Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes

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Introduction
Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for the treatment of type 2 diabetes (1,2). DPP-4 inhibitors prevent the degradation of gut-derived hormones known as incretins which are released into the circulation in response to a meal (3,4). The incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), account for the majority of the postprandial incretin response, and regulate blood glucose levels through several distinct mechanisms including enhancement of insulin release, suppression of glucagon release, suppression of appetite and reduced gastric emptying (5,6). Sitagliptin is an oral, potent and highly selective DPP-4 inhibitor for the treatment of type 2 diabetes (7). In prior studies in healthy subjects, sitagliptin provided sustained inhibition of DPP-4 over 24 h and was well tolerated without causing hypoglycaemia (8,9). Previously in patients with type 2 diabetes, single dose treatment with sitagliptin provided sustained DPP-4 inhibition over 24 h, increased active GLP-1 and GIP levels by two-fold at 2 and 24 h following administration, increased insulin and C-peptide levels, and reduced glucagon levels and glucose excursion after an oral glucose tolerance test (OGTT) (10).

The present study was performed to assess the dose–response to sitagliptin monotherapy on efficacy and tolerability over 12 weeks in patients with type 2 diabetes who had inadequate glycaemic control on diet and exercise. A glipizide treatment group was included to provide information in the same study population on the efficacy profile, risk of hypoglycaemia and changes in body weight with a sulfonylurea, a commonly used class of oral antihyperglycaemic agents (OHAs). Glipizide is a second-generation sulfonylurea that is generally well tolerated, with good

SUMMARY
The aim of this study was to assess the efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes who have inadequate glycaemic control on diet and exercise. In a randomised, double-blind, placebo- and active-controlled study, 743 patients with type 2 diabetes and a mean baseline HbA1c of 7.9% were randomised to receive one of six treatments for 12 weeks: placebo, sitagliptin 5, 12.5, 25 or 50 mg b.i.d., or glipizide 5 mg/day (electively titrated up to 20 mg/day). At week 12, treatment with sitagliptin at all doses tested led to a significant (p < 0.001) reduction in HbA1c relative to placebo, with the largest reductions occurring in the 50-mg b.i.d. group. The placebo-subtracted differences in HbA1c for the sitagliptin dose groups ranged from −0.38% to −0.77% in a dose-dependent manner, and −1.00% in the glipizide group. Sitagliptin also produced significant reductions in fasting plasma glucose and mean daily glucose across the dose range studied. Sitagliptin treatment was well tolerated and resulted in no significant weight change relative to placebo. There was a modest weight gain observed with glipizide treatment relative to placebo. Hypoglycaemia adverse experiences were reported with the highest incidence in the glipizide group (17%) compared with the placebo (2%) or sitagliptin groups (0–4%, not dose-dependent). In summary, in this study sitagliptin improved glycaemic control, with 50 mg b.i.d. being the most effective dose, and was generally well-tolerated in patients with type 2 diabetes.

What’s known
- Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for the treatment of type 2 diabetes.
- Sitagliptin is a DPP-4 inhibitor recently approved by the US FDA.
- There is limited long-term clinical data published for sitagliptin in patients with type 2 diabetes.

What’s new
- These data represent some of the first clinical efficacy and safety results with sitagliptin over an extended (12 weeks) period.

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efficacy in lowering glucose and a risk of hypoglycaemia that is similar to that of other sulfonylurea agents (11). The present study was not designed as a non-inferiority trial, and thus glipizide served as a benchmark therapy rather than as a direct comparator agent.

Methods

Patients
Male and female patients 21–75 years of age with type 2 diabetes, either currently on OHA monotherapy (except thiazolidinediones) with HbA1c ≥6% and ≤9% or not currently on an OHA with HbA1c ≥6.5% and <10%, were eligible to participate if they met screening criteria. Patients with type 1 diabetes, unstable cardiac disease, active liver or gallbladder disease, creatinine clearance <60 ml/min, or elevated (>2-fold the upper limit of normal) alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine phosphokinase (CK) were excluded.

Patients provided written informed consent. The protocol was reviewed and approved by the appropriate committees and authorities at each study site and performed in accordance with the Declaration of Helsinki.

Study design
This was a multinational, double-blind, randomised, placebo- and active-controlled, parallel-group, dose-range finding study (Sitagliptin Protocol #010). At screening, patients not on an OHA with an HbA1c ≥6.5% to <10% entered a diet and exercise period of 2–6 weeks. Patients on OHA monotherapy with HbA1c ≥6% to ≤9% had their OHA discontinued and entered a diet and exercise period of 6 weeks. If HbA1c was ≥6.5 and <10% and fasting plasma glucose (FPG) was ≥7.22 mmol/l (130 mg/dl) and ≤13.32 mmol/l (240 mg/dl) after the diet and exercise run-in period, patients were eligible to be randomised after completing a 2-week single-blind placebo run-in period. Patients were randomised based on a computer-generated random allocation schedule to one of six treatment groups: placebo, sitagliptin 5, 12.5, 25 or 50 mg b.i.d., or glipizide 5 mg (titrated based upon protocol-specified criteria, as described below, up to 20 mg) for 12 weeks. To ensure balance across treatment arms, two stratification variables were used in the randomisation process: (i) OHA status at screening (on or not on an OHA) and (ii) HbA1c ≤8.5% or >8.5% prior to randomisation (at entry to the placebo run-in period). Patients were instructed to take their study medication (sitagliptin or matching placebo and glipizide or matching placebo) twice daily, prior to the morning and evening meals. Patients received counselling on diet and exercise consistent with ADA recommendations at study entry and throughout the study.

Following randomisation, in a 5-day window prior to each study visit, patients were asked to collect 7-point home-glucose measurements (pre-meal, 2 h postmeal and at bedtime) in order to calculate mean daily glucose (MDG), which was used to determine whether the glipizide dose was to be up-titrated. At 2-week intervals over the first 6 weeks of treatment, glipizide was up-titrated by 5 mg/day if all the following criteria were met: MDG was >8.88 mmol/l (160 mg/dl), all fingerstick glucose values from the week prior to a study site visit were >5.55 mmol/l (100 mg/dl) and there were no episodes of hypoglycaemia prior to the visit. If patients experienced unexplained hypoglycaemia at any time during the study, glipizide was down-titrated to 5 mg/day and held there for the remainder of the study. If patients continue to experience hypoglycaemic episodes following down-titration to glipizide 5 mg/day, they were discontinued from the study.

After an overnight fast, blood was collected for the assessment of HbA1c, FPG, insulin and lipid parameters [including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and free fatty acids (FFA)] at baseline and at various time points during the study. MDG as described above was also an end point. Homeostasis model assessment-β cell function (HOMA-β) was determined to estimate β-cell function (12) and HOMA-insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated to assess changes in insulin resistance (12,13).

In a subset of patients, a standard meal tolerance test (MTT) was administered at baseline (prior to the first dose of study medication) and at week 12. Patients took study medication 30 min prior to the standard meal, which was ingested within 15 min and consisted of two nutrition bars and one nutrition drink (~680 kcal; 111 g carbohydrate, 14 g fat, 26 g protein). Plasma glucose, insulin and C-peptide concentrations were measured at 0, 60 and 120 min from the meal start for determination of 2-h postprandial glucose (PPG), area under the glucose concentration–time curve (AUC), insulin AUC and C-peptide AUC.

Study end points

Efficacy
These following end points were examined for change or percent change from baseline at week 12:
HbA1c, FPG, MDG, MTT-related variables including 2-h PPG and glucose AUC, lipid parameters, HOMA-β, HOMA-IR and QUICKI.

**Safety assessments**

Safety and tolerability were assessed by study site investigators throughout the study, with review of data on adverse experiences, physical examinations, vital signs, electrocardiograms (ECGs) and body weight. All adverse experiences were rated by investigators for intensity and relationship to study drug. Laboratory evaluations included blood chemistry, haematology and urinalysis. Adverse experiences of special interest included hypoglycaemia and gastrointestinal-related symptoms. Hypoglycaemia was assessed by study site investigators through reviewing daily glucose logs and patient self-report of signs and symptoms of hypoglycaemia. Body weight was measured throughout the study.

Laboratory measurements and ECGs were performed at central laboratories (PPD Global Central Labs, LLC, Highland Heights, KY and Zaventem, Belgium and Covance Central Diagnostics, Inc., Reno, NV respectively) by technicians blinded to treatment group.

**Statistical analysis**

Efficacy analyses were based on the all-patients-treated population, consisting of all randomised patients who received at least one dose of study drug and who had both a baseline (randomisation visit) and at least one postrandomisation measurement. An analysis of covariance (ANCOVA) model compared treatment groups for continuous efficacy parameters, focusing on change from baseline at week 12, with baseline values and prior OHA status as covariates. The between-group differences (relative to placebo) for efficacy end points (HbA1c was the primary end point) were assessed by testing the difference in the least-squares (LS) mean change (or mean percent) from baseline at week 12. Missing data were handled using the last observation carried forward method. A stepwise linear contrast test based on the ANCOVA model was used to examine the dose–response relationship in the mean HbA1c change from baseline for placebo and the 5-, 12.5-, 25- and 50-mg twice-daily doses of sitagliptin. The glipizide group was included in the ANCOVA model, but was excluded from the stepwise linear contrast test. In this study, glipizide was included as a benchmark treatment, but there were no prespecified hypotheses to test for the changes in efficacy and safety results in this group.

Safety and tolerability were assessed in patients who received at least one dose of study drug. Summary statistics were reviewed for change from baseline values in laboratory safety measurements, vital signs, body weight and ECG data, and for differences in adverse experiences.

**Results**

**Baseline demographics and characteristics**

Of the 2186 patients screened, 743 were randomised to study drug and 651 completed the 12-week study (Table 1). Three randomised patients who did not take a dose of double-blind study drug were included in the baseline data summary, but not in the safety and efficacy analyses. Discontinuation rates were slightly higher in the glipizide group compared with the placebo and sitagliptin groups, with withdrawal of consent and clinical adverse experiences as the

| Table 1 Disposition of randomised patients |
|------------------------------------------|
| **Number of patients** | **Placebo** | **Sitagliptin** | **Glipizide** |
| | (n = 125) | (n = 125) | (n = 125) | (n = 125) | (n = 125) | (n = 125) |
| **Completed study** | 108 | 107 | 116 | 108 | 112 | 100 |
| **Discontinued** | 17 | 18 | 7 | 15 | 12 | 23 |
| **Reasons for discontinuation** | | | | | | |
| Clinical adverse experience | 1 | 1 | 3 | 1 | 2 | 7 |
| Laboratory adverse experience | 0 | 1 | 0 | 0 | 1 | 0 |
| Lack of efficacy | 9 | 7 | 2 | 8 | 1 | 2 |
| Lost to follow-up | 0 | 2 | 0 | 0 | 0 | 1 |
| Other | 1 | 2 | 0 | 3 | 1 | 1 |
| Moved | 0 | 0 | 0 | 0 | 0 | 2 |
| Withdraw consent | 5 | 4 | 2 | 2 | 6 | 9 |
| Protocol deviation | 1 | 1 | 0 | 1 | 1 | 1 |
most commonly noted reasons for discontinuation in the glipizide group. Baseline demographics and glycemic parameters were generally well balanced across treatment groups (Table 2).

### Efficacy

At week 12, significant changes from baseline in HbA1c were observed for all sitagliptin doses ($p < 0.001$) (Table 3). A significant dose–response in reducing HbA1c was seen across all sitagliptin doses tested and placebo ($p < 0.001$). Based on the placebo-subtracted HbA1c changes from baseline, there was a stepwise, although not statistically significant, increase in efficacy across the dose range through the 50-mg b.i.d. dose, which provided the largest change in HbA1c from baseline ($95\% \text{ CI} = 0.77\% \text{ to } 0.96\%$). The pair-wise comparisons among the sitagliptin doses did not reach statistical significance, except for the comparisons with the 5-mg b.i.d. group ($p < 0.01$). With time, there was an apparent plateau in HbA1c in the sitagliptin groups, with similar reductions from baseline at weeks 8 and 12, while in the placebo group, no apparent plateau was reached with a further rise from baseline at week 12 relative to week 8 (Figure 1). A reduction from baseline (95% CI) in HbA1c of $-1.00\% \text{ to } -1.19\%$ was observed in the glipizide group relative to placebo.

A significant dose–response relationship was observed across sitagliptin doses of 12.5-, 25- and 50-mg b.i.d., and placebo in reducing FPG from baseline ($p < 0.001$) (Table 3). The trend test for the sitagliptin 5-mg b.i.d. vs. placebo did not reach statistical significance ($p = 0.051$). The sitagliptin 50-mg b.i.d. group showed numerically greater FPG reduction from baseline compared with the other sitagliptin doses, with a placebo-subtracted change (95% CI) of $-1.45 \text{ mmol/l} \text{ to } -1.94 \text{ mmol/l}$ $[32.7 \text{ mg/dl} \text{ to } 41.9 \text{ mg/dl}]$. Although pair-wise comparison among 12.5-, 25- and 50-mg b.i.d. doses did not reach statistical significance, a significant difference was observed when 25- and 50-mg b.i.d. groups were compared with the 5-mg b.i.d. group ($p < 0.05$). The change from baseline (95% CI) in MDG was $-2.82 \text{ mmol/l} \text{ to } -3.37 \text{ mmol/l}$ $[50.7 \text{ mg/dl} \text{ to } 60.7 \text{ mg/dl}]$ with glipizide relative to placebo.

### Table 2 Summary of demographics and baseline characteristics

| Parameter                      | Placebo (n = 125) | 5 mg b.i.d. (n = 125) | 12.5 mg b.i.d. (n = 123) | 25 mg b.i.d. (n = 123) | 50 mg b.i.d. (n = 124) | Glipizide (n = 123) |
|-------------------------------|------------------|----------------------|--------------------------|------------------------|----------------------|----------------------|
| Age, years (range)            | 55.3 ± 9.7 (31–75) | 55.1 ± 9.5 (30–76) | 56.2 ± 9.0 (34–75)       | 55.6 ± 9.0 (34–76)     | 55.1 ± 9.8 (28–75)    | 54.7 ± 10.7 (21–76)  |
| Gender, n (%)                 |                  |                      |                          |                        |                      |                      |
| Women                         | 47 (37.6)        | 63 (50.4)            | 64 (52.0)                | 52 (42.3)              | 59 (47.6)            | 53 (43.1)            |
| Men                           | 78 (62.4)        | 62 (49.6)            | 59 (48.0)                | 71 (57.7)              | 65 (52.4)            | 70 (56.9)            |
| Race, n (%)                   |                  |                      |                          |                        |                      |                      |
| Asian                         | 3 (2.4)          | 7 (5.6)              | 6 (4.9)                  | 6 (4.9)                | 3 (2.4)              | 6 (4.9)              |
| Black                         | 10 (8.0)         | 8 (6.4)              | 6 (4.9)                  | 11 (8.9)               | 6 (4.8)              | 4 (3.3)              |
| Multi-racial                  | 9 (7.2)          | 8 (6.4)              | 7 (5.7)                  | 8 (6.5)                | 9 (7.3)              | 8 (6.5)              |
| White                         | 83 (66.4)        | 86 (68.8)            | 78 (63.4)                | 75 (61.0)              | 86 (69.4)            | 75 (61.0)            |
| Other                         | 20 (16.0)        | 16 (12.8)            | 26 (21.1)                | 23 (18.7)              | 20 (16.1)            | 30 (24.4)            |
| BMI (kg/m²)                   | 31.6 ± 5.8       | 30.8 ± 5.1           | 30.5 ± 5.0               | 31.4 ± 6.9             | 30.4 ± 4.9           | 30.6 ± 5.3           |
| Known duration of diabetes, years | 4.8 ± 4.7     | 4.3 ± 4.1            | 4.9 ± 5.0                | 5.0 ± 5.2              | 4.2 ± 4.0            | 4.7 ± 4.2            |
| HbA1c, % (range)              | 7.9 ± 1.0 (6.4–10.3) | 7.9 ± 1.0 (6.4–10.3) | 7.9 ± 0.9 (6.3–10.6)       | 7.9 ± 0.9 (6.3–10.3)     | 7.8 ± 1.0 (6.3–10.3)    | 7.9 ± 1.0 (6.3–11.0)  |
| FPG, mmol/l                   | 9.6 ± 2.5        | 9.5 ± 2.2            | 9.4 ± 2.0                | 9.6 ± 2.2              | 9.4 ± 2.2            | 9.5 ± 2.2            |

Data are expressed as mean ± standard deviation or frequency. BMI, body mass index; FPG, fasting plasma glucose.
## Table 3 Baseline, week 12 and change from baseline results for fasting glycaemic end points

| Parameter       | Placebo | Sitagliptin 5 mg b.i.d. | 12.5 mg b.i.d. | 25 mg b.i.d. | 50 mg b.i.d. | Glipizide |
|-----------------|---------|-------------------------|---------------|-------------|-------------|-----------|
| **HbA1c, %**    | 121     | 122                     | 122           | 120         | 121         | 119       |
| Baseline        | 7.88 (0.96) | 7.89 (0.94)         | 7.85 (0.88)   | 7.89 (0.94) | 7.83 (0.95) | 7.82 (0.95) |
| Week 12         | 8.14 (1.23) | 7.77 (1.22)            | 7.48 (0.98)   | 7.50 (1.14) | 7.34 (1.01) | 7.11 (0.91) |
| Change from baseline | 0.23 (0.10, 0.37) | -0.15 (−0.29, −0.01) | -0.41 (−0.55, −0.27) | -0.43 (−0.56, −0.29) | -0.54 (−0.68, −0.40) | -0.76 (−0.90, −0.62) |
| Change from placebo | −0.38 (−0.58, −0.19)* | −0.64 (−0.84, −0.45)* | −0.66 (−0.85, −0.47)* | −0.77 (−0.96, −0.58)* | −1.00 (−1.19, −0.80)* |
| **FPG, mmol/l** | 123     | 124                     | 123           | 121         | 122         | 121       |
| Baseline        | 9.59 (2.52) | 9.53 (2.19)           | 9.41 (1.99)   | 9.61 (2.23) | 9.41 (2.21) | 9.52 (2.22) |
| Week 12         | 10.04 (2.88) | 9.52 (3.15)           | 8.76 (2.00)   | 8.89 (2.53) | 8.46 (2.03) | 8.18 (1.71) |
| Change from baseline | 0.44 (0.09, 0.79) | −0.04 (−0.39, 0.30) | −0.72 (−1.07, −0.37) | −0.72 (−1.08, −0.37) | −1.01 (−1.36, −0.66) | −1.38 (−1.73, −1.03) |
| Change from placebo | −0.48 (−0.97, 0.00)* | −1.16 (−1.65, −0.67)* | −1.16 (−1.66, −0.67)* | −1.45 (−1.94, −0.96)* | −1.82 (−2.31, −1.32)* |
| **MDG, mmol/l** | 119     | 120                     | 121           | 117         | 118         | 116       |
| Baseline        | 11.42 (2.81) | 11.50 (2.73)         | 11.08 (2.58)  | 11.58 (2.49) | 11.24 (2.90) | 11.32 (2.74) |
| Week 12         | 11.72 (3.72) | 10.62 (3.11)         | 9.91 (2.58)   | 10.05 (2.39) | 9.83 (2.52) | 8.84 (1.74) |
| Change from baseline | 0.27 (−0.12, 0.66) | −0.88 (−1.27, −0.49) | −1.33 (−1.72, −0.94) | −1.51 (−1.90, −1.12) | −1.51 (−1.9, −1.12) | −2.55 (−2.94, −2.16) |
| Change from placebo | −1.15 (−1.69, −0.61)* | −1.60 (−2.14, −1.06)* | −1.78 (−2.33, −1.23)* | −1.78 (−2.33, −1.23)* | −2.82 (−3.37, −2.27)* |
| **Fasting insulin, pmol/l** | 115     | 117                     | 119           | 115         | 116         | 106       |
| Baseline        | 88.2 (73.8) | 81.0 (47.4)          | 77.4 (51.0)   | 90.6 (65.4) | 78.6 (54.0) | 86.4 (71.4) |
| Week 12         | 88.8 (66.0) | 88.8 (61.8)         | 82.8 (58.2)   | 89.4 (65.4) | 90.0 (72.6) | 111.6 (140.4) |
| Change from baseline | 1.8 (−10.8, 15.0) | −2.7 (−5.4, 19.8) | 3.6 (−8.4, 16.2) | 0.6 (−12.0, 13.8) | 10.2 (−2.4, 22.8) | 25.8 (12.6, 39.0) |
| Change from placebo | −4.8 (−13.2, 22.8) | −1.8 (−16.2, 19.8) | −1.2 (−19.2, 16.8) | 7.8 (−9.6, 25.8) | 24.0 (−6.0, −42.0) |
| **HOMA-β, %**   | 112     | 115                     | 118           | 114         | 115         | 105       |
| Baseline        | 61.2 (66.9) | 52.1 (40.1)          | 50.2 (43.1)   | 58.8 (49.8) | 49.8 (39.3) | 54.1 (43.9) |
| Week 12         | 58.3 (58.9) | 60.3 (51.9)          | 58.7 (40.1)   | 63.5 (48.5) | 67.4 (54.9) | 78.3 (69.1) |
| Change from baseline | −0.6 (−8.1, 6.9) | 8.3 (0.9, 15.7) | 8.2 (0.9, 15.5) | 6.7 (−0.8, 14.1) | 17.3 (9.8, 24.7) | 25.4 (17.7, 33.2) |
| Change from placebo | −8.9 (−1.6, 19.4) | 8.8 (−1.6, 19.3) | 7.3 (−3.3, 17.8) | 17.8 (7.2, 28.4)* | 26.0 (15.3, 36.8) |
Relative to placebo, small, inconsistent increases in fasting insulin were observed across the sitagliptin treatment groups. Fasting insulin was increased in the glipizide group (Table 3). HOMA-\(\beta\) was numerically increased across the sitagliptin dose groups and significantly increased relative to placebo in the sitagliptin 50-mg b.i.d. group (Table 3). HOMA-\(\beta\) also increased in the glipizide group (Table 3). Changes in QUICKI and HOMA-IR were not significantly different from placebo in the sitagliptin groups (Table 3).

In a subset of patients (n = 221) consenting to an MTT, treatment with sitagliptin across all doses tested led to greater reductions in both 2-h PPG and total glucose AUC relative to baseline, with the 50-mg b.i.d. dose providing the largest 2-h PPG change from baseline (95% CI) of \(-2.69\) mmol/l (\(-3.69, -1.71\)) \([-48.5\) mg/dl \((-66.4, -30.7)\]) (Table 4). Small increases were observed for insulin and C-peptide AUC in the sitagliptin groups (with the exception of a slight decrease in C-peptide AUC in the 25-mg b.i.d. group) (Table 4). Glipizide reduced 2-h PPG and total glucose AUC relative to baseline, and increased total C-peptide and insulin AUC (Table 4). Given the small sample size of this subset of patients, no statistical testing was performed between the active drug and placebo groups for these end points.

Treatment with sitagliptin produced small but statistically significant decreases in triglycerides (at doses above 5 mg b.i.d.) and increases in HDL-C (at doses above 12.5 mg b.i.d.) relative to placebo (Table 5). For triglycerides, the difference was due to a smaller rise relative to the increase in placebo group. While there were slight increases in total cholesterol and LDL-C in all treatment groups, including placebo, there were no statistically significant differences in any sitagliptin group relative to placebo. Treatment with sitagliptin (at doses above 5 mg

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**Table 3 (Continued)**

| Parameter | Placebo | Sitagliptin 5 mg b.i.d. | Sitagliptin 12.5 mg b.i.d. | Sitagliptin 25 mg b.i.d. | Sitagliptin 50 mg b.i.d. | Glipizide |
|-----------|---------|------------------------|--------------------------|------------------------|------------------------|----------|
| HOMA-IR   |         |                        |                          |                        |                        |          |
| n         | 113     | 115                    | 118                      | 115                    | 114                    | 106      |
| Baseline  | 6.0 (4.9)| 6.2 (4.9)              | 6.3 (4.8)                | 5.5 (4.4)              | 5.7 (4.5)              | 6.0 (5.4) |
| Week 12   | 4.3 (1.3)| 4.3 (1.3)              | 4.6 (1.3)                | 4.3 (1.3)              | 4.2 (1.3)              | 4.3 (1.3) |
| Change from baseline | -1.7 (1.9) | -1.8 (1.9)              | -1.7 (1.9)              | -1.2 (1.9)              | -1.5 (1.9)              | -1.7 (1.9) |
| QUICKI    | 0.310 (0.040) | 0.310 (0.032) | 0.311 (0.039) | 0.310 (0.039) | 0.310 (0.040) | 0.309 (0.039) |
| n         | 113     | 114                    | 115                      | 115                    | 114                    | 106      |
| Baseline  | 0.310 (0.040) | 0.310 (0.032) | 0.311 (0.039) | 0.310 (0.039) | 0.310 (0.040) | 0.309 (0.039) |
| Week 12   | 0.326 (0.030) | 0.326 (0.030) | 0.326 (0.030) | 0.326 (0.030) | 0.326 (0.030) | 0.326 (0.030) |
| Change from baseline | -0.020 (0.009) | -0.020 (0.009) | -0.020 (0.009) | -0.020 (0.009) | -0.020 (0.009) | -0.020 (0.009) |

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**Figure 1** LS mean change (SE) from baseline in HbA\(_1\)c over 12 weeks.
b.i.d.) produced small but statistically significant decreases in FFA relative to placebo. No changes from baseline in any lipid end point were observed for glipizide relative to placebo (Table 5).

**Safety**

Sitagliptin was generally well tolerated, with a clinical adverse experience profile similar to placebo. The incidence of drug-related clinical adverse experiences was modestly higher in the glipizide group compared with the placebo and sitagliptin groups. This difference was due to the increased incidence of hypoglycaemia adverse experiences in the glipizide group compared with the placebo and sitagliptin treatment groups (Table 6). Three patients in the glipizide group discontinued treatment because of hypoglycaemia compared with no patients in the placebo or sitagliptin groups. No other clinically meaningful trends were observed for clinical or laboratory adverse experiences. There were no serious clinical or laboratory drug-related adverse experiences or deaths. The incidence of laboratory adverse experiences was low across the treatment groups, and no specific laboratory adverse experience occurred at a meaningfully higher rate in the sitagliptin treatment groups compared with placebo, including incidences of elevations of ALT, AST or CK. No meaningful differences were observed in vital signs or ECG changes.

By week 12, treatment with sitagliptin had no meaningful effect on body weight relative to baseline or placebo. The between-group differences in LS mean change from baseline (95% CI) for sitagliptin relative to placebo were: 0.1 kg [0.5, 0.6] for 5 and 12.5 mg b.i.d., 0.3 kg [−0.2, 0.9] for 25 mg b.i.d., and 0.4 [−0.2, 0.9] for 50 mg b.i.d. (p > 0.1 for all comparisons). Treatment with glipizide led to an increase in body weight relative to baseline (LS mean change from baseline [95% CI] = 0.9 kg [0.5, 1.3]) and relative to placebo (between-group difference in LS mean change from baseline [95% CI] = 1.3 kg [0.8, 1.8]).

**Discussion**

In this dose–response trial in patients with type 2 diabetes inadequately controlled on diet and exercise,
DPP-4 inhibition and glycaemic control

Table 5 Baseline, week 12 and percent change from baseline results for lipid end points

| Parameter | Placebo | Sitagliptin 5 mg b.i.d. | 12.5 mg b.i.d. | 25 mg b.i.d. | 50 mg b.i.d. | Glipizide |
|-----------|---------|-------------------------|----------------|-------------|-------------|----------|
| TC, mmol/l |         |                         |                |             |             |          |
| n         | 117     | 120                     | 121            | 117         | 119         | 112      |
| Baseline  | 5.01 (0.95) | 5.02 (0.94)            | 5.08 (0.93)    | 4.97 (0.92) | 4.98 (1.12) | 4.96 (1.12) |
| Week 12   | 5.05 (0.94) | 5.07 (1.00)            | 5.08 (0.97)    | 5.0 (1.02)  | 5.09 (1.12) | 4.98 (1.04) |
| Change from baseline | 1.6 (–0.7, 4.0) | 1.9 (–0.5, 4.2)        | 1.0 (–1.3, 3.4) | 1.2 (–1.2, 3.6) | 3.4 (1.0, 5.7) | 1.8 (–0.7, 4.2) |
| Change from placebo | –       | 0.2 (–3.9, 3.6)         | –0.6 (–3.9, 2.7) | –0.4 (–3.8, 2.9) | 1.7 (–1.6, 5.1) | 0.1 (–3.3, 3.5) |
| LDL-C, mmol/l |         |                         |                |             |             |          |
| n         | 117     | 120                     | 121            | 117         | 119         | 112      |
| Baseline  | 3.00 (0.81) | 2.96 (0.78)            | 3.05 (0.82)    | 2.96 (0.80) | 3.00 (0.98) | 2.95 (1.01) |
| Week 12   | 2.97 (0.85) | 2.96 (0.80)            | 3.07 (0.84)    | 2.96 (0.85) | 3.07 (0.97) | 2.93 (0.90) |
| Change from baseline | 0.9 (–2.9, 4.6) | 1.7 (–1.9, 5.4)        | 3.0 (–0.7, 6.7) | 1.9 (–1.8, 5.6) | 5.5 (1.8, 9.2) | 2.0 (–1.8, 5.8) |
| Change from placebo | –       | 0.9 (–4.3, 6.1)         | 2.1 (–3.1, 7.3) | 1.0 (–4.2, 6.3) | 4.7 (–0.6, 9.9) | 1.1 (–4.2, 6.3) |
| HDL-C, mmol/l |         |                         |                |             |             |          |
| n         | 117     | 120                     | 121            | 117         | 119         | 112      |
| Baseline  | 1.11 (0.26) | 1.16 (0.27)            | 1.16 (0.27)    | 1.12 (0.25) | 1.16 (0.23) | 1.14 (0.25) |
| Week 12   | 1.11 (0.27) | 1.17 (0.29)            | 1.18 (0.26)    | 1.16 (0.26) | 1.20 (0.24) | 1.16 (0.28) |
| Change from baseline | 0.6 (–1.7, 2.9) | 1.1 (–1.1, 3.4)        | 3.0 (0.8, 5.3) | 4.1 (1.8, 6.4) | 4.6 (2.3, 6.8) | 2.8 (0.4, 5.1) |
| Change from placebo | –       | 0.5 (–2.7, 3.7)         | 2.4 (–0.8, 5.6) | 3.5 (0.2, 6.7)* | 3.9 (0.7, 7.1)* | 2.1 (–1.1, 5.4) |
| TG, mmol/l |         |                         |                |             |             |          |
| n         | 117     | 120                     | 121            | 117         | 119         | 112      |
| Baseline  | 1.97 (1.15) | 2.02 (1.11)            | 1.99 (1.19)    | 1.99 (0.98) | 1.81 (0.91) | 1.93 (0.96) |
| Week 12   | 2.15 (1.32) | 2.16 (1.46)            | 1.85 (0.99)    | 1.96 (0.94) | 1.81 (0.99) | 1.96 (0.94) |
| Change from baseline | 13.9 (6.9, 20.9) | 9.8 (2.9, 16.7)        | –0.5 (–7.3, 6.4) | 4.9 (–2.1, 11.9) | 3.6 (–3.3, 10.6) | 7.0 (–0.1, 14.1) |
| Change from placebo | –       | –4.1 (–13.8, 5.7)       | –14.4 (–24.1, –4.6)* | –9.0 (–18.8, 0.8) | –10.3 (–20.1, –0.5)* | –6.9 (–16.8, 3.0) |
| FFA, mmol/l |         |                         |                |             |             |          |
| n         | 117     | 119                     | 121            | 115         | 117         | 107      |
| Baseline  | 0.6 (0.2) | 0.6 (0.3)               | 0.6 (0.2)      | 0.6 (0.4)  | 0.6 (0.2)  | 0.6 (0.2)  |
| Week 12   | 0.6 (0.3) | 0.6 (0.3)               | 0.5 (0.2)      | 0.6 (0.2)  | 0.5 (0.2)  | 0.6 (0.3)  |
| Change from baseline | 11.7 (3.7, 19.7) | 1.9 (–6.0, 9.9)        | –4.2 (–12.1, 3.7) | 1.6 (–6.5, 9.7) | –6.3 (–14.3, 1.8) | 0.2 (–8.1, 8.6) |
| Change from placebo | –       | –9.8 (–21.0, 1.5)       | –15.9 (–27.1, –4.7)* | –10.1 (–21.5, 1.3)* | –18.0 (–29.3, –6.7)* | –11.4 (–23.0, 0.1) |

Baseline and week 12 data are presented as mean (SD). Change from baseline is the LS mean percent change from baseline at week 12 (95% CI). Change from placebo is the between-treatment difference in LS mean percent change from baseline at week 12 (95% CI). *p < 0.05 from trend test for sitagliptin q.d. dose vs. placebo.

Treatment with sitagliptin monotherapy led to statistically significant and clinically meaningful reductions in HbA1c and FPG after 12 weeks of treatment. Additionally, sitagliptin produced significant reductions in postprandial glycaemic excursion following an MTT. Collectively, these improvements demonstrate that sitagliptin provided clinically important glucose-lowering in both the fasting and postprandial states. These findings are supported by the significant decrease in MDG with sitagliptin, reflecting improvements in both fasting and postmeal glucose control. In this dose–response study, sitagliptin 50 mg b.i.d. (total daily dose of 100 mg per day) appeared to provide the maximal glycaemic effect on HbA1c and FPG. For MDG, the plateau in response occurred at and above the 25-mg b.i.d. dose, but this end point tends to have greater variability, thus reducing the ability to discriminate between doses.

Glipizide provided modestly greater numerical reductions in glycaemic end points compared with sitagliptin, but with a substantially higher incidence of hypoglycaemia adverse events and weight gain relative to sitagliptin or placebo. Although initial glycaemic lowering was modestly greater with glipizide over 12 weeks, the long-term effects of these active treatments are important to assess in longer duration studies.

Although not directly assessed in the current study, the improvements in glycaemic control were consistent with the mechanism of action of sitagliptin, which inhibits DPP-4 activity and, in turn, the degradation of active GLP-1 and GIP (7–10). These
incretin hormones regulate glucose levels via numerous mechanisms including increases in insulin release, suppression of glucagon release and reductions in gastric emptying (5,6). Previously, single doses of sitagliptin significantly decreased glucose AUC by up to 26% during an OGTT in patients with type 2 diabetes (10). Additionally, sitagliptin significantly increased insulin and C-peptide concentrations and lowered glucagon concentrations following the OGTT (10).

In the present study, postprandial insulin AUC and, in most dose groups, C-peptide AUC were increased with sitagliptin treatment, although the increases were small. These effects on C-peptide and insulin, in the context of lowered glucose concentrations with sitagliptin, suggest an augmentation of insulin response after a meal. The increase in HOMA-\(\beta\) in the sitagliptin 50-mg b.i.d. group compared with placebo suggests that insulin release was enhanced with sitagliptin in the fasting state; as expected, HOMA-\(\beta\) was also increased with glipizide.

Small but favourable effects on several lipid end points were observed with sitagliptin therapy, including increases in HDL-C and decreases in triglyceride and FFA relative to placebo. The mechanism of lipid improvement with sitagliptin is not known. Improvements in glycaemic control can lead to favourable effects on these end points; however, glipizide did not improve lipid end points – despite slightly greater glycaemic improvements – suggesting that there are either other mechanisms involved or opposing mechanisms associated with the use of glipizide.

Treatment with sitagliptin was well-tolerated in this clinical trial. The incidence of drug-related adverse experiences was generally similar across the sitagliptin and placebo treatment groups, and lower than that observed in the glipizide treatment group. A very low and similar incidence of hypoglycaemia adverse experiences was observed with sitagliptin and placebo treatments. The low incidence of hypoglycaemia, despite effective glucose lowering and stimulation of insulin release, observed with sitagliptin treatment is consistent with the evidence that GLP-1 stimulates insulin release in a glucose-dependent manner (14). No increase in the incidence of gastrointestinal adverse experiences was observed with sitagliptin compared with placebo or glipizide. Although pharmacological doses of GLP-1 have been associated with gastrointestinal side effects such as nausea, the more moderate elevations in GLP-1 achieved with DPP-4 inhibition [an approximately twofold increase in GLP-1 AUC (10)] may not lead to a notable increase in the incidence of gastrointestinal side effects.

Treatment with sitagliptin had a generally neutral effect on body weight relative to placebo. In contrast, as noted above, treatment with glipizide led to a moderate weight gain compared with placebo. GLP-1-based therapies have been associated with weight loss, and this observation raised the possibility that DPP-4 inhibition would also cause weight reduction. As improved glycaemic control may lead to weight gain (15), the minimal body weight changes from baseline could suggest that there is a tendency for weight reduction with sitagliptin counterbalanced by the tendency of improved glycaemic control to increase weight. Further studies of the body weight effects of sitagliptin will be of importance.

In summary, in this study, sitagliptin monotherapy provided effective glucose-lowering, consistent across

| Table 6 Safety and tolerability results |
|----------------------------------------|
| Number (%) of patients | Placebo (n=125) | Sitagliptin (n=124) | Glipizide (n=123) |
| One or more clinical adverse experiences (AEs) | 67 (53.6) | 68 (54.8) | 77 (62.6) |
| Drug-related clinical AEs* | 12 (9.6) | 11 (8.9) | 34 (27.6) |
| Serious clinical AEs (SAEs) | 4 (3.2) | 2 (1.6) | 6 (4.9) |
| Drug-related clinical SAEs* | 0 | 0 | 0 |
| Discontinued due to clinical AEs | 0 | 0 | 0 |
| Discontinued due to drug-related clinical AEs | 0 | 0 | 0 |
| Discontinued due to clinical SAEs | 0 | 0 | 0 |
| Discontinued due to drug-related clinical SAEs | 0 | 0 | 0 |
| Adverse experiences of clinical interest |
| Hypoglycaemia | 3 (2.4) | 0 | 21 (17.1) |

* Determined by the investigator to be possibly, probably or definitely drug-related.
glycaemic end points, in patients with type 2 diabetes. Of the sitagliptin doses examined in this study, sitagliptin 100 mg per day (50 mg b.i.d.) demonstrated the greatest glycaemic efficacy across various parameters, with favourable, albeit modest, improvements in several important lipid end points. Sitagliptin was also generally well tolerated, with a low rate of hypoglycaemia and no change in body weight.

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