CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 25, NO. 3, 2009, 569–583

0300-7995
doi:10.1185/03007990802705679




ORIGINAL ARTICLE

# Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study

Debora Williams-Herman, Jeremy Johnson, Rujun Teng, Edmund Luo, Michael J. Davies, Keith D. Kaufman, Barry J. Goldstein and John M. Amatruda

*Merck Research Laboratories, Rahway, NJ, USA*

*Address for correspondence:* Debora Williams-Herman, MD, Merck Research Laboratories, RY34-A232, Rahway, NJ 07065, USA. debora_williamsherman@merck.com

*Key words:* dipeptidyl peptidase-4 inhibitors – DPP-IV – Incretins – MK-0431



## ABSTRACT

*Objective:* To assess the 54-week efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes and inadequate glycemic control ($HbA_{1c}$ 7.5–11%) on diet and exercise.

*Methods and materials:* This was multinational study conducted at 140 clinical sites in 18 countries. Following an initial 24-week, double-blind, placebo-controlled period, patients entered a double-blind continuation period for an additional 30 weeks. Following the week 24 evaluation, patients remained on their previously assigned active, oral treatments: sitagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d. (S100 + M2000), sitagliptin 50 mg b.i.d. + metformin 500 mg b.i.d. (S100 + M1000), metformin 1000 mg b.i.d. (M2000), metformin 500 mg b.i.d. (M1000), and sitagliptin 100 mg q.d. (S100). Patients initially randomized to placebo were switched to M2000 (designated PBO/M2000) at week 24. This report summarizes the overall safety and tolerability data for the 54-week study and presents efficacy results for patients randomized to continuous treatments who entered the 30-week continuation period.

*Results:* Of the 1091 randomized patients, 906 completed the 24-week placebo-controlled phase and 885 patients continued into the 30-week continuation period (S100 + M2000 $n = 161$, S100+M1000 $n = 160$, M2000 $n = 153$, M1000 $n = 147$, S100 $n = 141$, PBO/M2000 $n = 123$). At baseline, patients included in the efficacy analysis had mean age of 54 years, mean BMI of 32 $kg/m^2$, mean $HbA_{1c}$ of 8.7% (8.5–8.8% across groups), and mean duration of type 2 diabetes of 4 years. At week 54, in the all-patients-treated analysis of continuing patients, least-squares (LS) mean changes in $HbA_{1c}$ from baseline were −1.8% (S100 + M2000), −1.4% (S100 + M1000), −1.3% (M2000), −1.0% (M1000), and −0.8% (S100). The proportions of continuing patients with an $HbA_{1c} < 7\%$ at week 54 were 67% (S100 + M2000), 48% (S100 + M1000), 44% (M2000), 25% (M1000), and 23% (S100). For the patients completing treatment through week 54, LS mean changes in $HbA_{1c}$ from baseline were −1.9% (S100 + M2000), −1.7% (S100 + M1000), −1.6% (M2000), −1.2% (M1000), and −1.4% (S100). Glycemic response was generally durable over time across treatments. All treatments improved measures of $\beta$-cell function (e.g., HOMA-$\beta$, proinsulin/insulin ratio). Mean body weight decreased from baseline in the combination and metformin monotherapy groups and was unchanged from baseline in the sitagliptin monotherapy group. The incidence of hypoglycemia was low (1–3%) across treatment groups. The incidence of gastrointestinal adverse experiences with the co-administration of sitagliptin and metformin was similar to that observed with metformin alone.

*Limitations:* The patient population evaluated in the 54-week efficacy analysis was a population of patients who entered the continuation period without receiving glycemic rescue therapy in the 24-week placebo-controlled period. Because the baseline $HbA_{1c}$ inclusion criteria ranged from 7.5 to 11% and the glycemic rescue criterion was an $HbA_{1c} > 8\%$ after week 24, there was a greater likelihood of glycemic rescue in the monotherapy groups; this led to more missing data in the continuation all-patients-treated population(CAPT) analysis and fewer patients contributing to the completers analysis in the monotherapy groups.

*Conclusions:* In this study, initial treatment with sitagliptin, metformin, or the combination therapy of sitagliptin and metformin provided substantial and durable glycemic control, improved markers of $\beta$-cell function, and was generally well-tolerated over 54 weeks in patients with type 2 diabetes.

## Introduction

Patients treated with a single antihyperglycemic agent (AHA) often fail to reach glycemic goals or, once achieved, do not maintain these goals long term[1,2]. Recent treatment recommendations from the Canadian Diabetes Association include initiation of combination therapies for the treatment of patients with marked hyperglycemia[3]. Furthermore, durability of treatment effect is not the same among the AHAs. In a large clinical trial, treatment with either rosiglitazone or metformin demonstrated greater durability compared with the sulfonylurea glyburide over 4 years[1]. Because type 2 diabetes is a progressive disease and treatment requires prolonged lifestyle and/or pharmacologic management, the long-term efficacy, durability, and safety of newer AHAs are important considerations.

Sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4), is a newer treatment for type 2 diabetes that was shown to be efficacious as monotherapy and as add-on therapy in studies ranging from 12 to 52 weeks[4–13]. In a pooled safety analysis in 6139 patients treated for up to 2 years, treatment with sitagliptin was well-tolerated compared with non-sitagliptin treatment[14]. In patients with type 2 diabetes over 24 weeks, initial combination therapy with sitagliptin and metformin was shown to provide substantial and additive glycemic improvements and was generally well-tolerated relative to placebo[15]. Further, the gastrointestinal tolerability profile of the initial combination of sitagliptin and metformin was similar to that of metformin monotherapy. The objectives of the present study were to evaluate the longer-term efficacy and safety of this initial combination therapy over 54 weeks in patients with type 2 diabetes. The aforementioned 24-week study[15] was continued for an additional 30 weeks to provide the results for the 54-week study period.

## Methods

This was a 54-week, multinational, randomized, double-blind, parallel-group study (Clinicaltrials.gov: NCT00103857) consisting of a 24-week placebo-controlled period (phase A[15]) and a 30-week continuation period (continuation phase). This study was conducted at 140 clinical sites in 18 countries (see Appendix in Goldstein *et al.*[15] for a list of countries and study investigators). Patients provided written informed consent to participate in this 54-week trial. The protocol was reviewed and approved by the appropriate committees and authorities and performed in accordance with the Declaration of Helsinki.

The design, inclusion and exclusion criteria, and primary results were previously published for the 24-week placebo-controlled portion of this study[15]. Briefly, patients with type 2 diabetes (18–78 years of age) who were on or not on an oral AHA at the screening visit were eligible to participate. After a screening diet/exercise run-in period (including a drug wash-off period for those on oral AHAs at screening) of 6–10 weeks (or 8–12 weeks for those on thiazolidinediones), patients with $HbA_{1c} \geq 7.5\%$ to $\leq 11.0\%$ entered a 2-week, single-blind, placebo run-in period. All patients with adequate compliance ($\geq 75\%$ as assessed by tablet counts) during the placebo run-in period had baseline assessments and were randomized to one of six oral treatments for 24 weeks using a computer-generated allocation schedule: placebo ($n = 176$), sitagliptin 100 mg q.d. ($n = 179$), metformin 500 mg b.i.d. ($n = 182$), metformin 1000 mg b.i.d. ($n = 182$), sitagliptin 50 mg b.i.d. + metformin 500 mg b.i.d. (low dose; $n = 190$), and sitagliptin 50 mg b.i.d. + metformin 1000 mg b.i.d. (high dose; $n = 182$). All patients received the same number of active or placebo-matched tablets throughout the study. At week 24, patients initially randomized to placebo were switched, in a double-blind manner, to metformin 1000 mg b.i.d. for 30 weeks, with gradual up-titration of 500 mg/week over the initial 4 weeks. All other patients continued on their prior study medication for an additional 30 weeks. Compliance was assessed by tablets counts throughout the study.

Patients not meeting progressively stricter glycemic goals were provided open-label rescue therapy with glyburide (glibenclamide) as previously described[15]. Throughout the 30-week continuation phase, the criterion for initiation of glycemic rescue therapy was an $HbA_{1c}$ value of >8.0%.

### Efficacy endpoints

The endpoints included change from baseline (i.e., change from randomization) at week 54 for $HbA_{1c}$, fasting plasma glucose (FPG), 2-hour postprandial glucose (PPG), fasting serum insulin, fasting serum proinsulin, proinsulin/insulin ratio, homeostasis model assessment $\beta$-cell function (HOMA-$\beta$), and HOMA-insulin resistance (HOMA-IR), fasting lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], non-HDL-C, and triglycerides), and body weight. The proportion of continuing patients with an $HbA_{1c} < 7\%$ at week 54 was calculated, as was the proportion patients who had an $HbA_{1c} < 7\%$ at both week 24 and week 54.

A standard meal-tolerance test was administered at baseline (prior to first dose of study medication) and

at week 54. Patients took study medication 30 minutes prior to the standard meal, which was ingested within 15 minutes and consisted of one nutrition bar and one nutrition drink (~460 kcal; 75 g carbohydrate, 9 g fat, 18 g protein). Blood was collected at 0, 60, and 120 minutes from the meal start. Plasma glucose, serum insulin, and serum C-peptide were measured and used to determine 2-hour PPG, area under the glucose concentration–time curve (AUC), insulin AUC, C-peptide AUC, and the insulin AUC/glucose AUC ratio.

## Safety endpoints

Data were collected on clinical and laboratory adverse experiences, physical examinations, vital signs, and electrocardiograms (ECGs) throughout the study. All clinical adverse experiences were rated by investigators for intensity and relationship to study drug. Laboratory evaluations included complete blood chemistry, hematology, and urinalysis. Clinical adverse experiences of interest included hypoglycemia and prespecified, select, gastrointestinal adverse experiences (abdominal pain, nausea, vomiting, and diarrhea).

Patients were counseled regarding the symptoms of hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion) and received instruction on blood glucose monitoring and treating symptoms of hypoglycemia. If any symptoms occurred that may have been related to hypoglycemia, patients were requested to immediately perform a fingerstick glucose measurement, but to avoid delay in treating these symptoms. To assist the investigator in assessing the severity of an event, patients were provided with, and instructed in the use of, a hypoglycemia assessment log to document potential hypoglycemia episodes and collect information on the severity of the events (such as the requirement for the assistance of another person or medical treatment). Symptomatic events assessed by the investigator as hypoglycemia were reported as clinical adverse experiences of hypoglycemia; documentation of a glucose determination at the time the patient had symptoms was not required. Events of hypoglycemia were analyzed as follows: those not requiring assistance; those requiring the (non-medical) assistance of others; and those requiring medical intervention or exhibiting markedly depressed level of consciousness, including loss of consciousness, or seizure.

Laboratory measurements and ECGs were analyzed 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 as previously described[10].

## Statistical analyses

The primary efficacy analysis was based on the continuation all-patients-treated population (CAPT), which consisted of all randomized patients who had a baseline measurement, did not receive glycemic rescue therapy in phase A, received at least one dose of study medication in the continuation phase, and had at least one efficacy measurement during the continuation phase. Results for patients randomized to receive active therapy throughout this 54-week study are the focus of this article. To avoid the confounding influence of glycemic rescue therapy on efficacy comparisons, data collected after initiation of rescue therapy were treated as missing. An analysis of covariance (ANCOVA) model evaluated treatment groups for continuous efficacy parameters, focusing on change from baseline at week 54, with baseline values and prior oral AHA status as covariates. Missing data were handled with the last observation-carried-forward (LOCF) method within the continuation phase, but not from phase A to the continuation phase. Additional efficacy analyses were performed on a population that consisted of all randomized patients who had baseline and week 54 glycemic measurements and did not require glycemic rescue medication during the study (week 54 completers population) for select key endpoints: $HbA_{1c}$, FPG and 2-hour PPG. No missing data were imputed in the week 54 completers analysis. The within-group differences (least-squares [LS] mean changes from baseline at week 54) with 95% confidence intervals (CI) and sample sizes were summarized for the efficacy endpoints for the patients who were continuously treated with active therapy in phase A and the continuation phase. No inferential testing was performed between groups in the continuation phase.

Patients switched from placebo to metformin at week 24 do not represent the original randomized population because they included only those who did not discontinue during phase A (placebo-controlled period) and who were able to complete the 24-week phase A period without requiring glycemic rescue therapy. Further, because the metformin in this switch group and the continuous treatment in the other groups were not initiated simultaneously at randomization, the durations of the active treatment period differed between groups. Therefore, the results from the switch group were not included in the efficacy analyses.

The safety analysis was based on the 54-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. The primary safety analysis excluded adverse experiences obtained after initiation of glycemic rescue therapy. In addition to the results for the patients continuously

treated with active therapy over 54 weeks, results for patients initially randomized to placebo for 24 weeks and then switched to metformin 1000 mg b.i.d. for the remaining 30 weeks were included in the safety analysis.

## Results

Of the 1091 patients who were randomized at baseline, 885 (81%) continued into the 30-week continuation phase. A total of 788 (72%) patients completed all 54 weeks of treatment, representing similar proportions (65–77%) of patients from each treatment group (Table 1). The baseline characteristics by treatment group for the randomized population were reported previously[15]. In the present analysis, for the CAPT population, the baseline demographics and efficacy characteristics for the treatment groups were generally well balanced, although the combination therapy groups tended to have higher mean FPG values (Table 2). Over the 54-week study with progressively stricter glycemic rescue criteria, the proportion of patients in the co-administration groups (28% [low dose] and 15% [high dose]) requiring glycemic rescue therapy was lower when compared with their respective monotherapy groups (44% on metformin 500 mg b.i.d., 32% on metformin 1000 mg b.i.d., and 56% on sitagliptin).

### Efficacy

The efficacy results focus on the CAPT population, which included 72% of patients treated with active therapies in both phase A and the continuation phase (range = 59–84% across active treatment groups). The LS mean changes from baseline in $HbA_{1c}$ at week 54 were −1.8%, −1.4%, −1.3%, −1.0% and −0.8% for the high-dose co-administration, low-dose co-administration, metformin 1000 mg b.i.d., metformin 500 mg b.i.d., and sitagliptin groups, respectively (Table 3). Continued improvement in the $HbA_{1c}$ response was noted through week 24, with most groups showing a nadir in $HbA_{1c}$ near week 30 (Figure 1A). Greater reductions in $HbA_{1c}$ from baseline were observed in patients with higher baseline $HbA_{1c}$ levels (Figure 2). The proportions of patients with an $HbA_{1c} < 7\%$ at week 54 were 67%, 48%, 44%, 25%, and 23% for the high-dose co-administration, low-dose co-administration, metformin 1000 mg b.i.d., metformin 500 mg b.i.d., and sitagliptin groups, respectively. Among the patients in the CAPT population with an $HbA_{1c} < 7\%$ in the week 24 analysis, the proportions with an $HbA_{1c} < 7\%$ in the week 54 analysis were 86% (*n*/*N*: 92/107), 80% (57/71), 77% (52/68), 55% (21/38), and 68% (23/34) for the high-dose co-administration, low-dose co-administration, metformin 1000 mg b.i.d., metformin 500 mg b.i.d., and sitagliptin groups, respectively.

For the week 54 completers population, 51% of patients treated with active therapies in both phase A and the continuation phase (range = 32–68% of patients across active-treatment groups) were included in this analysis. Relative to the CAPT analysis, the completers analysis showed larger LS mean $HbA_{1c}$ changes from baseline for all groups at week 54 (−1.9% [95% CI: −2.1, −1.8; $n = 124$] for high-dose co-administration, −1.7% [−1.8, −1.5; $n = 106$] for low-dose co-administration, −1.6% [−1.7, −1.4; $n = 101$] for metformin 1000 mg b.i.d., −1.2% [−1.4, −1.1; $n = 77$] for metformin 500 mg b.i.d., and −1.4% [−1.6, −1.2; $n = 58$] for sitagliptin) (Figure 1B). The proportions of patients in the completers population with an $HbA_{1c} < 7\%$ at week 54 were 77%, 63%, 57%, 35%, and 41% for the high-dose co-administration, low-dose co-administration, metformin 1000 mg b.i.d., metformin 500 mg b.i.d., and sitagliptin groups, respectively.

In the CAPT population, FPG decreased relative to baseline at week 54 in all groups, with larger reductions observed in the co-administration groups compared with their respective monotherapy groups (Table 3 and Figure 3). In the completers analysis, the LS mean FPG changes from baseline were −59.4 mg/dL (95% CI: −64.8, −53.9; $n = 123$) for high-dose co-administration, −49.8 mg/dL (−55.7, −44.0; $n = 109$) for low-dose co-administration, −43.8 mg/dL (−49.8, −37.8; $n = 100$) for metformin 1000 mg b.i.d., −35.6 mg/dL (−42.5, −28.7; $n = 77$) for metformin 500 mg b.i.d., and −26.0 mg/dL (−34.0, −18.1; $n = 58$) for sitagliptin.

Following a standard meal at week 54, 2-hour PPG, total glucose AUC, and the ratio of insulin AUC to glucose AUC were improved with all active treatments relative to baseline in the CAPT population (Table 4). The changes in these parameters with co-administration were larger when compared with the sitagliptin and respective metformin monotherapy groups. Total insulin and C-peptide AUCs were increased relative to baseline with sitagliptin at week 54 (Table 4). In the completers analysis, the LS mean 2-hour PPG changes from baseline were −111.1 mg/dL (95% CI: −119.6, −102.5; $n = 114$) for high-dose co-administration, −96.2 mg/dL (−105.5, −86.9; $n = 98$) for low-dose co-administration, −82.3 mg/dL (−91.7, −72.9; $n = 93$) for metformin 1000 mg b.i.d., −64.3 mg/dL (−75.0, −53.5; $n = 72$) for metformin 500 mg b.i.d., and −66.2 mg/dL (−78.6, −53.8; $n = 54$) for sitagliptin.

***Table 1.*** *Disposition of randomized patients over 54 weeks*

| | Screened $N = 3544$<br>Randomized $n = 1091$* | | | | | |
|---|---|---|---|---|---|---|
| | Placebo/metformin 1000 mg b.i.d. | Sitagliptin 100 mg q.d. | Metformin 500 mg b.i.d. | Metformin 1000 mg b.i.d. | Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. | Sitagliptin 50 mg b.i.d + MF 1000 mg b.i.d. |
| Randomized, *n* | 176 | 179 | 182 | 182 | 190 | 182 |
| Discontinued prior to continuation phase, *n* | 53 | 38 | 35 | 29 | 30 | 21 |
| Entered continuation phase†, *n* | 123 | 141 | 147 | 153 | 160 | 161 |
| Discontinued in continuation phase, *n* | 8 | 19 | 21 | 17 | 12 | 20 |
| Reasons for discontinuations over 54 weeks | | | | | | |
| Clinical AE, *n* | 9 | 8 | 7 | 11 | 6 | 3 |
| Laboratory AE, *n* | 2 | 4 | 2 | 0 | 0 | 2 |
| Lack of efficacy‡, *n* | 14 | 11 | 14 | 7 | 4 | 3 |
| Lost to follow-up, *n* | 9 | 5 | 4 | 7 | 5 | 10 |
| Other, *n* | 5 | 4 | 3 | 0 | 0 | 5 |
| Moved, *n* | 1 | 0 | 1 | 1 | 2 | 3 |
| Withdrew consent, *n* | 15 | 17 | 16 | 16 | 15 | 10 |
| Met protocol-specific discontinuation criteria, *n* | 3 | 2 | 5 | 2 | 6 | 5 |
| Protocol deviation, *n* | 3 | 6 | 4 | 2 | 4 | 0 |
| Completed, *n* (%) | 115 (65) | 122 (68) | 126 (69) | 136 (75) | 148 (78) | 141 (77) |

*Disposition of patients not randomized published in Goldstein *et al.*[15]
†Includes patients who did and did not initiate glycemic rescue therapy in phase A
‡Includes patients not meeting the progressively stricter protocol-specified glycemic criteria and/or not meeting the investigator's expectations of glycemic improvement
MF, metformin

***Table 2.*** *Baseline characteristics of patients who entered the 30-week continuation phase without initiating glycemic rescue therapy during the initial 24-week placebo-controlled phase (continuation APT population)*

| Parameter | Placebo/MF 1000 mg b.i.d. $N = 78$ | Sitagliptin 100 mg q.d. $N = 106$ | Metformin 500 mg b.i.d. $N = 122$ | Metformin 1000 mg b.i.d. $N = 137$ | Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. $N = 148$ | Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. $N = 157$ |
|---|---|---|---|---|---|---|
| Age, years | 53.6 ± 11.3 | 53.5 ± 9.1 | 53.7 ± 9.9 | 54.2 ± 9.5 | 53.7 ± 10.0 | 53.6 ± 9.4 |
| Males, *n* (%) | 38 (49) | 55 (52) | 58 (48) | 62 (45) | 78 (53) | 65 (41) |
| BMI, kg/m$^2$ | 32 ± 7 | 31 ± 6 | 32 ± 7 | 32 ± 7 | 32 ± 7 | 32 ± 6 |
| $HbA_{1c}$,%(range) | 8.4 ± 0.9 (7.0–10.6) | 8.7 ± 1.0 (7.2–11.4) | 8.7 ± 1.0 (7.2–11.0) | 8.5 ± 0.8 (6.9–10.9) | 8.8 ± 1.0 (6.8–11.0) | 8.7 ± 0.9 (6.6–11.2) |
| FPG, mg/dL | 174 ± 41 | 183 ± 39 | 189 ± 41 | 188 ± 43 | 198 ± 47 | 195 ± 49 |
| Duration of T2DM, years | 3.8 ± 5.0 | 3.9 ± 4.6 | 4.1 ± 3.8 | 4.1 ± 4.0 | 4.1 ± 4.4 | 4.6 ± 4.4 |

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

Measures of $\beta$-cell function, the proinsulin/insulin ratio and HOMA-$\beta$, were improved relative to baseline at week 54 in all treatment groups, with larger improvement observed in the co-administration groups relative to their respective monotherapy groups (Table 3). HOMA-IR was similarly reduced relative to baseline in the co-administration groups compared with their respective metformin monotherapy group (Table 3).

Co-administration of sitagliptin and metformin generally showed small numeric improvements compared with baseline and compared with one or both monotherapies for TC, LDL-C, non-HDL-C, and triglycerides (Table 5). Changes from baseline in HDL-C were similar between the co-administration group and its respective metformin monotherapy group. Treatment with sitagliptin 100 mg q.d. had a generally neutral effect on lipids (Table 5). Similar within-group results were observed in the 24-week placebo-controlled period (Table 6).

After 54 weeks (CAPT population), body weight was reduced relative to baseline in the co-administration groups (low-dose group ($n = 143$): −0.7 kg [95% CI: −1.3, −0.0]; high-dose group ($n = 153$): −1.7 kg [−2.4, −1.1]) and in the metformin monotherapy groups (500 mg b.i.d. group ($n = 116$): −1.0 kg [95% CI: −1.7, −0.3]; 1000 mg b.i.d. group ($n = 132$): −1.5 kg [−2.2, −0.8]). There was no change from baseline for patients in the sitagliptin group ($n = 100$; 0.6 kg [95% CI: −0.2, 1.4]).

## Safety/tolerability

After 54 weeks of treatment, the incidences of adverse experiences were generally similar in the co-administration groups and their respective metformin monotherapy groups (Table 7). Lower incidences were observed in the sitagliptin and placebo/metformin groups relative to the other groups (Table 7). The incidences of drug-related adverse experiences were generally similar between the co-administration and the metformin monotherapy groups, with the lowest incidence observed in the sitagliptin group. The incidences of serious adverse experiences were slightly higher in the placebo/metformin switch group compared with the other groups. A single serious drug-related adverse experience was reported over the 54 weeks: ketoacidosis in a placebo-treated patient who discontinued treatment, reported in phase A[15]. Over the 54 weeks, two patients died: one patient in the placebo group died of sudden cardiac death during the initial 24 weeks of this study and the other patient in the high-dose co-administration group died of an electrical shock during the continuation phase. One patient who discontinued from the low-dose metformin group during

***Table 3.*** *Efficacy endpoints for groups receiving active therapy in both phase A and in the continuation phase (continuation APT population)*

| Parameter | Sitagliptin 100 mg q.d. | Metformin 500 mg b.i.d. | Metformin 1000 mg b.i.d. | Sitagliptin 50 mg mg b.i.d. + MF 500 mg b.i.d. | Sitagliptin 50 mg mg b.i.d. + MF 1000 mg b.i.d. |
|---|---|---|---|---|---|
| $HbA_{1c}$ (%), *n* | 106 | 117 | 134 | 147 | 153 |
| Baseline | 8.7 ± 1.0 | 8.7 ± 0.9 | 8.5 ± 0.8 | 8.8 ± 1.0 | 8.7 ± 0.9 |
| Week 54 | 7.8 ± 1.2 | 7.7 ± 0.9 | 7.3 ± 1.0 | 7.3 ± 1.1 | 6.9 ± 1.0 |
| Change from baseline | −0.8 (−1.0, −0.6) | −1.0 (−1.2, −0.8) | −1.3 (−1.5, −1.2) | −1.4 (−1.6, −1.3) | −1.8 (−2.0, −1.7) |
| FPG (mg/dL), *n* | 105 | 117 | 134 | 146 | 153 |
| Baseline | 183.0 ± 39.3 | 188.1 ± 41.3 | 187.6 ± 43.3 | 197.2 ± 46.9 | 195.1 ± 49.2 |
| Week 54 | 171.2 ± 44.2 | 159.8 ± 40.9 | 148.9 ± 40.5 | 149.5 ± 43.1 | 135.4 ± 39.3 |
| Change from baseline | −16.0 (−23.2, −8.7) | −29.0 (−35.9, −22.2) | −39.6 (−46.0, −33.2) | −42.5 (−48.6, −36.3) | −55.6 (−61.6, −49.6) |
| Fasting proinsulin (pmol/L), *n* | 61 | 75 | 100 | 115 | 131 |
| Baseline | 26.4 ± 24.5 | 33.5 ± 32.4 | 36.7 ± 32.9 | 35.1 ± 35.2 | 37.8 ± 31.2 |
| Week 54 | 27.1 ± 27.0 | 23.8 ± 21.6 | 22.4 ± 23.0 | 22.9 ± 22.2 | 22.9 ± 27.3 |
| Change from baseline | −3.7 (−8.4, 1.1) | −10.7 (−15.0, −6.5) | −13.4 (−17.1, −9.7) | −12.3 (−15.7, −8.8) | −13.4 (−16.6, −10.2) |
| Proinsulin/insulin ratio, *n* | 61 | 75 | 100 | 114 | 130 |
| Baseline | 0.41 ± 0.18 | 0.43 ± 0.30 | 0.45 ± 0.21 | 0.49 ± 0.31 | 0.50 ± 0.37 |
| Week 54 | 0.36 ± 0.31 | 0.31 ± 0.21 | 0.29 ± 0.19 | 0.28 ± 0.23 | 0.26 ± 0.20 |
| Change from baseline | −0.09 (−0.14, −0.04) | −0.14 (−0.19, −0.10) | −0.16 (−0.20, −0.13) | −0.19 (−0.22, −0.16) | −0.21 (−0.24, −0.18) |
| HOMA-$\beta$, *n* | 88 | 102 | 126 | 133 | 143 |
| Baseline | 40.8 ± 33.1 | 47.5 ± 38.4 | 44.3 ± 35.1 | 42.0 ± 38.6 | 44.0 ± 35.2 |
| Week 54 | 58.4 ± 54.5 | 56.8 ± 39.5 | 61.9 ± 46.7 | 76.3 ± 63.9 | 86.1 ± 90.0 |
| Change from baseline | 18.1 (7.3, 28.9) | 9.7 (−0.3, 19.7) | 17.5 (8.5, 26.5) | 34.7 (25.9, 43.5) | 41.9 (33.5, 50.4) |
| HOMA-IR, *n* | 88 | 102 | 126 | 133 | 143 |
| Baseline | 5.5 ± 4.2 | 6.3 ± 4.8 | 6.2 ± 4.4 | 6.3 ± 5.6 | 6.6 ± 5.6 |
| Week 54 | 6.2 ± 6.0 | 5.4 ± 4.7 | 4.6 ± 3.3 | 5.6 ± 4.6 | 4.8 ± 4.6 |
| Change from baseline | 0.3 (−0.5, 1.1) | −0.9 (−1.6, −0.1) | −1.6 (−2.3, −0.9) | −0.7 (−1.3, −0.0) | −1.6 (−2.2, −0.9) |

*n* = number of patients with evaluable data included in the analysis; baseline and week 54 data are expressed as mean ± standard deviation; change from baseline data are expressed as LS mean change (95% CI)

MF, metformin; FPG, fasting plasma glucose; HOMA-$\beta$, homeostasis model of assessment for $\beta$-cell function; HOMA-IR, homeostasis model of assessment for insulin resistance

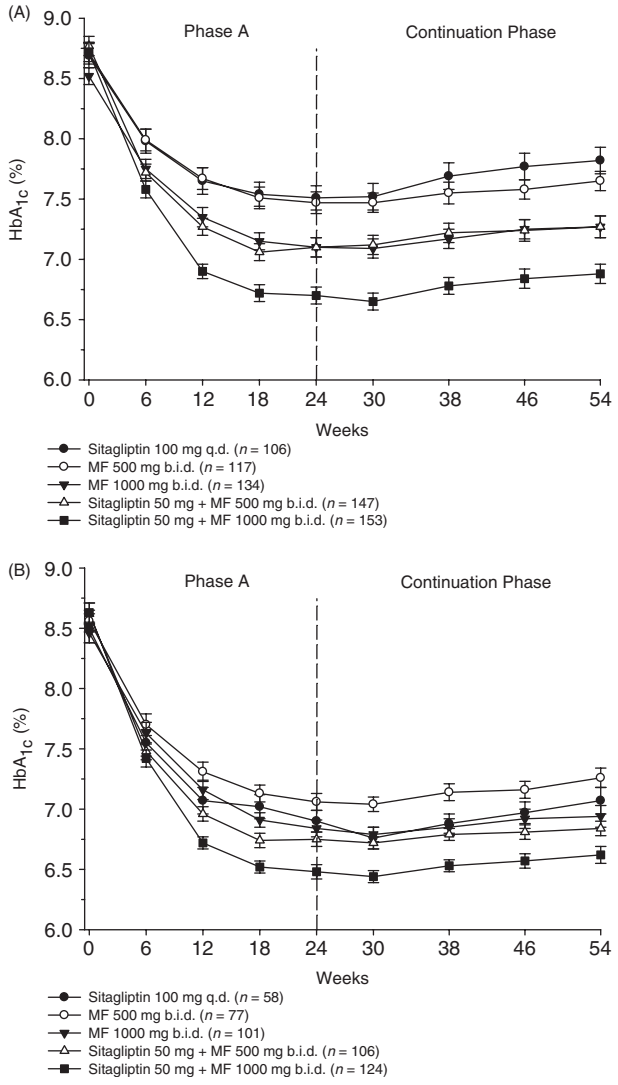


***Figure 1.*** *$HbA_{1c}$ over time (mean ± standard error). A. continuation APT population, B. week 54 completers population*

phase A due to esophageal carcinoma was subsequently reported to have died during the study period. An additional patient died of a cerebral hemorrhage prior to randomization. The proportions of patients discontinuing treatment due to an adverse experience or a drug-related adverse experience were low and similar across groups (Table 7).

The incidences of hypoglycemia were low (1–3%) and similar across groups (Table 7). Two patients in the metformin 500 mg b.i.d. group had hypoglycemia episodes that required non-medical assistance. No episode of hypoglycemia exhibited marked severity (i.e., altered consciousness or the requirement for medical assistance). The proportions of patients reporting gastrointestinal adverse experiences were similar between the co-administration and metformin monotherapy groups (Table 7). Similar findings were noted for the prespecified, select, gastrointestinal adverse experiences (Table 7).

## Discussion

Sitagliptin inhibits the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[16], the incretin hormones involved in glucose homeostasis[17]. Sitagliptin lowers blood glucose through its effects on incretins by enhancing insulin release and reducing glucagon secretion following a meal in patients with type 2 diabetes[18]. In addition to improving glycemic control, sitagliptin has been shown to improve $\beta$-cell function using surrogate markers (HOMA-$\beta$ and proinsulin/insulin ratio) and a model-based approach[4,19–21]. Metformin suppresses hepatic glucose output and improves insulin resistance[22]. There is also evidence that metformin may increase total GLP-1 release[23,24]. Based on these complementary effects on glucoregulation and the safety profiles of each agent, initial combination therapy with sitagliptin and metformin might be considered a useful clinical therapy for patients with type 2 diabetes. This was confirmed in a 24-week placebo-controlled trial demonstrating that the combination of sitagliptin and metformin was generally well-tolerated and produced additive and substantial improvement in overall glycemic control[15].

The 24-week study, previously reported[15], was continued for an additional 30 weeks to provide information about the longer-term efficacy and safety results for the initial combination therapy of sitagliptin and metformin. In this 54-week study, the combinations of sitagliptin and metformin provided substantial reductions (1.4% and 1.8% for the low and high doses, respectively) in $HbA_{1c}$. In the completers analyses, numerically greater glycemic responses were observed in all treatment groups compared with the CAPT analyses. Consistent with the finding that baseline $HbA_{1c}$ impacts treatment response[25], changes from a baseline at week 54 ranged from −2.0% in the sitagliptin group to −3.1% in the high-dose combination group in a subgroup of patients with baseline $HbA_{1c}$ ≥10%. The substantial reduction in $HbA_{1c}$ enabled two-thirds of the continuation patients in the high-dose combination group to reach the $HbA_{1c}$ target of <7.0% at week 54. Furthermore, among CAPT patients in the high-dose combination group who had an $HbA_{1c}$ <7.0% at week 24, 86% had an $HbA_{1c}$ <7.0% at week 54. Importantly, treatment with initial combination therapy was durable, as demonstrated by the $HbA_{1c}$ and FPG curves over time. Although the combination treatments have greater effects on $HbA_{1c}$, the curves over time have similar shapes, suggesting similar durability among treatments.

Substantial reductions in glucose in the fasting and postprandial state were observed at week 54 in all

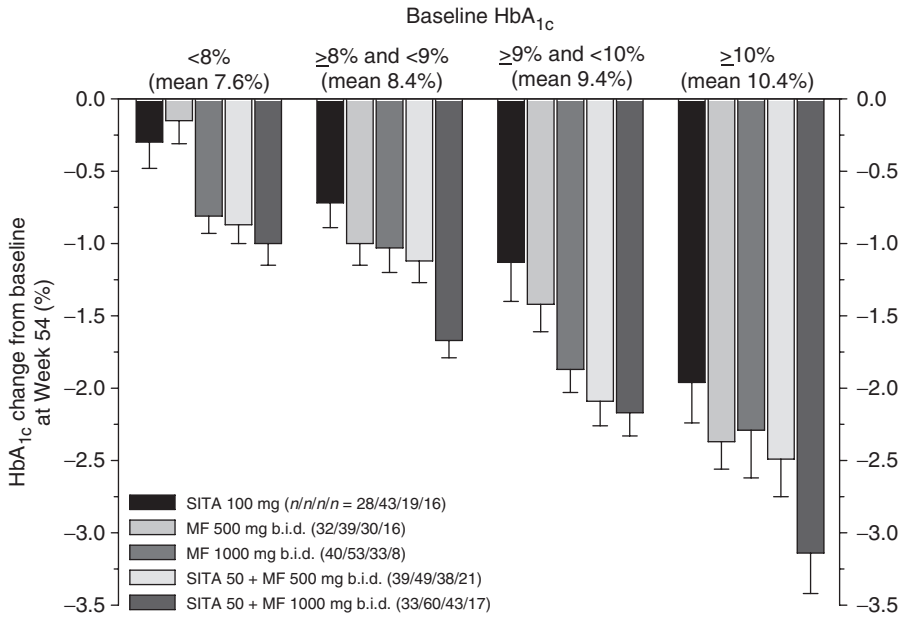


***Figure 2.*** *Mean change (SE) from baseline in $HbA_{1c}$ by baseline $HbA_{1c}$ subgroup (*n *per subgroup for continuation APT population within legend). SITA, sitagliptin; MF, metformin*

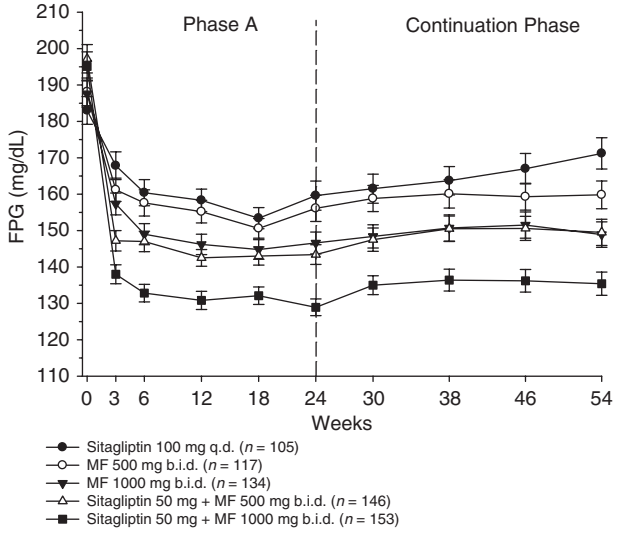


***Figure 3.*** *Fasting plasma glucose (FPG) over time (mean ± standard error; continuation APT population)*

groups with the largest reductions in the combination groups. Furthermore, the combination of sitagliptin and metformin improved measures of $\beta$-cell function (e.g., HOMA-$\beta$; P/I ratio) and insulin resistance. The ratio of insulin secreted per unit glucose following a standard meal was also increased with combined treatment, suggesting enhanced $\beta$-cell responsiveness. Collectively, these improvements demonstrate the complementary mechanisms of action of sitagliptin and metformin, which together target the three core pathophysiologic defects of type 2 diabetes: declining $\beta$-cell function, increased insulin resistance, and excess hepatic glucose output[26,27].

All treatments were generally well tolerated for 54 weeks. The additional 30 weeks of treatment extend and support the findings reported for the 24-week placebo-controlled portion of this study[15]. Despite the substantial and durable improvements in glycemic control observed with all active treatments, the incidence of hypoglycemia was low and similar across the treatment groups over 54 weeks. The incidences of overall and select gastrointestinal adverse experiences were similar for the combination and metformin monotherapy groups. Because some incretin-based therapies have been shown to have gastrointestinal side-effects[17], it is noteworthy that sitagliptin did not exacerbate the gastrointestinal side-effects commonly associated with metformin[28], even when used as initial therapy. The combination of sitagliptin and metformin provided weight loss from baseline similar to that observed with metformin monotherapy, whereas sitagliptin alone was weight neutral over 54 weeks. This suggests that sitagliptin does not affect the weight loss usually observed with metformin[28].

This study had some limitations. First, the patient population evaluated was not a randomized population in that this study evaluated randomized patients who had a baseline measurement, did not receive glycemic rescue therapy in phase A, took at least one dose of study medication in the continuation phase, and had at least one efficacy measurement during the continuation phase. Second, because the baseline $HbA_{1c}$ inclusion criteria ranged from 7.5 to 11% and the glycemic rescue criterion was an $HbA_{1c} > 8\%$ after week 24, there was a greater likelihood of glycemic rescue in the monotherapy groups; this led to more missing

***Table 4.*** *Postprandial responses to a standard meal for groups receiving active therapy in both phase A and in the continuation phase (CAPT population)*

| Parameter | Sitagliptin 100 mg q.d. | Metformin 500 mg b.i.d. | Metformin 1000 mg b.i.d. | Sitagliptin 50 mg b.i.d + MF 500 mg b.i.d. | Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. |
|---|---|---|---|---|---|
| 2-hour PPG (mg/dL), *n* | 87 | 92 | 116 | 121 | 132 |
| Baseline | 260.1 ± 75.8 | 268.7 ± 63.9 | 276.5 ± 77.4 | 281.6 ± 78.8 | 280.3 ± 77.3 |
| Week 54 | 222.4 ± 69.9 | 212.7 ± 61.1 | 197.2 ± 55.9 | 186.2 ± 60.2 | 166.6 ± 56.1 |
| Change from baseline | −45.9 (−57.2, −34.6) | −58.6 (−69.6, −47.6) | −76.3 (−86.1, −66.5) | −89.6 (−99.2, −80.0) | −107.9 (−117.1, −98.7) |
| Glucose AUC (mg·h/dL), *n* | 86 | 94 | 112 | 123 | 129 |
| Baseline | 492.0 ± 106.7 | 502.0 ± 96.8 | 519.9 ± 116.2 | 523.0 ± 123.0 | 521.7 ± 122.5 |
| Week 54 | 437.0 ± 112.8 | 418.9 ± 94.4 | 382.9 ± 93.4 | 369.1 ± 98.5 | 331.8 ± 92.6 |
| Change from baseline | −67.7 (−86.7, −48.7) | −89.0 (−107.1, −70.9) | −129.5 (−146.1, −112.9) | −145.7 (−161.5, −129.8) | −180.6 (−196.1, −165.1) |
| Insulin AUC (μIU·h/mL), *n* | 78 | 87 | 104 | 105 | 118 |
| Baseline | 75.9 ± 48.6 | 89.7 ± 53.1 | 85.6 ± 51.0 | 83.1 ± 61.0 | 77.2 ± 50.4 |
| Week 54 | 92.4 ± 55.8 | 91.4 ± 63.7 | 80.5 ± 50.2 | 88.3 ± 52.7 | 81.0 ± 45.6 |
| Change from baseline | 15.4 (7.6, 23.2) | 4.1 (−3.3, 11.5) | −4.7 (−11.5, 2.0) | 5.6 (−1.1, 12.3) | 1.9 (−4.5, 8.2) |
| C-peptide AUC (ng·h/mL), *n* | 86 | 96 | 116 | 120 | 129 |
| Baseline | 10.4 ± 4.4 | 11.0 ± 4.2 | 11.0 ± 4.2 | 10.1 ± 4.4 | 10.4 ± 4.4 |
| Week 54 | 11.6 ± 4.0 | 10.9 ± 4.5 | 10.4 ± 4.0 | 10.8 ± 4.1 | 10.6 ± 4.5 |
| Change from baseline | 1.2 (0.7, 1.8) | 0.1 (−0.4, 0.6) | −0.5 (−1.0, −0.1) | 0.6 (0.2, 1.1) | 0.1 (−0.4, 0.5) |
| Insulin AUC/glucose AUC, *n* | 77 | 85 | 99 | 105 | 114 |
| Baseline | 0.17 ± 0.12 | 0.19 ± 0.13 | 0.19 ± 0.15 | 0.18 ± 0.15 | 0.17 ± 0.13 |
| Week 54 | 0.23 ± 0.17 | 0.23 ± 0.18 | 0.23 ± 0.15 | 0.25 ± 0.15 | 0.26 ± 0.15 |
| Change from baseline | 0.06 (0.04, 0.09) | 0.05 (0.02, 0.07) | 0.04 (0.02, 0.06) | 0.08 (0.06, 0.10) | 0.09 (0.07, 0.11) |

*n* = number of patients with evaluable data included in the analysis; baseline and week 54 data are expressed as mean ± standard deviation; change from baseline data are expressed as LS mean change (95% CI)
MF, metformin; PPG, postprandial plasma glucose; AUC, area under the concentration–time curve

***Table 5.*** *Fasting lipid profiles for groups receiving active therapy in both phase A and in the continuation phase (CAPT population)*

| Parameter | Sitagliptin 100 mg q.d. | Metformin 500 mg b.i.d | Metformin 1000 mg b.i.d. | Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. | Sitagliptin 50 mg b.i.d + MF 1000 mg b.i.d. |
|---|---|---|---|---|---|
| TC (mg/dL), *n* | 96 | 111 | 130 | 139 | 149 |
| Baseline | 193.0 ± 42.3 | 186.4 ± 41.6 | 188.8 ± 42.0 | 195.7 ± 47.2 | 191.3 ± 41.6 |
| Week 54 | 193.5 ± 42.3 | 186.4 ± 39.7 | 188.6 ± 39.5 | 189.1 ± 43.2 | 182.5 ± 39.6 |
| % change from baseline | 1.8 (−1.2, 4.8) | 0.3 (−2.5, 3.1) | 1.5 (−1.1, 4.0) | −1.3 (−3.8, 1.2) | −3.0 (−5.4, −0.6) |
| HDL-C (mg/dL), *n* | 95 | 111 | 130 | 137 | 149 |
| Baseline | 42.0 ± 9.5 | 42.8 ± 9.0 | 43.3 ± 10.8 | 43.7 ± 9.3 | 43.9 ± 11.1 |
| Week 54 | 42.1 ± 9.1 | 45.2 ± 11.0 | 46.4 ± 12.0 | 45.4 ± 11.3 | 46.6 ± 13.5 |
| % change from baseline | 0.9 (−3.0, 4.8) | 5.8 (2.3, 9.4) | 7.9 (4.6, 11.2) | 5.1 (1.9, 8.3) | 7.2 (4.1, 10.3) |
| LDL-C (mg/dL), *n* | 94 | 111 | 128 | 136 | 149 |
| Baseline | 115.1 ± 35.1 | 105.3 ± 32.3 | 107.3 ± 33.4 | 115.1 ± 39.1 | 112.2 ± 35.1 |
| Week 54 | 113.5 ± 34.5 | 102.3 ± 33.6 | 102.5 ± 36.7 | 110.1 ± 37.1 | 103.7 ± 33.5 |
| % change from baseline | 1.2 (−4.5, 6.9) | −2.0 (−7.3, 3.2) | −0.9 (−5.8, 3.9) | −0.3 (−5.1, 4.4) | −4.1 (−8.6, 0.4) |
| Non-HDL-C (mg/dL), *n* | 95 | 111 | 130 | 137 | 149 |
| Baseline | 150.5 ± 40.3 | 143.6 ± 41.4 | 145.5 ± 42.8 | 151.4 ± 47.3 | 147.3 ± 40.4 |
| Week 54 | 151.1 ± 42.5 | 141.3 ± 39.6 | 142.2 ± 40.2 | 143.4 ± 42.8 | 135.9 ± 39.0 |
| % change from baseline | 2.7 (−1.3, 6.8) | −1.0 (−4.8, 2.7) | 0.2 (−3.2, 3.7) | −2.5 (−5.9, 0.8) | −5.7 (−8.9, −2.4) |
| Triglycerides (mg/dL), *n* | 96 | 111 | 130 | 139 | 149 |
| Baseline* | 147.5 ± 87.4 | 167.0 ± 104.2 | 150.0 ± 92.1 | 155.0 ± 104.2 | 158.0 ± 97.7 |
| Week 54* | 162.5 ± 94.0 | 173.0 ± 120.0 | 174.5 ± 124.7 | 147.0 ± 95.8 | 143.0 ± 94.0 |
| Median % change from baseline | 0.4 (−8.9, 9.7) | 4.9 (−3.3, 13.0) | 8.4 (0.5, 16.4) | −4.6 (−11.9, 2.7) | −7.1 (−13.9, −0.2) |

*n* = number of patients with evaluable data included in the analysis; baseline and week 54 data are expressed as mean ± standard deviation (SD) or *median ± SD for median; % change from baseline data are expressed as LS mean percent change (95% CI) or median percent change (95% CI)
MF, metformin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

***Table 6.*** *Fasting lipid profiles at week 24 during the placebo-controlled phase of this study (phase A)*

| Parameter | Placebo | Sitagliptin 100 mg q.d. | Metformin 500 mg b.i.d. | Metformin1000 mg b.i.d. | Sitagliptin 50 mg b.i.d. + MF 500 mg b.i.d. | Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. |
|---|---|---|---|---|---|---|
| TC (mg/dL), *n* | 143 | 151 | 162 | 159 | 172 | 166 |
| Baseline | 182.3 ± 34.7 | 192.5 ± 48.4 | 190.0 ± 43.4 | 190.1 ± 42.0 | 195.2 ± 44.5 | 192.8 ± 41.7 |
| Week 24 | 188.5 ± 40.4 | 195.2 ± 51.3 | 188.5 ± 37.1 | 190.7 ± 42.7 | 192.0 ± 38.5 | 185.7 ± 38.3 |
| % change from baseline | 2.8 (0.3, 5.3) | 3.1 (0.7, 5.5) | 1.1 (−1.3, 3.4) | 1.8 (−0.6, 4.1) | 0.7 (−1.6, 3.0) | −2.1 (−4.4, 0.2)‡ |
| % change from placebo | — | 0.3 (−3.2, 3.8) | −1.8 (−5.2, 1.6) | −1.1 (−4.5, 2.4) | −2.1 (−5.5, 1.2) | −4.9 (−8.3, −1.5)† |
| HDL-C (mg/dL), *n* | 143 | 150 | 160 | 160 | 171 | 166 |
| Baseline | 42.9 ± 9.5 | 42.7 ± 9.5 | 43.2 ± 9.4 | 42.7 ± 10.5 | 43.1 ± 9.2 | 44.2 ± 10.9 |
| Week 24 | 44.2 ± 9.4 | 43.2 ± 10.1 | 44.6 ± 10.4 | 45.0 ± 12.4 | 44.3 ± 10.4 | 46.0 ± 12.2 |
| % change from baseline | 4.2 (1.6, 6.7) | 1.8 (−0.7, 4.3) | 3.7 (1.3, 6.1) | 5.9 (3.5, 8.3) | 3.6 (1.3, 6.0) | 5.8 (3.4, 8.1)§ |
| % change from placebo | — | −2.4 (−6.0, 1.2) | −0.5 (−4.0, 3.0) | 1.7 (−1.8, 5.2) | −0.5 (−4.0, 2.9) | 1.6 (−1.9, 5.1) |
| LDL-C (mg/dL), *n* | 143 | 149 | 159 | 157 | 169 | 165 |
| Baseline | 105.5 ± 31.5 | 111.4 ± 35.1 | 106.8 ± 34.2 | 108.2 ± 34.4 | 114.7 ± 37.1 | 113.1 ± 35.5 |
| Week 24 | 110.3 ± 37.0 | 113.0 ± 35.3 | 103.6 ± 31.5 | 104.6 ± 33.8 | 111.0 ± 32.4 | 107.7 ± 32.1 |
| % change from baseline | 5.1 (0.5, 9.7) | 4.4 (−0.1, 8.9) | 0.5 (−3.9, 4.9) | 1.7 (−2.7, 6.1) | 1.4 (−2.8, 5.6) | −1.1 (−5.4, 3.1) |
| % change from placebo | — | −0.7 (−7.1, 5.8) | −4.6 (−10.9, 1.8) | −3.4 (−9.8, 3.0) | −3.7 (−10.0, 2.6) | −6.2 (−12.5, 0.1) |
| Non-HDL-C (mg/dL), *n* | 143 | 150 | 160 | 159 | 171 | 166 |
| Baseline | 139.4 ± 33.9 | 149.5 ± 47.2 | 146.7 ± 43.4 | 147.5 ± 42.5 | 152.0 ± 44.1 | 148.6 ± 40.4 |
| Week 24 | 144.4 ± 39.8 | 151.9 ± 51.2 | 143.9 ± 36.4 | 145.7 ± 42.1 | 147.5 ± 39.4 | 139.7 ± 37.7 |
| % change from baseline | 3.0 (−0.4, 6.3) | 4.2 (0.9, 7.4) | 1.5 (−1.6, 4.7) | 1.3 (−1.9, 4.4) | 0.3 (−2.8, 3.3) | −3.9 (−7.0, −0.8)‡ |
| % change from placebo | — | 1.2 (−3.5, 5.9) | −1.4 (−6.0, 3.1) | −1.7 (−6.3, 2.9) | −2.7 (−7.3, 1.8) | −6.9 (−11.5, −2.4)† |
| Triglycerides (mg/dL), *n* | 143 | 151 | 163 | 159 | 172 | 166 |
| Baseline* | 150.0 ± 83.7 | 149.0 ± 97.7 | 172.0 ± 113.5 | 154.0 ± 110.7 | 157.0 ± 103.7 | 158.0 ± 97.7 |
| Week 24* | 150.0 ± 82.8 | 155.0 ± 113.5 | 179.0 ± 107.0 | 182.0 ± 126.5 | 148.0 ± 91.2 | 142.5 ± 82.8 |
| Median % change from baseline | 1.1 (−5.1, 7.3) | −1.6 (−7.5, 4.3) | 1.1 (−6.5, 8.7) | 6.7 (−1.8, 15.3) | −3.7 (−9.2, 1.9) | −10.1 (−15.6, −4.7) |
| Median % change from placebo | — | 0.1 (−7.2, 7.6) | 4.3 (−3.3, 12.3) | 7.8 (−0.6, 16.4) | −3.8 (−10.8, 3.2) | −9.7 (−16.3, −2.9) |

*n* = number of patients with evaluable data included in the analysis; baseline and week 24 data are expressed as mean ± standard deviation (SD) or *median ± SD for median; % change from baseline or placebo data are expressed as LS mean percent change (95% CI) or median percent change (95% CI)
†$p \leq 0.05$ for the between-group difference relative to placebo
‡$p \leq 0.05$ for the between-group difference comparing co-administration and both of its respective components
§$p \leq 0.05$ for the between-group difference comparing co-administration and sitagliptin 100 mg q.d.
Description of the statistical methods used to evaluate these data is published in Goldstein *et al.*[15]
MF, metformin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

***Table 7.*** *Summary of clinical adverse experiences through 54 weeks (APaT population)*

| Number (%) of patients* | Placebo/ MF 1000 mg b.i.d.† $N=176$ | Sitagliptin 100 mg q.d. $N=179$ | Metformin 500 mg b.i.d $N=182$ | Metformin 1000 mg b.i.d. $N=182$ | Sitagliptin 50 mg b.i.d + MF 500 mg b.i.d. $N=190$ | Sitagliptin 50 mg b.i.d. + MF 1000 mg b.i.d. $N=182$ |
|---|---|---|---|---|---|---|
| One or more AEs | 97 (55) | 105 (59) | 114 (63) | 129 (71) | 130 (68) | 126 (69) |
| Drug-related AEs‡ | 21 (12) | 15 (8) | 24 (13) | 32 (18) | 29 (15) | 34 (19) |
| Serious AEs (SAEs) | 13 (7) | 12 (7) | 6 (3) | 3 (2) | 7 (4) | 7 (4) |
| Drug-related SAEs‡ | 1 (<1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Who died | 1 (<1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (<1) |
| Discontinued due to AEs | 9 (5) | 5 (3) | 6 (3) | 7 (4) | 6 (3) | 4 (2) |
| Discontinued due to drug-related AEs | 2 (1) | 0 (0) | 2 (1) | 5 (3) | 3 (2) | 2 (1) |
| Discontinued due to SAEs | 7 (4) | 4 (2) | 4 (2) | 1 (<1) | 1 (<1) | 0 (0) |
| Discontinued due to drug-related SAEs | 1 (<1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *Special AEs of Clinical Interest* | | | | | | |
| Hypoglycemia | 4 (2) | 2 (1) | 2 (1) | 2 (1) | 4 (2) | 5 (3) |
| All gastrointestinal AEs | 28 (16) | 36 (20) | 37 (20) | 57 (31) | 50 (26) | 53 (29) |
| Selected gastroin testinal AEs | | | | | | |
| Diarrhea | 11 (6) | 7 (4) | 13 (7) | 22 (12) | 17 (9) | 23 (13) |
| Nausea | 4 (2) | 2 (1) | 6 (3) | 18 (10) | 10 (5) | 11 (6) |
| Abdominal pain§ | 5 (3) | 8 (5) | 7 (4) | 10 (6) | 5 (3) | 7 (4) |
| Vomiting | 1 (1) | 1 (1) | 0 (0) | 6 (3) | 4 (2) | 7 (4) |

*Excludes data after initiation of glycemic [glyburide/glibenclamide] rescue therapy
†Patients were switched from placebo to metformin 1000 mg b.i.d. at week 24
‡Considered by the investigator to be drug-related
§Including abdominal pain, abdominal discomfort, upper abdominal pain, and stomach discomfort
MF, metformin, AE, adverse experiences

data in the CAPT analysis and fewer patients contributing to the completers analysis in the monotherapy groups. The present study assesses the efficacy and safety of these treatments for 54 weeks. This study has been extended for an additional 50 weeks to further assess the safety and efficacy of combination therapy with sitagliptin and metformin.

## Conclusions

In this study of patients with type 2 diabetes and inadequate glycemic control on diet and exercise, therapy with sitagliptin, metformin, or the combination of sitagliptin and metformin provided substantial and durable glycemic control, improved markers of $\beta$-cell function, and was generally well-tolerated over 54 weeks.

## Acknowledgments

***Declaration of interest:*** The study was funded by Merck & Co., Inc., Whitehouse Station, NJ, USA. A list of study investigators was previously published in Goldstein *et al.*[15].

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

## References

1. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43
2. Turner RC, Cull CA, Frighi V, et al. 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;281:2005-12
3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic treatment of Diabetes. Can J Diabetes 2008;32(Suppl 1):S53-S61
4. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006; 29:2632-7
5. Raz I, Hanefeld M, Xu L, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia 2006;49:2564-71
6. Hermansen K, Kipnes M, Luo E, et al. 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. Diabetes Obes Metab 2007 26;9:733-45
7. Hanefeld M, Herman GA, Wu M, et al. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Curr Med Res Opin 2007;23:1329-39
8. Nonaka K, Kakikawa T, Sato A, et al. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2008;79:291-8
9. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9:194-205
10. Rosenstock J, Brazg R, Andryuk PJ, et al. 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;28:1556-68
11. Scott R, Wu M, Sanchez M, et al. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract 2007;61:171-80
12. Raz I, Chen Y, Wu M, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin 2008;24:537-50
13. Scott R, Loeys T, Davies MJ, et al. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2008;10:959-69
14. Williams-Herman D, Round E, Swern AS, et al. Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis. BMC Endocr Disord 2008;8:14
15. Goldstein BJ, Feinglos MN, Lunceford JK, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007;30: 1979-87
16. Herman GA, Stein PP, Thornberry NA, et al. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: focus on sitagliptin. Clin Pharmacol Ther 2007;81:761-7
17. Drucker DJ, Nauck MA. GLP-1R agonists (incretin mimetics) and DPP-4 inhibitors (incretin enhancers) for the treatment of type 2 diabetes. Lancet 2006;368:1696-705
18. 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 following an oral glucose tolerance test in patients with type 2 diabetes. J Clin Endocrinol Metab 2006;91:4612-19
19. Charbonnel B, Karasik A, Liu J, et al. 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;29:2638-43
20. Xu L, Dalla Man C, Charbonnel B, et al. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on beta-cell function in patients with type 2 diabetes: a model-based approach. Diabetes Obes Metab 2008 May;12; doi: 10.1111/j.1463-1326.2008.00887.x
21. Brazg R, Xu L, Dalla Man C, et al. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-hour glycemic control and $\beta$-cell function in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:186-93
22. Scarpello JH, Howlett HC, Metformin therapy and clinical uses. Diab Vasc Dis Res 2008;5:157-67
23. Mannucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care 2001;24: 489-94
24. Migoya EM, Miller J, Larson P, et al. Sitagliptin, a selective DPP-4 inhibitor, and metformin have complementary effects to increase active GLP-1 concentrations (abstract). Diabetes 2007;56(Suppl 1):A74

25. Bloomgarden ZT, Dodis R, Viscoli CM, et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 2006;29:2137-9
26. Basu A, Shah P, Nielsen M, et al. Effects of type 2 diabetes on the regulation of hepatic glucose metabolism. J Investig Med 2004;52:366-74
27. Bergman RN, Finegood DT, Kahn SE. The evolution of beta-cell dysfunction and insulin resistance in type 2 diabetes. Eur J Clin Invest 2002;32(Suppl 3):35-45
28. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002;287:360-72

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-4881_3, *Accepted for publication:* 19 December 2008
*Published Online:* 15 January 2009
doi:10.1185/03007990802705679