incidence; table 5). Two patients in the sitagliptin group had hypoglycaemic episodes for which they received medical assistance. One was a patient with low fingerstick glucose values down to 54 mg/dl (3.0 mmol/l) with no precipitating factors or other details reported. The other reported a fingerstick glucose value of 42 mg/dl (2.3 mmol/l) that was preceded by a missed meal; while food administered in the clinic increased blood glucose to 89 mg/dl (4.9 mmol/l), the response was not considered adequate, and the patient received intravenous glucose. The patient went on to remain asymptomatic with fingerstick glucose values 59–156 mg/dl (3.3–8.7 mmol/l)

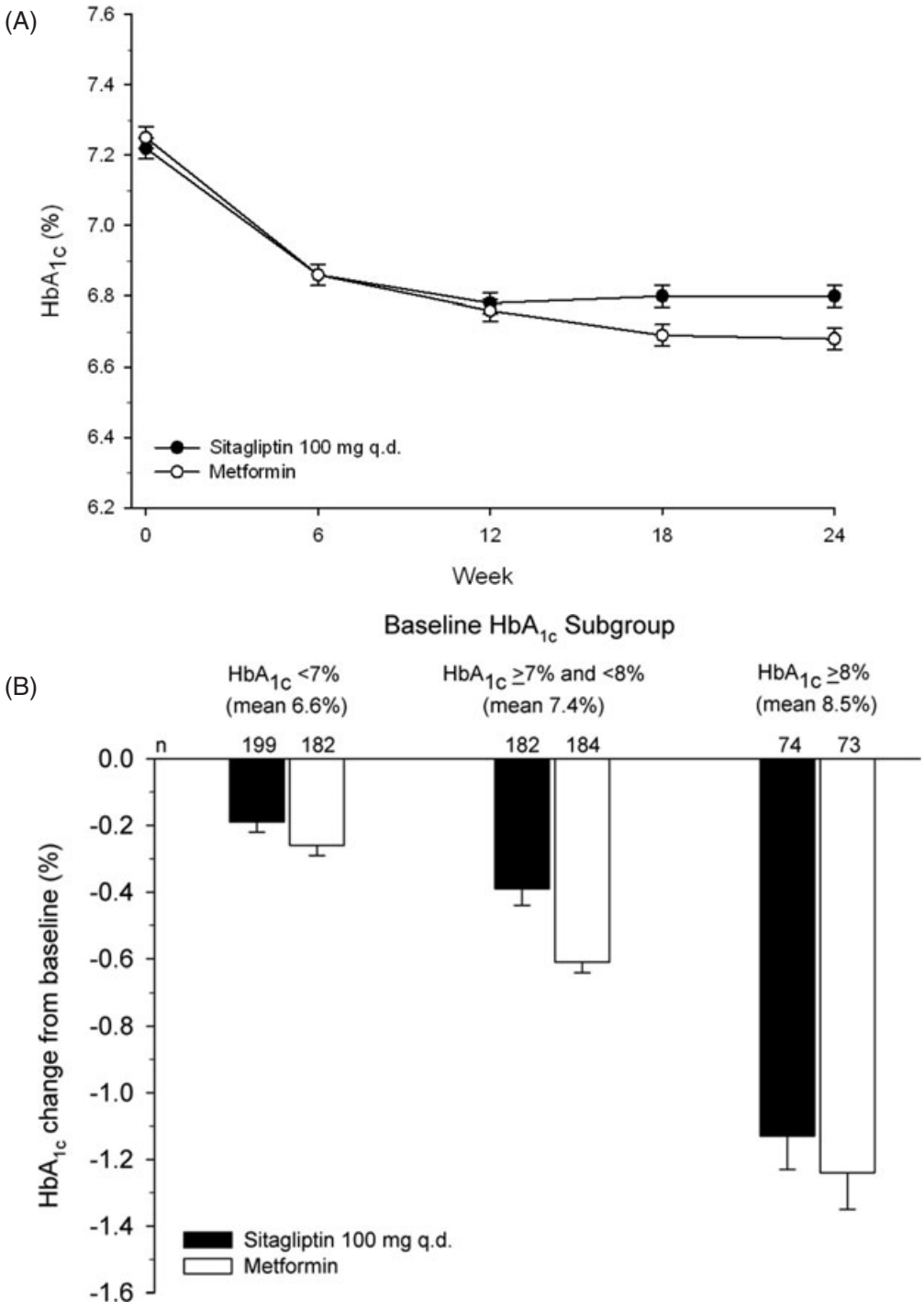

Figure 2. (A) HbA_{1c} over time (mean ± s.e.) for the per-protocol population. (B) HbA_{1c} change from baseline (LS mean change ± s.e.) at week 24 by baseline HbA_{1c} subgroups.

while taking sitagliptin, but subsequently discontinued therapy.

Additional AEs occurring in ≥1% of patients in either treatment group are summarized in table 5. There were no AEs that occurred more frequently in the sitagliptin group relative to the metformin group in which the 95% CIs for the between-treatment difference in incidence excluded zero.

Body weight was reduced from baseline in both the sitagliptin [LS mean change from baseline (95% CI) −0.6 kg (−0.9, −0.4); n = 458] and metformin [−1.9 kg (−2.2, −1.7); n = 446] groups, with a significantly larger change ($p < 0.001$) observed with metformin relative to sitagliptin.

No clinically meaningful differences were noted in the proportions of patients treated with sitagliptin or metformin

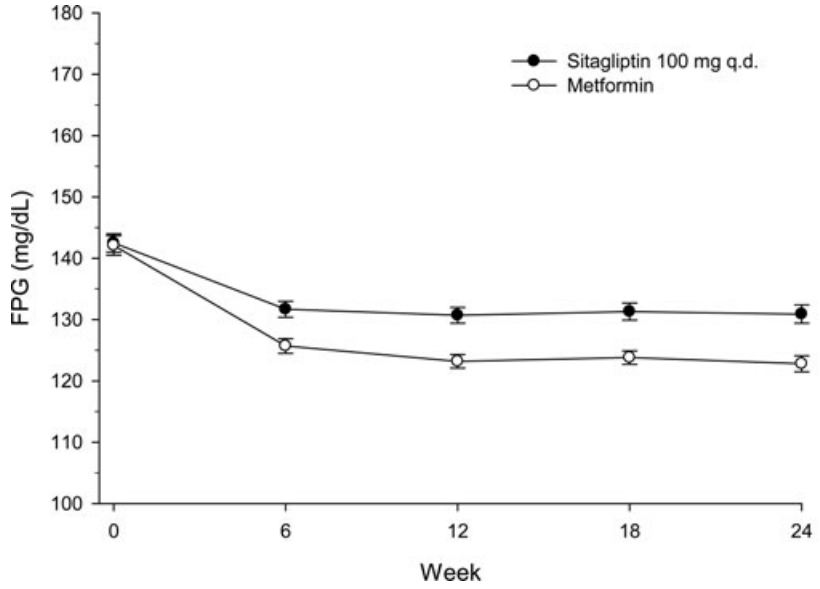

Figure 3. Fasting plasma glucose (FPG) over time (mean ± s.e.) for the per-protocol population.

Table 3. Lipid endpoints at baseline and week 24 (PP population).

	n	Week 0 (Baseline) Mean ± s.d.	Week 24 Mean ± s.d.	LS mean % change from baseline (95% CI)	Difference in LS mean % change (95% CI)
Total cholesterol (mg/dl)					
Sitagliptin 100 mg q.d.	441	187.1 ± 40.3	194.4 ± 39.8	5.5 (3.8, 7.3)	3.3 (0.9, 5.8)
Metformin	427	189.5 ± 42.2	190.4 ± 43.9	2.2 (0.4, 4.0)	
HDL cholesterol (mg/dl)					
Sitagliptin 100 mg q.d.	440	47.0 ± 11.9	49.4 ± 12.3	6.2 (4.7, 7.8)	−0.8 (−3.0, 1.4)
Metformin	427	47.8 ± 11.2	50.6 ± 12.9	7.0 (5.4, 8.6)	
LDL cholesterol (mg/dl)					
Sitagliptin 100 mg q.d.	441	109.0 ± 35.8	115.4 ±36.2	11.2 (8.0, 14.5)	8.7 (4.1, 13.3)
Metformin	426	110.9 ± 37.6	108.5 ± 36.7	2.5 (−0.8, 5.8)	
Non-HDL cholesterol (mg/dl)					
Sitagliptin 100 mg q.d.	440	140.1 ± 40.3	145.1 ± 40.4	6.5 (4.0, 9.0)	4.8 (1.2, 8.3)
Metformin	427	141.8 ± 41.6	139.8 ± 42.7	1.7 (−0.8, 4.2)	
Triglycerides (mg/dl)*					
Sitagliptin 100 mg q.d.	441	136.0	134.0	−3.7 (−7.2, − 0.2)	−3.8 (−8.2, 0.5)
Metformin	427	136.0	136.0	−1.2 (−5.2, 2.7)	

n, number of patients with evaluable data included in the analysis; Baseline and week 24 data are expressed as mean ± standard deviation unless otherwise indicated; change from baseline data are expressed as LS mean change (95% CI) unless otherwise indicated.
*Median or median per cent change.

with values meeting predefined limits of change criteria for any of the measured chemistry and haematology parameters or in blood pressure or other vital signs.

Discussion

Metformin is now the most widely recommended oral agent used as initial monotherapy for the treatment of type 2 diabetes mellitus. It combines weight loss with a well established record of efficacy and safety, with a low risk of hypoglycaemia. Insulin secretagogues, such as sulfonylurea agents, are associated with both weight gain and hypoglycaemia, and the α-glucosidase inhibitors are associated with significant gastrointestinal side effects. DPP-4 inhibitors potentially could be used as initial therapy as they are glucose-dependent β-cell sensitizers that are well tolerated with a low risk of hypoglycaemia or weight gain. Sitagliptin, a DPP-4 inhibitor approved for the treatment of type 2 diabetes since 2006 in the USA and 2007 in the EU, has been shown to be non-inferior to glipizide when added to metformin monotherapy with a lower incidence of hypoglycaemia (5.3 vs. 34.1%) and a weight difference of −2.5 kg [11]. Comparing the safety and efficacy of sitagliptin to metformin in treatment-naive patients who are not at their A1C goal and require treatment with oral antihyperglycaemic therapy was the rationale of this study.

Table 4. Summary of clinical AEs (APaT population).

Number (%) of patients	Sitagliptin 100 mg q.d. **N = 528**	Metformin **N = 522**
One or more AEs	198 (37.5)	215 (41.2)
Drug-related AEs*	31 (5.9)	87 (16.7)
Serious AEs (SAEs)	10 (1.9)	8 (1.5)
Drug-related SAEs*	1 (0.2)	0
Who died	1 (0.2)	0
Discontinued because of AEs	9 (1.7)	19 (3.6)
Discontinued because of drug-related AEs	3 (0.6)	12 (2.3)
Discontinued because of SAEs	3 (0.6)	3 (0.6)
Discontinued because of drug-related SAEs	1 (0.2)	0

AEs, adverse experiences.
*Considered by the investigator to be related to study drug.

The entry criterion for inclusion in this trial was an HbA_{1c} value between 6.5 and 9.0%, which was lower than typical registration trials with antihyperglycaemic agents. This range was chosen to compare sitagliptin with metformin in clinical scenarios in which these agents would be used as monotherapy. The lower bound of the HbA_{1c} inclusion criterion (6.5%) was selected because several clinical guidelines, including those from the International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACEs), suggest that an HbA_{1c} $\leq$6.5% is the appropriate target for patients with type 2 diabetes and reduces the risk for microvascular events [1]. Moreover, in a recent position statement by the American Diabetes Association, American College of Cardiology and American Heart Association [6], the authors, acknowledging the potential risk of lowering HbA_{1c} to <7% on the basis of evidence from recent trials, stressed individualization of treatment regimens and recommended lower goals than HbA_{1c} <7% in patients with a short duration of diabetes and no significant cardiovascular disease, such as those included in this study. The upper bound of the HbA_{1c} entry criteria was set at 9.0% in this study because, consistent with a recent analysis showing an approximately 1% reduction in HbA_{1c} for patients with a baseline HbA_{1c} between 9 and 10% [12], it was not expected that many patients with higher baseline HbA_{1c} levels would achieve a treatment goal <6.5%, let alone <7%, when treated with a single antihyperglycaemic agent. Thus, the patient population of this study was representative of an early diabetic population with mild-to-moderate hyperglycaemia (~84% with baseline HbA_{1c} <8%) that would usually initiate treatment with a single antihyperglycaemic agent, that is, those who had a reasonable chance of achieving HbA_{1c} goals with monotherapy. Furthermore, a comparison of sitagliptin vs. metformin was considered appropriate in this population, as some patients with mild-to-moderate hyperglycaemia, especially older patients, may need agents that do not increase the risk of hypoglycaemia, such as sitagliptin and metformin [3,7].

In this head-to-head monotherapy study, the efficacy and safety of sitagliptin was compared with metformin in treatment-naïve patients with type 2 diabetes with mild-to-moderate hyperglycaemia. In the PP population, prespecified as the primary population for analysis, the mean dose of metformin achieved was approximately 1900 mg/day and 88% of patients were on metformin 2000 mg/day at study end. Because metformin at the dose of 2000 mg/day provided maximal efficacy in a dose-ranging study (500–2500 mg daily) [13], this study can be considered a reasonable comparison of the maximally efficacious doses for sitagliptin and metformin. Although there was a small, statistically significant difference in HbA_{1c} reduction between groups (0.14%), sitagliptin was non-inferior to metformin for the improvement of HbA_{1c}, based on prespecified non-inferiority criteria. In addition, with both treatments there were larger HbA_{1c} reductions for patients with higher baseline HbA_{1c}. Importantly, the small, between-treatment difference in the HbA_{1c} change from baseline was generally consistent across the baseline HbA_{1c} subgroups. The glucose-lowering efficacy observed with both treatments in this study was less when compared with results obtained in prior studies, but this was likely because of the population of patients with milder disease enrolled in this trial. The present findings are consistent with those of Bloomgarden et al. [12], which show that different oral antihyperglycaemic agents have similar efficacy when the data are corrected for differences in baseline HbA_{1c} values.

Changes in FPG levels in both treatment groups exhibited similar trends over time, with a marked decrease in the first 6 weeks and levels that then remained stable for the duration of the study. The magnitude of the decrease in FPG levels was modestly greater in the metformin group than in the sitagliptin group. The between-treatment difference may be related to the mechanisms of action of both agents and baseline FPG levels, with the reduction of FPG by metformin being because of its primary mechanism of action (inhibition of hepatic glucose production) [3]. The reduction of FPG by sitagliptin is because of the incretin-mediated effects on insulin (stimulate release) and/or glucagon (inhibit secretion). Both effects are glucose-dependent and begin to dissipate as blood glucose approaches normal levels [14,15]. Therefore, in this study with patients who had low mean baseline FPG (~142 mg/dl [7.9 mmol/l]), the glucose-dependent effects of sitagliptin on FPG were likely diminished as sitagliptin reduced FPG to near-normal levels (mean FPG at nadir was ~130 mg/dl [7.2 mmol/l]; figure 3).

In previous clinical studies in patients with more severe hyperglycaemia at baseline, sitagliptin monotherapy was shown to significantly improve measures of β-cell function, including HOMA-β, the proinsulin/insulin ratio, and the insulinogenic index, relative to placebo, without effects on measures of insulin resistance [4,5,16–18]. In this study, both treatments similarly increased HOMA-β. Both treatments decreased the proinsulin/insulin ratio, with a greater improvement observed in the metformin group. The present results are similar to those observed in a previous trial in which treatment with both sitagliptin and metformin monotherapy led to similar improvements in measures of β-cell function [6]. The reason for the improvement in HOMA-$\beta$with metformin therapy is uncertain; however, recent data suggest that metformin increases GLP-1 secretion by a DPP-4-independent mechanism [19]. In addition, reductions in insulin resistance (HOMA-IR) were observed with metformin and with sitagliptin.

Table 5. AEs reported in ≥1% of patients (APaT population).

Number (%) of patients	Sitagliptin 100 mg q.d. N = 528	Metformin N = 522	Difference: sitagliptin vs. metformin % (95% CI)[†]
Prespecified gastrointestinal AEs			
Diarrhoea	19 (3.6)	57 (10.9)	−7.3 (−10.6, − 4.2)**
Nausea	6 (1.1)	16 (3.1)	−1.9 (−3.9, − 0.2)*
Abdominal pain[‡]	11 (2.1)	20 (3.8)	−1.7 (−4.0, 0.3)
Vomiting	2 (0.4)	7 (1.3)	−1.0 (−2.4, 0.2)
Other AEs			
Constipation	9 (1.7)	5 (1.0)	0.7 (−0.8, 2.3)
Dyspepsia	1 (0.2)	7 (1.3)	−1.2, (−2.6, − 0.0)
Gastritis	6 (1.1)	11 (2.1)	−1.0 (−2.7, 0.6)
Fatigue	6 (1.1)	6 (1.1)	−0.0 (−1.5, 1.4)
Pyrexia	0	5 (1.0)	−1.0 (−2.2, − 0.1)
Bronchitis	4 (0.8)	7 (1.3)	−0.6 (−2.1, 0.8)
Influenza	12 (2.3)	11 (2.1)	0.2 (−1.7, 2.1)
Nasopharyngitis	10 (1.9)	17 (3.3)	−1.4 (−3.4, 0.6)
Upper respiratory tract infection	5 (0.9)	11 (2.1)	−1.2 (−2.9, 0.4)
Urinary tract infection	3 (0.6)	13 (2.5)	−1.9 (−3.7, − 0.4)
Hypoglycaemia	9 (1.7)	17 (3.3)	−1.7 (−3.8, 0.2)
Arthralgia	5 (0.9)	5 (1.0)	−0.0 (−1.4, 1.4)
Back pain	9 (1.7)	9 (1.7)	−0.0 (−1.7, 1.7)
Osteoarthritis	1 (0.2)	5 (1.0)	−0.8 (−2.0, 0.3)
Pain in extremity	7 (1.3)	2 (0.4)	0.9 (−0.3, 2.4)
Dizziness	9 (1.7)	5 (1.0)	0.7 (−0.8, 2.3)
Headache	17 (3.2)	17 (3.3)	−0.0 (−2.3, 2.2)
Cough	1 (0.2)	8 (1.5)	−1.3 (−2.8, − 0.2)
Hypertension	12 (2.3)	4 (0.8)	1.5 (−0.0, 3.2)

AE, adverse experiences.

*$p < 0.05$;

**$p < 0.001$ for sitagliptin vs. metformin.

[†]Positive differences indicate that the incidence rate for the sitagliptin group is higher than that of the metformin group and vice versa. '0.0' and '−0.0' represent rounding for values that are slightly greater and slightly less than zero, respectively.

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

The safety and tolerability findings with sitagliptin and metformin, each used in monotherapy, in this study were consistent with previously published findings [20,21]. Of clinical interest, there was a lower incidence of gastrointestinal-related side effects with sitagliptin and a low incidence of hypoglycaemia in both groups. The lipid changes observed in this study are consistent with those observed in a 24-week, placebo-controlled study showing that, relative to placebo, sitagliptin and metformin monotherapy had generally neutral effects on TC, LDL-C, non-HDL-C and triglycerides [20]. In the context of equivalent glycaemic improvement, body weight was reduced more with metformin than with sitagliptin.

Recent data indicate that early and aggressive treatment of both type 1 and type 2 diabetes reduces the long-term risk of both micro-and macro-vascular complications [22]. A published safety analysis of pooled data from 12 large, double-blind clinical trials up to 2 years in duration did not indicate any signal for increased risk of cardiovascular events with sitagliptin [23]. A large outcomes trial is presently underway and will provide additional data on the impact of treatment with sitagliptin on cardiovascular outcomes when used as part of usual care [24].

In summary, treatment with sitagliptin monotherapy was non-inferior to metformin in improving glycaemic control as measured by HbA_{1c} in treatment-naïve patients with type 2 diabetes. Both treatments were generally well tolerated, with a lower incidence of gastrointestinal-related AEs but less weight loss observed with sitagliptin. The results of this study provide additional data on the use of sitagliptin as initial monotherapy for patients with type 2 diabetes mellitus.

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Appendix

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