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Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin

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Aim: To assess the efficacy and safety of a 24-week treatment with sitagliptin, a highly selective once-daily oral dipeptidyl peptidase-4 (DPP-4) inhibitor, in patients with type 2 diabetes who had inadequate glycaemic control [glycosylated haemoglobin (HbA_{1c}) $\geq$7.5% and $\leq$10.5%] while on glimepiride alone or in combination with metformin.

Methods: After a screening, diet/exercise run-in and drug wash-off period, a glimepiride $\pm$ metformin dose titration/stabilization period and a 2-week, single-blind placebo run-in, 441 patients (of ages 18–75 years) were randomized to receive the addition of sitagliptin 100 mg once daily or placebo in a 1 : 1 ratio for 24 weeks. Of these patients, 212 were on glimepiride ($\geq$4 mg/day) monotherapy and 229 were on glimepiride ($\geq$4 mg/day) plus metformin ($\geq$1500 mg/day) combination therapy. Patients exceeding pre-specified glycaemic thresholds during the double-blind treatment period were provided open-label rescue therapy (pioglitazone) until study end. The primary efficacy analysis evaluated the change in HbA_{1c} from baseline to Week 24. Secondary efficacy endpoints included fasting plasma glucose (FPG), 2-h post-meal glucose and lipid measurements.

Results: Mean baseline HbA_{1c} was 8.34% in the sitagliptin and placebo groups. After 24 weeks, sitagliptin reduced HbA_{1c} by 0.74% ($p < 0.001$) relative to placebo. In the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA_{1c} by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone. The addition of sitagliptin reduced FPG by 20.1 mg/dl ($p < 0.001$) and increased homeostasis model assessment-β, a marker of β-cell function, by 12% ($p < 0.05$) relative to placebo. In patients who underwent a meal tolerance test ($n = 134$), sitagliptin decreased 2-h post-prandial glucose (PPG) by 36.1 mg/dl ($p < 0.001$) relative to placebo. The addition of sitagliptin was generally well tolerated, although there was a higher incidence of overall (60 vs. 47%) and drug-related adverse experiences (AEs) (15 vs. 7%) in the sitagliptin group than in the placebo group. This was largely because of a higher incidence of hypoglycaemia AEs (12 vs. 2%, respectively) in the sitagliptin group compared with the placebo group. Body weight modestly increased with sitagliptin relative to placebo (+0.8 vs. −0.4 kg; $p < 0.001$).

Conclusions: Sitagliptin 100 mg once daily significantly improved glycaemic control and β-cell function in patients with type 2 diabetes who had inadequate glycaemic control with glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy and the observed degree of glycaemic improvement.

Keywords: combination therapy, dipeptidyl peptidase-IV, DPP-IV, glimepiride, incretins, metformin, MK-0431, sitagliptin
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Introduction

Treatment with a single antihyperglycaemic agent is often unsuccessful at achieving and/or maintaining long-term glycaemic control in patients with type 2 diabetes, so many patients require combination therapies [1]. Monotherapy with metformin or a sulphonylurea is the most commonly used initial oral hypoglycaemic agent (OHA) regimen to treat patients with type 2 diabetes. Sulphonylureas improve blood glucose levels by stimulating insulin secretion from pancreatic β-cells in a non-glucose–dependent manner [2]. Metformin, a biguanide, acts primarily by lowering hepatic glucose production and may also improve insulin resistance [3,4]. As with all OHAs, monotherapy with a sulphonylurea may not achieve or maintain glycaemic control; therefore novel, efficacious and well-tolerated therapies that can be added to a sulphonylurea agent are needed. Similarly, dual-combination therapy with a sulphonylurea agent and metformin also may not achieve or maintain glycaemic control [1]. In this setting, use of insulin is often the next therapeutic step, although triple OHA therapy [e.g. adding a thiazolidinedione, a peroxisome proliferator–activated receptor γ (PPARγ) agent, to ongoing dual therapy with metformin and a sulphonylurea] is increasingly being used in clinical practice. Insulin requires parenteral administration, which many patients find undesirable, and the addition of a thiazolidinedione can lead to oedema and an increase in body weight. Hence, there is a need for additional OHA options that can be added to the dual combination of sulphonylurea and metformin to avoid the need to switch to insulin.

Sitagliptin is a once-daily, orally active, potent and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor approved in many countries for the treatment of patients with type 2 diabetes [5]. DPP-4 is an enzyme involved in the degradation of the intact (active) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to inactive metabolites. GLP-1 and GIP are released by the intestine into the circulation in response to a meal, and both hormones increase glucose-dependent insulin secretion; in addition, GLP-1 suppresses glucagon release. By inhibiting the degradation of active incretins, sitagliptin increases active incretin concentrations, thereby enhancing their glucoregulatory effects [6–10]. Sitagliptin, administered as monotherapy or as add-on therapy to metformin or to a PPARγ agent, has been shown to improve glycaemic control and is well tolerated in patients with type 2 diabetes [11–14].

Although both sitagliptin and sulphonylureas stimulate insulin secretion from pancreatic β-cells, the mode by which these agents exert their effects differs [15,16]. Sitagliptin, acting through increases in active GLP-1 and GIP levels, increases insulin concentrations in a glucose-dependent fashion through increased intracellular levels of cyclic adenosine 3′,5′-monophosphate (cAMP), whereas sulphonylureas act in a non-glucose–dependent fashion through the sulphonylurea receptor. Sitagliptin has been shown to lower glucagon concentrations, which is likely to also contribute to the glucose lowering obtained with this agent. The role of glucagon in sulphonylurea action in patients with type 2 diabetes mellitus is less well defined. Given the different mechanisms of action of sitagliptin and sulphonylurea agents, combination therapy with these two agents would seem a rational approach to improving glycaemic control. Previous studies have shown that sitagliptin provides effective add-on combination treatment with metformin [14,17]. If sitagliptin is effective in combination with a sulphonylurea agent, then triple combination therapy with metformin and a sulphonylurea agent would likely be effective as well.

In this study, the efficacy and tolerability profile of adding sitagliptin 100 mg or placebo to ongoing treatment with glimepiride alone or glimepiride in combination with metformin was assessed over a 24-week period. In addition to assessment in the overall study population, the efficacy and tolerability of sitagliptin relative to placebo in the individual subpopulations of patients on glimepiride alone or on glimepiride and metformin were examined separately.

Patients and Methods

Study Population

Men and women, ≥18 and ≤75 years of age, with type 2 diabetes were recruited for this study. Only the following patients were eligible to be screened: (i) already taking glimepiride alone (at any dose) or in combination with metformin (at any dose), (ii) taking another OHA in monotherapy or in dual- or triple-combination therapy or (iii) patients not taking any OHAs over the prior 8 weeks. At the screening visit, patients were excluded if they had a history of type 1 diabetes; were treated with insulin within 8 weeks of the screening visit; had renal dysfunction (creatinine clearance <45 ml/min or <60 ml/min if on metformin); or had a history of hypersensitivity, intolerance or a contraindication to the use of glimepiride, sulphonylurea agents, metformin or pioglitazone (which was included in this study as rescue therapy).

The study was conducted in accordance with the guidelines on good clinical practice and with ethical standards

for human experimentation established by the Declaration of Helsinki. Ethics review committee/institutional review board approval was obtained for each study site. Written informed consent was obtained from all patients before any study procedure was performed.

Study Design

This was a multinational, randomized, double-blind, parallel-group study with a single-blind placebo run-in period followed by a double-blind placebo-controlled treatment period. At the screening visit, patients were instructed to receive glimepiride alone (Stratum 1) or glimepiride plus metformin (Stratum 2) based upon their OHA regimen at the screening visit and their baseline glycosylated haemoglobin (HbA_{1c}). An interactive voice response system (IVRS) was used to monitor enrollment and assign study drug and to ensure that approximately 50% of patients were assigned to each stratum. The study was designed to detect a true difference of 0.5% in the mean change from baseline in HbA_{1c} between sitagliptin and placebo for a two-tailed test at $\alpha = 0.05$ (two sided) with greater than 99% power for the entire cohort and with greater than 90% power for each stratum.

Patients with HbA_{1c} $\geq$7.5% and $\leq$10.5% who were already taking a stable dose of glimepiride ($\geq$4 mg/day up to a maximum daily dose of 8 mg/day) alone or in combination with metformin ($\geq$1500 mg/day up to a maximum daily dose of 3000 mg/day) for at least 10 weeks directly entered a 2-week, single-blind placebo run-in period. Patients who were not on OHA with HbA_{1c} $\geq$9%, who were taking other OHAs in monotherapy with HbA_{1c} $\geq$7.5%, or who were taking other OHAs in dual or triple therapy with HbA_{1c} $\geq$6.5% and $\leq$10.5%, discontinued their prior regimen and were switched to treatment with glimepiride alone or glimepiride in combination with metformin. Following the switch in treatments, these patients entered a dose titration period of up to 4 weeks and then a dose stabilization run-in period of up to 10 weeks. If HbA_{1c} was $\geq$7.5% and $\leq$10.5% after this run-in period, patients entered a 2-week, single-blind placebo run-in period. Patients with adequate compliance ($\geq$75%) during this placebo run-in period underwent baseline evaluations and were randomized through an IVRS in a 1 : 1 ratio to the addition of either once-daily sitagliptin 100 mg or placebo to ongoing stable doses of glimepiride, alone or in combination with metformin.

During the 24-week treatment period, patients not meeting specific, progressively lower glycaemic goals [fasting plasma glucose (FPG) >270 mg/dl between randomization (Day 1) and Week 6, FPG >240 mg/dl after Week 6 through Week 12, or FPG >200 mg/dl after Week 12 through Week 24] were provided open-label rescue therapy (pioglitazone 30 mg/day) until the completion of the study period. Patients receiving rescue therapy remained in the study to provide additional safety experience with the combination of sitagliptin and glimepiride ± metformin. Patients were discontinued from the study if they were on rescue therapy for at least 4 weeks and had an FPG consistently >200 mg/dl.

Study Assessments

The primary efficacy parameter was mean change from baseline in HbA_{1c} at Week 24. This endpoint was assessed initially in the overall study population. If the results for the overall study population were found to be significant, then subsequent analyses were performed to examine treatment effects within the two strata. Secondary efficacy endpoints included change from baseline in FPG and per cent change from baseline in plasma lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and non-HDL-C] at Week 24. Homeostasis model assessment-β cell function (HOMA-β) and the proinsulin/insulin ratio were calculated to assess β-cell function [18,19]. HOMA-insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated to assess changes in insulin resistance [18,20].

Change from baseline in HbA_{1c} was also evaluated among several pre-specified subgroups including baseline HbA_{1c} level (greater than, or less than or equal to median value; and by categories: <8%, $\geq$8% and <9%, $\geq$9%), prior OHA status (not taking OHA, taking OHA monotherapy or taking oral combination therapy), gender, race, age (greater than or lesser than or equal to median values at baseline), body mass index (BMI) greater than or lesser than or equal to median value at baseline), duration of diabetes (greater than or lesser than or equal to median baseline duration of diabetes), HOMA-IR (greater than or lesser than or equal to median value at baseline), HOMA-β (greater than or lesser than or equal to median value at baseline) and metabolic syndrome status as defined by National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) criteria.

Safety and tolerability were assessed by physical examinations, vital signs and 12-lead electrocardiograms (ECGs), and safety laboratory measurements comprising haematology (including complete blood count, differential and absolute neutrophil count), serum chemistry (including alanine aminotransferase, aspartate aminotransferase, total

bilirubin and alkaline phosphatase) and urinalysis. Adverse experiences (AEs) were monitored throughout the study, and the severity and relationship to study drug for any AE were determined by the investigator. AEs of special interest included hypoglycaemia and selected gastrointestinal-related AEs (abdominal pain, nausea, vomiting and diarrhoea).

All assays were performed by technicians blinded to treatment sequence at PPD Global Central Labs, LLC (Highland Heights, KY and Zaventem, Belgium). HbA_{1c} was determined by high-performance liquid chromatography (Tosoh A1C 2.2; Tosoh Medics, Foster City, CA, USA). Plasma glucose was determined with the hexokinase method (Roche Diagnostics, Basel, Switzerland). Serum insulin was determined by chemiluminescence (Elecsys 2010; Roche Diagnostics). Serum proinsulin was determined with an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). TG was measured by enzymatic determination of glycerol (Roche Diagnostics). After selective removal of apo B–containing lipoproteins by heparin and manganese chloride precipitation for HDL isolation, HDL-C and TC were quantified enzymatically (Roche Diagnostics). LDL-C was calculated using the Friedewald equation. Non-HDL-C was calculated by subtracting HDL-C from TC.

Statistical Analyses

The primary efficacy endpoint, the change from baseline in HbA_{1c} at Week 24, was analysed using an analysis of covariance (ANCOVA) model. Analyses were adjusted for baseline HbA_{1c} values and stratum (on metformin or not on metformin at Visit 3). Efficacy analyses were based on the all-patients-treated (APT) population that consisted of all randomized patients who received at least one dose of study drug and who had both baseline and at least one post-baseline efficacy measurement. Missing data were handled using the last-observation-carried-forward method. The differences between sitagliptin and placebo for HbA_{1c} and other efficacy endpoints were assessed by testing the difference in the least squares (LS) mean change (or per cent change) from baseline at Week 24. The entire cohort (with both strata combined) was analysed as the primary efficacy population; however, additional key analyses included the full range of primary and secondary efficacy endpoints in each stratum individually. The proportion of patients meeting HbA_{1c} goal of $<7.0\%$ at Week 24 was compared between treatment groups. An ANCOVA model similar to that described above was utilized to evaluate the consistency of the HbA_{1c}-lowering effect of sitagliptin relative to placebo across pre-defined subgroups (see Study Assessment section) by examining the between-group LS mean differences and 95% confidence intervals. For each subgroup factor, the ANCOVA model included terms for treatment, stratum, subgroup, treatment-by-subgroup interaction and baseline HbA_{1c}. For the subgroup factor of prior antihyperglycemia therapy status, the stratum was not included in the ANOVA model. No formal treatment-by-subgroup interaction testing was performed to evaluate the statistical significance of these findings. A time-to-glycaemic-rescue analysis was performed using the Kaplan–Meier estimator and the log-rank test. The proportion of patients who received glycaemic rescue therapy was compared between treatment groups. To avoid the confounding influence of rescue therapy on efficacy comparisons in this 24-week study, data were treated as missing after the initiation of pioglitazone rescue therapy in the efficacy analyses. 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; and to convert C-peptide values to nmol/l, multiply by 0.331. The same conversion factors can be utilized for the conversion of the area under curve (AUC) values of glucose, insulin and C-peptide.

Safety and tolerability analyses were performed in the all-patients-as-treated (APaT) population, which included randomized patients who received at least one dose of double-blind study medication. Safety parameters assessed included AEs, laboratory safety analytes, body weight, vital signs and ECGs. Safety analyses excluded data after initiating rescue therapy. Inferential testing was performed on the between-group differences for hypoglycaemia, selected gastrointestinal AEs and change in body weight.

Results

Patients

Of 1098 patients screened, a total of 441 patients (441/1098; 40%) were randomized, which consisted of Stratum 1 [glimepiride alone (n = 212/441; 48%)] and Stratum 2 [glimepiride plus metformin combination therapy (n = 229/441; 52%)] at entry into the run-in period (figure 1). A total of 657 patients (657/1098; 60%) were excluded from participating in the study, with 548 of these (548/657; 83%) not meeting protocol eligibility criteria and 57 (57/657; 9%) withdrawing consent. Of the 441 randomized patients, 222 received sitagliptin 100 mg once daily (n = 106 in Stratum 1 and n = 116 in Stratum 2) and 219 received placebo (n = 106 in

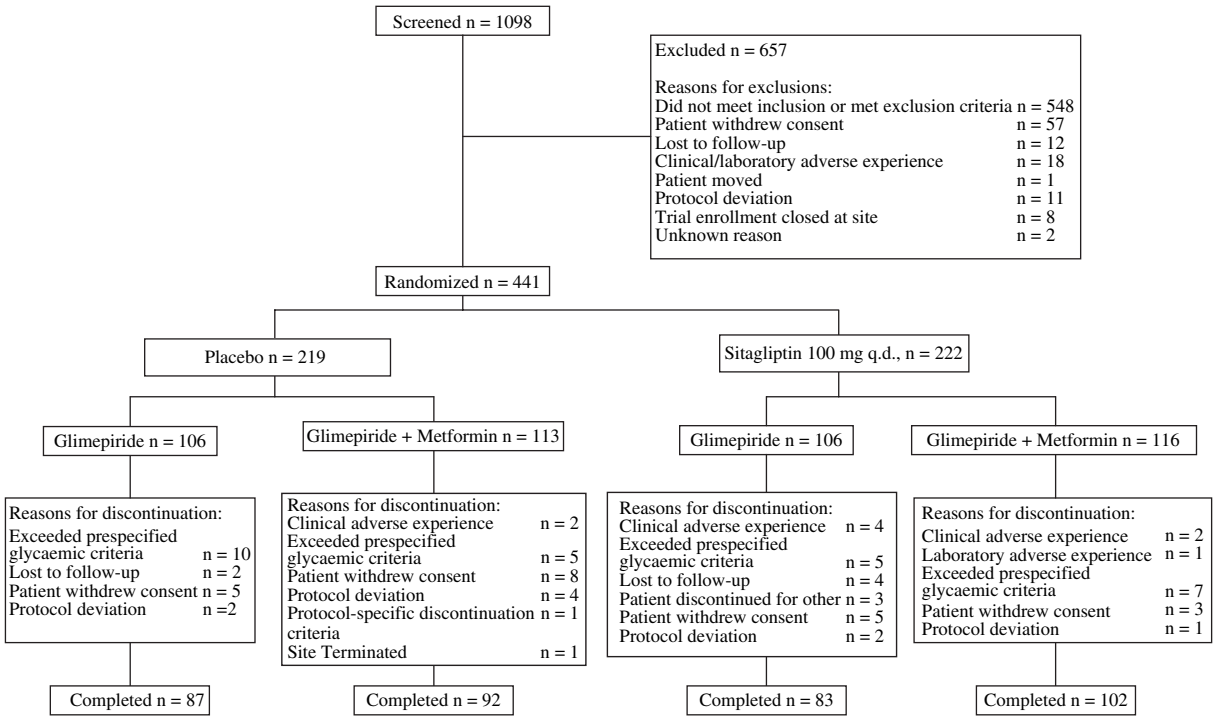

Fig. 1 Disposition of patients in the study.

Stratum 1 and n = 113 in Stratum 2). In total, 185 patients (185/222; 83%) in the sitagliptin arm and 179 patients (179/219; 82%) in the placebo arm completed the 24-week double-blind treatment period. A total of 425 patients (217 patients in the sitagliptin 100 mg group and 208 in the placebo group) with baseline and at least one valid on-treatment measurement comprised the APT population for the HbA_{1c} efficacy analysis (primary endpoint). All randomized patients were included in the APaT population for the safety and tolerability analyses.

There were no clinically meaningful differences in baseline demographic or anthropometric characteristics between treatment groups for the entire study population and across strata based on assigned OHA therapy (table 1). For the entire study population, the average duration of diabetes was 8.8 years, and the average baseline HbA_{1c} was 8.34%, with about 35% of patients having an HbA_{1c} <8%. The HbA_{1c} range at randomization was 6.7–10.6% (note: baseline HbA_{1c} values <7.5% were observed since inclusion criteria were assessed at Week -2). The average baseline FPG was 181.2 mg/dl. The baseline disease characteristics for the entire study population were similar between treatment groups. Patients on glimepiride plus metformin combination therapy (Stratum 2) had slightly lower HbA_{1c} values and longer duration of type 2 diabetes at baseline than patients on glimepiride alone (Stratum 1). Note that Stratum 2 included more patients on dual therapy, who typically have a longer mean duration of disease, because, per protocol, such patients were generally entered into Stratum 2 rather than Stratum 1 (table 1).

Efficacy

In the overall randomized cohort of patients (i.e. combined strata), treatment with sitagliptin 100 mg once daily significantly ($p < 0.001$) decreased HbA_{1c} from baseline relative to placebo, with a −0.74% (95% CI −0.90 to −0.57) between-treatment difference in LS mean change from baseline at Week 24 (table 2, figure 2 A). Sitagliptin also led to significant improvements in HbA_{1c} in each stratum. In patients receiving glimepiride alone (Stratum 1), sitagliptin led to a −0.57% (95% CI −0.82 to −0.32) placebo-subtracted reduction in HbA_{1c} at Week 24, while a placebo-subtracted decrease in HbA_{1c} of −0.89% (−1.10 to −0.68) was observed in patients on glimepiride plus metformin (table 2, figure 2B). Formal treatment by subgroup interaction testing was not performed in this study (see Patients and Methods); however, subgroups were assessed for consistency of the response in HbA_{1c} lowering. For the overall study population and in the two strata, the magnitudes of the placebo-subtracted HbA_{1c} reduction with sitagliptin

Table 1 Baseline demographics and characteristics of randomized patients

	Sitagliptin 100 mg q.d.			**Placebo**		
Characteristic	**Entire cohort (n = 222)**	**Glimepiride (n = 106)**	**Glimepiride + metformin (n = 116)**	**Entire cohort (n = 219)**	**Glimepiride (n = 106)**	**Glimepiride + metformin (n = 113)**
Age, mean ± s.d. (years)	55.6 ± 9.6	54.4 ± 10.3	56.6 ± 8.8	56.5 ± 9.6	55.2 ± 10.2	57.7 ± 8.9
Age, range (years)	32–73	32–72	33–73	28–75	28–75	33–75
Sex, n (%)						
Male	117 (52.7)	56 (52.8)	61 (52.6)	117 (53.4)	58 (54.7)	59 (52.2)
Female	105 (47.3)	50 (47.2)	55 (47.4)	102 (46.6)	48 (45.3)	54 (47.8)
Race, n (%)						
Caucasian	136 (61.3)	61 (57.5)	75 (64.7)	140 (63.9)	59 (55.7)	81 (71.7)
Black	10 (4.5)	7 (6.6)	3 (2.6)	12 (5.5)	3 (2.8)	9 (8.0)
Hispanic	39 (17.6)	26 (24.5)	13 (11.2)	32 (14.6)	25 (23.6)	7 (6.2)
Asian	22 (9.9)	6 (5.7)	16 (13.8)	25 (11.4)	12 (11.3)	13 (11.5)
Other	15 (6.8)	6 (5.7)	9 (7.8)	10 (4.6)	7 (6.6)	3 (2.7)
Body weight, kg	86.5 ± 21.1	85.8 ± 22.5	87.2 ± 19.7	85.9 ± 21.8	85.1 ± 22.6	86.7 ± 21.1
Body mass index, kg/m^2	31.2 ± 6.3	31.0 ± 6.7	31.3 ± 5.9	30.7 ± 6.3	30.7 ± 6.4	30.7 ± 6.2
Duration of diabetes mellitus, years	8.3 ± 5.5	7.2 ± 5.0	9.3 ± 5.7	9.3 ± 6.8	8.0 ± 6.5	10.6 ± 6.8
Use of OHA at screening, n (%)						
Combination therapy	140 (63.1)	29 (27.4)	111 (95.7)	136 (62.1)	29 (27.4)	107 (94.7)
Monotherapy	71 (32.0)	66 (62.3)	5 (4.3)	72 (32.9)	69 (65.1)	3 (2.7)
Absence	11 (5.0)	11 (10.4)	0	11 (5.0)	8 (7.5)	3 (2.7)
HbA_{1c}, % (range)	8.34 ± 0.76 (6.70–10.50)	8.42 ± 0.79 (7.00–10.30)	8.27 ± 0.73 (6.70–10.50)	8.34 ± 0.74 (6.90–10.60)	8.43 ± 0.80 (6.90–10.40)	8.26 ± 0.68 (7.20–10.60)
HbA_{1c} distribution at baseline, n (%)						
HbA_{1c} <8%	81 (36.5)	36 (34.0)	45 (38.8)	73 (33.8)	34 (32.1)	39 (35.5)
HbA_{1c} ≥8% and <9%	95 (42.8)	44 (41.5)	51 (44.0)	101 (46.8)	45 (42.5)	56 (50.9)
HbA_{1c} ≥9%	46 (20.7)	26 (24.5)	20 (17.2)	42 (19.4)	27 (25.5)	15 (13.6)
Fasting plasma glucose, mg/dl	180.9 ± 37.7	182.6 ± 33.1	179.4 ± 41.6	181.6 ± 42.5	184.9 ± 42.3	178.4 ± 42.6
Post-prandial glucose, mg/dl	267.0 ± 58.4	279.6 ± 60.8	251.7 ± 52.2	271.1 ± 62.6	289.3 ± 65.4	257.4 ± 57.5
Fasting insulin, μIU/ml	14.5 ± 13.2	16.2 ± 16.0	12.9 ± 9.7	12.3 ± 9.7	13.1 ± 11.1	11.6 ± 8.1

HbA_{1c}, glycosylated haemoglobin; OHA, oral antihyperglycaemic agent; s.d., standard deviation.
Data are expressed as mean ± s.d. or frequency [n (%)], unless otherwise indicated.

were generally consistent across the pre-specified subgroups defined by demographic (e.g. age, gender, race/ethnic group, duration of diabetes) and anthropometric characteristics (e.g. BMI) (data not shown). In the entire cohort, moderately greater placebo-subtracted HbA_{1c} reductions from baseline were observed with progressively higher baseline HbA_{1c} values (i.e. patients with HbA_{1c} <8%, ≥8% to <9% and ≥9%). This pattern appeared to be driven entirely by the progressively greater change by baseline in HbA_{1c} that occurred in Stratum 2 [HbA_{1c} reductions of −0.55% (95% CI: −0.91 to −0.20), −0.97% (90% CI: −1.27 to −0.66) and −1.34% (95% CI: −1.88 to −0.80) in patients with baseline HbA_{1c} <8%, ≥8% to <9% and ≥9% respectively], with essentially no differences in change from baseline by baseline HbA_{1c} observed in Stratum 1.

Treatment with sitagliptin 100 mg once daily significantly increased the proportion of patients attaining an HbA_{1c} of <7.0% compared with placebo for the overall study population [17.1% (37/217) vs. 4.8% (10/208) respectively; $p < 0.001$]. For patients on glimepiride plus metformin (Stratum 2), 22.6% (26/115) of patients in the sitagliptin group attained an HbA_{1c} of <7.0% compared with 1.0% (1/105) of patients in the placebo group ($p < 0.001$). In patients receiving glimepiride alone (Stratum 1), there was no significant between-group difference in the proportion of patients reaching HbA_{1c} levels <7.0% [10.8% (11/102) for sitagliptin compared with 8.7% (9/103) for placebo; $p = 0.638$].

After 24 weeks of treatment, the addition of sitagliptin led to a significant ($p < 0.001$) reduction from baseline in FPG relative to placebo (table 2) for the overall study population as well as in each stratum. For the overall study population, the between-treatment difference in LS mean change from baseline (95% CI) in FPG was −20.1 mg/dl (−28.4 to −11.8). The between-treatment differences in LS mean change from baseline (95% CI) in FPG at Week 24 were −19.3 mg/dl (−31.9 to −6.7) for patients on glimepiride alone (Stratum 1) and −20.7 mg/dl

Table 2 LS mean change from baseline to Week 24 in glycaemic and meal tolerance test endpoints for the entire study population (entire cohort) and subset of patients receiving glimepiride alone (Stratum 1) or glimepiride in combination with metformin therapy (Stratum 2).

	Entire cohort			Subset of patients on glimepiride monotherapy (Stratum 1)			Subset of patients on glimepiride + metformin (Stratum 2)		
	LS mean change from baseline (95% CI)			LS mean change from baseline (95% CI)			LS mean change from baseline (95% CI)		
Efficacy parameter	Sitagliptin n = 217–219*	Placebo n = 208–213†	Difference in LS means (95% CI)	Sitagliptin n = 102–104*	Placebo n = 103–104†	Difference in LS means (95% CI)	Sitagliptin n = 115*	Placebo n = 105–109†	Difference in LS means (95% CI)
HbA_{1c}, %	−0.45 (−0.57 to −0.34)‡	0.28 (0.17 to 0.40)‡	−0.74 (−0.90 to −0.57)§	−0.30 (−0.48 to −0.12)‡	0.27 (0.09 to 0.45)‖	−0.57 (−0.82 to −0.32)§	−0.59 (−0.74 to −0.44)‡	0.30 (0.14 to 0.45)‡	−0.89 (−1.10 to −0.68)§
Fasting plasma glucose, mg/dl	−4.4 (−10.2 to 1.4)	15.7 (9.8 to 21.6)‡	−20.1 (−28.4 to −11.8)§	−0.88 (−9.8 to 8.0)	18.4 (9.5 to 27.3)‡	−19.3 (−31.9 to −6.7)¶	−7.8 (−15.5 to −0.2)‖	12.9 (5.0 to 20.8)‡	−20.7 (−31.7 to −9.7)§
2-h post-meal glucose, mmol/l	−22.7 (−35.5 to −9.9)‡	13.5 (0.3 to 26.7)‖	−36.1 (−54.6 to −17.7)§	−24.4 (−42.3 to −6.4)‖	10.7 (−10.2 to 31.6)	−35.1 (−62.6 to −7.5)¶	−21.3 (−40.1 to −2.5)‖	15.8 (−1.4 to 33.1)	−37.1 (−62.7 to −11.6)¶

CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; LS, least squares.
*For 2-h post-meal glucose, n = 69 for entire cohort, n = 38 for subset of patients on glimepiride and 31 for subset of patients on glimepiride + metformin.
†For 2-h post-meal glucose, n = 65 for entire cohort, n = 28 for subset of patients on glimepiride and 37 for subset of patients on glimepiride + metformin.
‡$p < 0.001$ for the within-treatment difference.
§$p < 0.001$ for the between-treatment difference.
‖$p < 0.050$ for the within-treatment difference.
¶$p < 0.050$ for the between-treatment difference.

(−31.7 to −9.7) for those on glimepiride plus metformin (Stratum 2).

Treatment with sitagliptin 100 mg once daily led to significant ($p = 0.020$) increases in fasting insulin and in HOMA-β at Week 24 for the overall study population (table 3). No statistically significant between-treatment differences were detected for fasting proinsulin, proinsulin/insulin ratio, fasting C-peptide, HOMA-IR or QUICKI (data not shown). Sitagliptin had neutral effects on plasma lipids relative to placebo (data not shown).

The baseline demographic, anthropometric and disease characteristics for the cohort of patients (n = 184) who participated in a nine-point meal tolerance test were generally similar to the overall study population (data not shown). Treatment with sitagliptin 100 mg led to significant ($p \leq 0.001$) reductions in 2-h post-prandial glucose (PPG) (36.1 mg/dl placebo-subtracted reduction) compared with placebo for the overall study population; a similar effect on PPG was observed in the two strata (table 2). For the entire study cohort, treatment with sitagliptin also significantly improved 2-h post-meal glucose AUC ($p < 0.001$), 2-h post-meal insulin AUC ($p = 0.007$), 2-h post-meal C-peptide AUC ($p < 0.001$), C-peptide total AUC ($p = 0.005$), glucose total AUC ($p < 0.001$) and insulin/glucose total AUC ratio ($p = 0.013$) relative to placebo (table 3).

Twice as many patients in the placebo group required rescue glycaemic therapy during the 24-week study compared with those in the sitagliptin group [24.7% (54/219) vs. 11.3% (25/222), respectively]. Time to initiation of rescue therapy, as assessed by Kaplan–Meier time-to-event analysis, was significantly ($p < 0.001$) later in the sitagliptin group compared with the placebo group.

Safety and Tolerability

The addition of sitagliptin 100 mg to ongoing therapy with glimepiride alone or in combination with metformin was generally well tolerated. In the entire cohort, prior to the initiation of glycaemic rescue therapy, the overall incidences of clinical AEs [132 (59.5%) vs. 103 (47.0%); between-treatment difference = 12.4% (95% CI: 3.1–21.4)] and drug-related clinical AEs [12 (14.9%) vs. 15 (6.8%); between-treatment difference = 8.0% (95% CI: 2.2–13.9)] were higher in the sitagliptin group as compared with the placebo group (table 4). The higher incidence of overall AEs observed in the sitagliptin group was accounted for by a higher incidence of the AE of hypoglycaemia (see table 4) and small differences in other AEs. The between-group difference

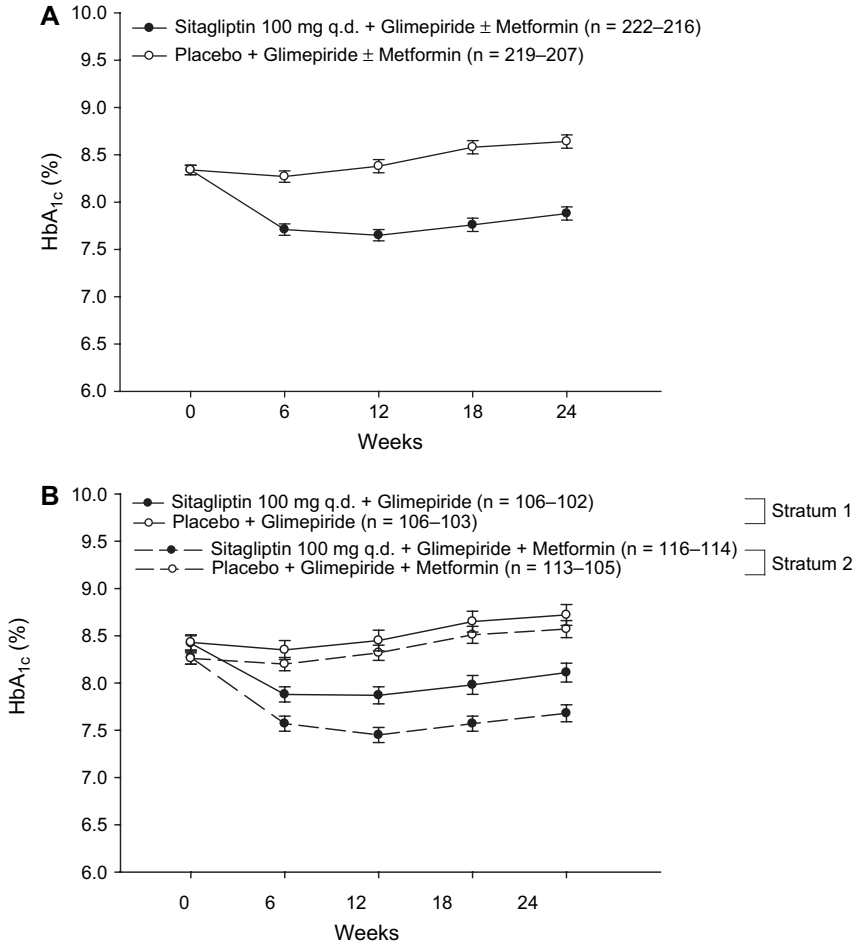

Fig. 2 Mean (SE) HbA_{1c} over time for sitagliptin 100 mg once daily vs. placebo in the entire study cohort (A) and in the subset of patients taking glimepiride monotherapy (Stratum 1) or glimepiride plus metformin combination therapy (Stratum 2) (B). HbA_{1c}, glycosylated haemoglobin.

observed in drug-related AEs was a result of the difference in hypoglycaemia AEs. No meaningful differences were observed between the two groups in the incidence of serious AEs, AEs leading to discontinuation (as a result of non-serious or serious AEs) or other summary measures of clinical AEs. One patient in the sitagliptin group (in Stratum 2) with a medical history of chronic obstructive pulmonary disease, interstitial lung disease, obesity and chronic smoking died from interstitial lung disease during the course of this study. The investigator deemed this serious adverse event to be definitely not related to study medication.

An analysis of safety results by stratum showed generally similar findings to that observed for the overall study population, with a slightly greater difference in the incidence of overall clinical AEs seen in Stratum 1 patients [15.1% (95% CI: 1.7–27.8) between-group difference] than in Stratum 2 patients [between-group difference 9.8% (95% CI: −2.9 to 22.1)]. Additionally, a higher incidence of drug-related AEs was observed with sitagliptin treatment relative to placebo in the subset of patients on glimepiride plus metformin (Stratum 2) [21 (18.1%) vs. 8 (7.1%); between-treatment difference = 11.0% (95% CI: 2.4–19.7)] but not in patients receiving glimepiride alone (Stratum 1) [12 (11.3%) vs. 7 (6.6%); between-treatment difference = 4.7% (95% CI: −3.2 to 12.9)]. Similar to what was seen for the entire cohort, the increased incidence of overall and drug-related clinical AEs with sitagliptin treatment in Stratum 2 was related to the increased incidence of hypoglycaemia adverse events and small differences in other AEs (see table 4). There were no clinically meaningful differences in incidence of serious

Table 3 LS mean change from baseline to Week 24 in glycaemic and meal tolerance test endpoints for the entire study cohort

	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)
Glycaemic parameters					
Fasting serum insulin, μIU/ml					
Sitagliptin + G ± M	188	14.8 (13.8)	16.2 (12.9)	1.8 (0.8 to 2.9)*	1.8 (0.2 to 3.4)†
Placebo + G ± M	162	12.4 (10.4)	12.9 (9.1)	0.1 (−1.1 to 1.2)	
HOMA-β (%)					
Sitagliptin + G ± M	186	50.7 (47.8)	61.4 (57.3)	11.3 (4.4 to 18.1)*	12.0 (1.8 to 22.1)†
Placebo + G ± M	156	47.4 (47.7)	47.4 (55.2)	−0.7 (−8.2 to 6.8)	
Proinsulin/insulin ratio					
Sitagliptin + G ± M	180	0.517 (0.363)	0.452 (0.271)	−0.057 (−0.091 to −0.022)‡	−0.028 (−0.080 to 0.025)
Placebo + G ± M	144	0.491 (0.286)	0.473 (0.269)	−0.029 (−0.068 to 0.010)	
Meal tolerance test parameters					
2-hr post-meal insulin, μIU/ml					
Sitagliptin + G ± M	63	55.6 (46.7)	65.7 (53.5)	10.6 (3.4 to 17.9)‡	14.4 (3.9 to 24.9)†
Placebo + G ± M	59	46.3 (27.1)	43.3 (32.1)	−3.8 (−11.3 to 3.7)	
2-hr post-meal C-peptide, ng/ml					
Sitagliptin + G ± M	70	7.1 (3.2)	7.6 (2.7)	0.6 (0.2 to 0.9)*	1.1 (0.6 to 1.6)§
Placebo + G ± M	65	6.5 (2.9)	6.1 (2.5)	−0.5 (−0.9 to −0.2)‡	
Glucose total AUC, mg × h/dl					
Sitagliptin + G ± M	67	497.1 (84.1)	465.1 (95.6)	−33.4 (−54.5 to −12.2)‡	−61.2 (−91.5 to −30.8)§
Placebo + G ± M	64	499.9 (97.9)	526.3 (103.8)	27.8 (6.2 to 49.4)‡	
Insulin total AUC, μIU × h/ml					
Sitagliptin + G ± M	51	92.8 (68.6)	98.9 (73.7)	6.5 (−3.1 to 16.2)	7.6 (−6.3 to 21.4)
Placebo + G ± M	50	69.4 (39.0)	68.8 (50.9)	−1.0 (−10.8 to 8.7)	
C-peptide total AUC, ng × h/ml					
Sitagliptin + G ± M	68	10.9 (4.7)	11.5 (4.6)	0.7 (0.2 to 1.1)‡	1.0 (0.3 to 1.7)†
Placebo + G ± M	65	9.7 (3.9)	9.5 (3.5)	−0.4 (−0.9 to 0.1)	
Insulin total AUC/glucose total AUC ratio					
Sitagliptin + G ± M	47	0.200 (0.150)	0.226 (0.164)	0.029 (0.003 to 0.054)‡	0.045 (0.010 to 0.081)†
Placebo + G ± M	48	0.151 (0.103)	0.137 (0.114)	−0.017 (−0.041 to 0.008)	

LS, least squares; s.d., standard deviation; CI, confidence interval; G, glimepiride; M, metformin; HOMA–β, homeostasis model assessment–β; AUC, area under curve.

*$p < 0.001$ for the within-treatment difference.

†$p < 0.050$ for the between-treatment difference.

‡$p < 0.050$ for the within-treatment difference.

§$p < 0.001$ for the between-treatment difference.

AEs, AEs leading to discontinuation and other summary measures of clinical AEs between the sitagliptin and placebo groups within each stratum. There also were no statistically significant differences between the treatment groups, or within each stratum, in the incidence of pre-specified gastrointestinal adverse events (abdominal pain, nausea, vomiting and diarrhoea) (table 4).

In the entire study cohort, 31 patients reported AEs of hypoglycaemia [27 (12.2%) in the sitagliptin group vs. 4 (1.8%) in the placebo group; between-group difference (95% CI) = 10.3 (5.7–15.4); $p < 0.001$] (table 4). None of the reported hypoglycaemia episodes was considered by the study investigator to be severe or required medical attention, and the majority of the episodes (55/75 episodes; 73%) had precipitating factors, such as skipped meals or increased physical activity. A higher incidence of hypoglycaemia was seen when sitagliptin was added to patients in Stratum 2 than in Stratum 1: in Stratum 2, 19 patients (16.4%) and 1 patient (0.9%) had hypoglycaemia episodes reported in the sitagliptin 100 mg q.d. and placebo groups, respectively ($p < 0.001$). In Stratum 1, 8 (7.5%) and 3 (2.8%) patients had hypoglycaemia episodes reported in the sitagliptin 100 mg q.d. and placebo groups, respectively ($p = 0.214$).

In the entire study cohort, there was a low, generally similar incidence of specific laboratory AEs in the sitagliptin and placebo groups. Laboratory AEs in patients who had at least one laboratory test performed post-baseline were reported by 13 of 220 (5.9%) patients in the sitagliptin group and 9 of 217 (4.1%) patients in the placebo group. Drug-related laboratory AEs were reported in one patient in the sitagliptin group and four patients in

Table 4 Summary of clinical AEs*

	Sitagliptin 100 mg q.d.			Placebo		
n (%)	Entire cohort (n = 222)	Glimepiride (n = 106)	Glimepiride + metformin (n = 116)	Entire cohort (n = 219)	Glimepiride (n = 106)	Glimepiride + metformin (n = 113)
One or more AEs	132 (59.5)	59 (55.7)	73 (62.9)	103 (47.0)	43 (40.6)	60 (53.1)
Drug-related AEs†	33 (14.9)	12 (11.3)	21 (18.1)	15 (6.8)	7 (6.6)	8 (7.1)
Serious AEs (SAEs)	12 (5.4)	5 (4.7)	7 (6.0)	8 (3.7)	6 (5.7)	2 (1.8)
Drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.5)‡	0 (0.0)	1 (0.9)‡	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations because of AEs	5 (2.3)	3 (2.8)	2 (1.7)	3 (1.4)	1 (0.9)	2 (1.8)
Discontinuations because of drug-related AEs†	1 (0.5)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.9)
Discontinuations because of SAEs	3 (1.4)	2 (1.9)	1 (0.9)	1 (0.5)	1 (0.9)	0 (0.0)
Discontinuations because of drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical AEs of special interest						
Hypoglycaemia	27 (12.2)	8 (7.5)	19 (16.4)	4 (1.8)	3 (2.8)	1 (0.9)
Overall gastrointestinal AEs	11 (5.0)	6 (5.7)	5 (4.3)	10 (4.6)	2 (1.9)	8 (7.1)
Selected gastrointestinal AEs						
Abdominal pain	5 (2.3)	3 (2.8)	2 (1.7)	2 (0.9)	0 (0.0)	2 (1.8)
Diarrhoea	3 (1.4)	2 (1.9)	1 (0.9)	6 (2.7)	2 (1.9)	4 (3.5)
Nausea	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.5)	0 (0.0)	1 (0.9)
Vomiting	3 (1.4)	1 (0.9)	2 (1.7)	1 (0.5)	0 (0.0)	1 (0.9)

AE, adverse experience.

*Excludes AEs after initiating glycaemic rescue therapy (pioglitazone).

†Considered by the investigator as possibly, probably or definitely related to study drug.

‡One patient receiving triple-combination therapy died from interstitial lung disease during the course of the study.

the placebo group. The sitagliptin-treated patient had a slight creatine phosphokinase (CK) elevation from a baseline level of 127 mU/ml (normal <120 mU/ml) to 200 mU/ml at Day 62 and was subsequently discontinued from the study because of meeting protocol-specified discontinuation criteria. This patient's final CK measurement returned to baseline levels while still on treatment.

Minimal between-treatment differences were observed in mean concentrations of safety laboratory tests in the entire study cohort and across treatment strata. Small mean changes over time were observed for alkaline phosphatase (−2.1 vs. 0.9 IU/l respectively) and bilirubin (−0.011 vs. 0.014 mg/dl respectively) between the sitagliptin and placebo groups. The time courses of mean change from baseline for alkaline phosphatase and bilirubin were similar, with both analytes reaching maximal reductions at the first post-randomization visit (Week 6) and remaining stable through Week 24. There were no meaningful differences between the groups with regard to mean changes from baseline in liver transaminase levels or in the incidence of episodes of elevations in liver transaminases. Small increases in mean changes from baseline in white blood cell count (357.7 vs. 63.9 cells/μl) and absolute neutrophil count (354.1 vs. 73.0 cells/μl) were observed in patients treated with sitagliptin compared with placebo respectively. No notable changes in other serum chemistry and haematology analyses were observed during the course of this study.

After 24 weeks, sitagliptin 100 mg led to a modest increase in mean body weight from baseline [LS mean change from baseline = 0.8 kg (95% CI: 0.4–1.2)] compared with a slight decrease in the placebo group (LS mean change from baseline = −0.4 kg (95% CI: −0.8 to 0.1)]. This resulted in a placebo-adjusted body weight gain of 1.1 kg (95% CI: 0.5–1.7) for the entire study population at Week 24. Similar changes in body weight with sitagliptin treatment relative to placebo were observed within each stratum. In Stratum 1, sitagliptin 100 mg also led to a significant increase in mean body weight [LS mean change from baseline = 1.1 kg (95% CI: 0.5–1.8)] compared with no change in placebo group [LS mean change from baseline = 0.0 kg (95% CI: −0.6 to 0.7)]. In Stratum 2, a small numerical increase in mean body weight [LS mean change from baseline = 0.4 kg (95%

CI: −0.1 to 0.9)] was observed with sitagliptin compared with a significant decrease in the placebo group [LS mean change from baseline = −0.7 kg (95% CI: −1.4 to −0.1)]. In both strata, a significant placebo-adjusted body weight gain of 1.1 kg was observed at Week 24.

Discussion

The efficacy and safety of sitagliptin 100 mg once daily were assessed in this 24-week, placebo-controlled randomized study in patients with type 2 diabetes with inadequate glycaemic control on glimepiride, either alone or in combination with metformin. Because this study was designed to evaluate the efficacy and safety of the addition of sitagliptin compared with placebo for the entire study cohort and within each stratum, no formal comparisons between the two strata were performed. For the entire patient cohort, sitagliptin provided substantial, statistically significant improvements in HbA_{1c} at Week 24 relative to placebo. For patients in each stratum, the addition of sitagliptin provided meaningful HbA_{1c}-lowering efficacy, with numerically greater reductions observed in patients on glimepiride and metformin (Stratum 2) relative to patients on glimepiride alone. The efficacy of sitagliptin was generally consistent across subgroups defined by demographic, anthropometric or disease characteristics. In addition to substantial HbA_{1c}-lowering efficacy, treatment with sitagliptin led to significant and clinically important improvements in FPG and 2-h PPG in the entire cohort and in each stratum. Sitagliptin treatment also led to an increase in a marker of fasting insulin secretion (i.e. HOMA-β).

Overall, more patients treated with sitagliptin achieved the American Diabetes Association recommended HbA_{1c} goal of <7.0% [21] at 24 weeks compared with patients treated with placebo, with the effect observed in Stratum 2 (patients on glimepiride and metformin), consistent with the numerically greater HbA_{1c}-lowering observed in this stratum.

As noted above, the addition of sitagliptin to the combination of glimepiride and metformin provided numerically greater improvement in HbA_{1c} than the addition of sitagliptin to glimepiride alone. In a recent study, both metformin and sitagliptin increased active GLP-1 levels in healthy volunteers – metformin likely operated through increased GLP-1 release and sitagliptin by inhibiting degradation – and the combination provided at least additive effects on intact GLP-1 (unpublished data; submitted for presentation). This complementary effect of sitagliptin and metformin on increasing intact GLP-1 levels could provide a basis for explaining the enhanced efficacy observed in the present study when sitagliptin was added to a background of glimepiride and metformin (Stratum 2) relative to when sitagliptin was added to glimepiride alone (Stratum 1).

Sitagliptin was generally well tolerated in the entire patient cohort and in each stratum. The higher percentages of patients in the sitagliptin 100 mg group compared with patients in the placebo group who had one or more clinical AEs and drug-related clinical AEs appeared to be related, at least in part, to a higher incidence of hypoglycaemia (see below). A modest but statistically significant body weight increase was observed with sitagliptin treatment in the entire patient cohort and in each treatment stratum, consistent with glycaemic improvement greater than placebo, and treatment with a sulphonylurea in this study. In previous clinical trials of add-on combination use (including add-on to metformin use and add-on to a PPARγ agent use), sitagliptin had a neutral effect on body weight [13,14]. The different effect of sitagliptin on body weight observed in this add-on combination use study compared to these previous studies may be attributable to the present study using background treatment with the sulphonylurea agent, glimepiride.

When added to glimepiride alone or glimepiride in combination with metformin, sitagliptin was associated with a higher incidence of hypoglycaemia, although none of the episodes was considered to be severe by the investigators and most were associated with precipitating factors, such as skipped meals or increased physical activity. Of note, the incidence of hypoglycaemia observed in this study is consistent with that observed with other antihyperglycaemic agents that are themselves not associated with hypoglycaemia (e.g. metformin, exenatide, thiazolidinediones) but do result in increased hypoglycaemia when added to ongoing therapy with a sulphonylurea agent [22,23]. Prior studies have shown that sitagliptin is associated with an incidence of hypoglycaemia that is similar to placebo when used in monotherapy or in combination therapy with other agents (i.e. metformin, PPARγ agonists) [9,12–14]. Hence, the incidence of hypoglycaemia observed in the current study is consistent with observations in other studies using similar treatment regimens.

In summary, this study showed that treatment with sitagliptin 100 mg once daily led to clinically meaningful reductions in HbA_{1c}, fasting glucose and PPG in dual combination with glimepiride alone and in triple combination with glimepiride plus metformin over a 24-week period. Overall, treatment with sitagliptin was well tolerated with a modest increase in weight, consistent with the achieved degree of glycaemic improvement. The higher incidence of hypoglycaemia events seen with sitagliptin in this study was similar to that

previously reported in other studies of sulphonylurea-containing dual and triple OHA combination therapies.

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References

1 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; **281:** 2005–2012.

2 Doar JW, Thompson ME, Wilde CE, Sewell PF. Diet and oral antidiabetic drugs and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. Br Med J 1976; **1:** 498–500.

3 Hundal RS, Krssak M, Dufour S *et al*. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; **49:** 2063–2069.

4 Inzucchi SE, Maggs DG, Spollett GR *et al*. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 1998; **338:** 867–872.

5 Product Information. JANUVIA (sitagliptin). Whitehouse Station: Merck & Co., Inc.October 2006.

6 Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes 1998; **47:** 1663–1670.

7 Deacon CF, Ahren B, Holst JJ. Inhibitors of dipeptidyl peptidase IV: a novel approach for the prevention and treatment of Type 2 diabetes? Expert Opin Investig Drugs 2004; **13:** 1091–1102.

8 Herman GA, Stevens C, Van Dyck K *et al*. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther 2005; **78:** 675–688.

9 Bergman AJ, Stevens C, Zhou Y *et al*. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. Clin Ther 2006; **28:** 55–72.

10 Herman GA, Bergman A, Stevens C *et al*. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. J Clin Endocrinol Metab 2006; **91:** 4612–4619.

11 Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006; **29:** 2632–2637.

12 Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia 2006; **49:** 2564–2571.

13 Rosenstock J, Brazg R, Andryuk P, Lu K, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-Blind, placebo-controlled parallel group study. Clin Ther 2006; **28:** 1556–1568.

14 Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled on metformin alone. Diabetes Care 2006; **29:** 2638–2643.

15 Idris I, Donnelly R. Dipeptidyl peptidase-IV inhibitors: a major new class of oral antidiabetic drug. Diabetes Obes Metab 2007; **9:** 153–165.

16 Del Prato S, Pulizzi N. The place of sulfonylureas in the therapy for type 2 diabetes mellitus. Metabolism 2006; **55:** S20–S27.

17 Brazg R, Thomas K, Zhao PL, Xu L, Chen X, Stein PP. Effect of adding MK-0431 to on-going metformin therapy in type 2 diabetic patients who have inadequate glycemic control on metformin (abstract). Diabetes 2005; **54:** A3.

18 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; **28:** 412–419.

19 Tura A, Pacini G, Kautzky-Willer A, Ludvik B, Prager R, Thomaseth K. Basal and dynamic proinsulin-insulin relationship to assess beta-cell function during OGTT in metabolic disorders. Am J Physiol Endocrinol Metab 2003; **285:** E155–E162.

20 Katz A, Nambi SS, Mather K *et al*. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; **85:** 2402–2410.
21 Standards of medical care for patients with diabetes mellitus. Diabetes Care 2003; **26** (Suppl. 1)**:** S33–S50.
22 Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004; **27:** 2628–2635.
23 Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2005; **27:** 1535–1547.