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# Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naïve patients with type 2 diabetes

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**Disclosures**
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## SUMMARY

**Aim:** The efficacy and safety of sitagliptin (SITA) monotherapy and SITA/metformin (MET) vs. pioglitazone (PIO) were assessed in patients with type 2 diabetes and moderate-to-severe hyperglycaemia (A1C = 7.5–12.0%). **Methods:** In an initial 12-week phase (Phase A), 492 patients were randomised 1 : 1 in a double-blind fashion to SITA (100 mg qd) or PIO (15 mg qd, up-titrated to 30 mg after 6 weeks). In Phase B (28 additional weeks), the SITA group was switched to SITA/MET (up-titrated to 50/1000 mg bid over 4 weeks) and the PIO group was up-titrated to 45 mg qd **Results:** At the end of Phase A, mean changes from baseline were −1.0% and −0.9% for A1C; −26.6 mg/dl and −28.0 mg/dl for fasting plasma glucose; and −52.8 mg/dl and −50.1 mg/dl for 2-h post-meal glucose for SITA and PIO, respectively. At the end of Phase B, improvements in glycaemic parameters were greater with SITA/MET vs. PIO: −1.7% vs. −1.4% for A1C ($p = 0.002$); −45.8 mg/dl vs. −37.6 mg/dl for fasting plasma glucose ($p = 0.03$); −90.3 mg/dl vs. −69.1 mg/dl for 2-h postmeal glucose ($p = 0.001$); and 55.0% vs. 40.5% for patients with A1C < 7% ($p = 0.004$). A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of oedema were observed with SITA/MET vs. PIO. The incidence of hypoglycaemia was similarly low in both groups. Body weight decreased with SITA/MET and increased with PIO (−1.1 kg vs. 3.4 kg; $p < 0.001$). **Conclusion:** Improvements in glycaemic control were greater with SITA/MET vs. PIO, with weight loss vs. weight gain. Both treatments were generally well tolerated.

**What's known**
- Patients with moderate-to-severe hyperglycaemia need aggressive treatment to counteract impaired insulin action, decreased insulin secretion and increased hepatic glucose production.
- The most widely prescribed drug for patients with type 2 diabetes is metformin, which has been shown to decrease hepatic glucose production and improve peripheral insulin sensitivity; sitagliptin, a DPP-4 inhibitor, reduces fasting and postprandial glucose concentrations.
- The combination of these two agents is an effective treatment for patients with type diabetes.

**What's new**
- When compared with pioglitazone (a PPARγ agent), the fixed-dose combination of sitagliptin and metformin in this study resulted in superior reductions in A1C, fasting plasma glucose and postmeal glucose. Markers of β-cell function showed favourable results in the sitagliptin/metformin group vs. the pioglitazone group.
- Incidences of oedema were significantly higher with pioglitazone whereas numerically higher incidences for nausea and abdominal pain were observed with sitagliptin/metformin.
- Sitagliptin/metformin resulted in weight loss vs. weight gain with pioglitazone.

## Introduction

The development of hyperglycaemia in patients with type 2 diabetes mellitus (T2DM) is associated with several defects, including impaired insulin action, decreased insulin secretion and increased hepatic glucose production due, in part, to defective insulin secretion and excessive glucagon concentrations (1–3). Although intensive treatment of hyperglycaemia reduces the incidence of chronic diabetic complications (4–6), many patients with T2DM do not achieve the recommended glycaemic goals with monotherapy. Accordingly, combinations of therapeutic agents with different mechanisms of action are often recommended, especially in patients with T2DM who present with greater degrees of hyperglycaemia (7,8).

Sitagliptin (SITA) is a DPP-4 inhibitor that reduces fasting and postprandial glucose concentrations by increasing endogenous levels of GLP-1 and GIP which, in a glucose-dependent manner, increase insulin synthesis and release and suppress glucagon secretion. SITA has also been shown to improve measures of beta cell function (9–13). Metformin



 
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(MET) is the most widely prescribed oral antihyperglycaemic agent. Treatment with MET has been shown to decrease hepatic glucose production and improve peripheral insulin sensitivity (14,15). The combined use of SITA and MET has been demonstrated to be an effective treatment for T2DM (16–18).

The present study assessed the efficacy and safety of SITA monotherapy, and compared the efficacy and safety of SITA/MET fixed-dose combination therapy vs. pioglitazone (PIO) monotherapy, a commonly used PPARγ agent, in patients with T2DM and moderate-to-severe hyperglycaemia.

## Materials & methods

### Patients

Men and women (aged ≥18 to ≤ 78 years) with T2DM and inadequate glycaemic control [defined by a glycosylated haemoglobin (A1C) level ≥ 7.5% and ≤ 12%] who were drug naïve [not taking an antihyperglycaemic agent (AHA) within the previous 3 months and not more than 4 weeks cumulatively in the previous 3 years] were eligible to be randomised. Patients were excluded if they had a history of type 1 diabetes or a history of ketoacidosis; had hypersensitivity or a contraindication to MET, SITA or PIO; were likely to require treatment with CYP2C8 inhibitors or CYP2C8 inducers; or had symptomatic hyperglycaemia or a site fingerstick glucose < 130 mg/dl or > 320 mg/dl at the randomisation visit.

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. Informed consent was obtained from all patients before any study procedure was performed.

### Study design

This was a multi-centre, randomised, double-blind, active-comparator study (Protocol number 068; ClinicalTrials.gov registry number NCT00541450). Following a 2-week, single-blind, placebo run-in period and diet and exercise counseling, patients were randomised 1 : 1 to SITA 100 mg qd or PIO 15 mg qd, up-titrated to 30 mg qd after 6 weeks (Figure 1). Patients who met predefined criteria for inadequate glycaemic control at any time during the first 12 weeks of the study were switched to SITA/MET if they were on SITA or to PIO 45 mg qd if they were on PIO. After the initial 12-week, double-blind active-controlled treatment period with SITA or PIO monotherapy (Phase A, weeks 0–12), patients continued in a 28-week, double-blind active-controlled treatment period (Phase B, weeks 12–40). At the beginning of Phase B, patients who had received SITA during Phase A were switched to SITA/MET (up-titrated to 50/1000 mg bid over 4 weeks) and patients who had received PIO 30 mg qd at the end of Phase A were up-titrated to PIO 45 mg qd. During the study, there were 12 clinic visits, and a post-study follow-up of 14 days following discontinuation or upon completion of the active treatment period to assess for the occurrence of serious adverse events.

### Study endpoints

The primary efficacy endpoint was A1C. The study had two primary hypotheses: (i) that SITA/MET lowers A1C to a greater extent than PIO after 40 weeks, and (ii) that SITA reduces A1C after 12 weeks. A prespecified analysis of the percentage of patients meeting the A1C goal of <7% at week 40 in each treatment group was also conducted.

Secondary efficacy endpoints included 2-h postmeal glucose (PMG) and fasting plasma glucose (FPG) at weeks 12 and 40. Additional secondary endpoints included serum lipids [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C),

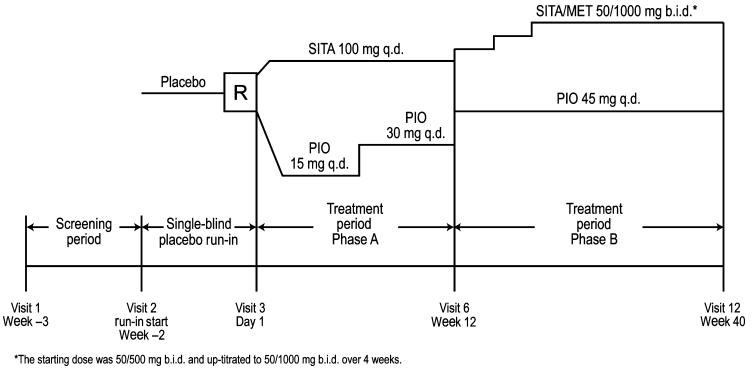


**Figure 1** Study design. R = randomisation

triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)] at week 40. Exploratory endpoints included HOMA-β, HOMA-IR and fasting proinsulin-to-insulin ratio at weeks 12 and 40.

Safety and tolerability were assessed throughout the study. Physical examinations, vital signs, and safety laboratory measurements, comprising haematology, serum chemistry and urinalysis, were performed. Adverse events were monitored throughout the study. Prespecified safety endpoints of interest included hypoglycaemia, oedema, selected gastrointestinal-related adverse events (abdominal pain, nausea, vomiting and diarrhea), and change from baseline in body weight.

### Statistical analyses

Continuous efficacy endpoints were analysed using an analysis of covariance (ANCOVA) model, with change from baseline at week 40 as the outcome variable, controlling for treatment and the baseline value of the respective endpoint. Change from baseline at week 12 was also analysed for A1C in patients treated with SITA using an analogous ANCOVA model. Efficacy analyses included all randomised patients who had both a baseline and at least one post-baseline measurement for the respective endpoint. Imputation of missing outcome data was performed using the last observation carried forward (LOCF) method. The percentages of patients at the A1C goals of <7.0% and <6.5% at week 40 in each treatment group were estimated and compared using the method of Miettinen and Nurminen (19). The Hochberg procedure (20) was used to control the Type I error rate at ≤0.05 for the tests of the two primary hypotheses.

The method of Miettinen and Nurminen was used to compare incidence percentages of adverse events between treatment groups for the 40-week treatment period. Prespecified adverse events of special interest were hypoglycaemia, oedema, abdominal pain, nausea, vomiting and diarrhea. Change from baseline in body weight at week 40 was assessed among patients who had data at week 40 using an ANCOVA model analogous to that used for the efficacy analyses.

## Results

### Patients

A total of 950 patients were screened for participation in the study and, of these, 492 were randomised to treatment (Figure 2). Three hundred and eight-seven (78.7%) patients completed the study and 105 (21.3%) patients discontinued prior to completion of the study (Figure 2). The reasons for discontinuation were generally similar between the treatment groups (Figure 2). There were no clinically meaningful differences in baseline demographic, anthropometric or disease characteristics between the treatment groups (Table 1). The mean age was 50.5 years in the SITA/MET group and 51.7 years in the PIO group. Baseline disease characteristics, including prior duration of diabetes and baseline A1C, FPG, and 2-h PMG, were similar between the treatment groups. The mean baseline A1C was 9.0% in the SITA/MET group and 9.1% in the PIO group.

### Efficacy

*Phase A (week 12)*

Significant LS mean changes from baseline in A1C at week 12 occurred for both SITA and PIO (−1.0% and −0.9%, respectively; Table 2; Figure 3A). A trend of greater A1C reduction from baseline with increasing baseline A1C levels was observed for both treatment groups (Table 2). Reductions in A1C with SITA were generally consistent for subgroups defined by demographic/anthropometric characteristics, including age (<65 vs. ≥65 years; ≤median vs. >median), gender, race (Asian, Black, White or other), ethnicity (Hispanic vs. non-Hispanic) and body mass index (BMI) (≤median vs. >median) (data not shown). Significant LS mean reductions from baseline were observed with both SITA and PIO for FPG and 2-h PMG (Table 2; Figures 3B and 3C). Both treatment groups exhibited increases from baseline in HOMA-β and decreases in HOMA-IR and the fasting proinsulin-to-insulin ratio (Table 2).

*Phase B (week 40)*

At the end of Phase B, a significantly greater mean change from baseline in A1C was observed with SITA/MET compared with PIO (−1.7% vs. −1.4%, respectively; Table 2; Figure 3A). The percentages of patients with A1C <7.0% and < 6.5% were significantly greater in the SITA/MET group (55.0% and 31.2%, respectively) compared with the PIO group (40.5% and 16.2%, respectively; Table 2). There was a trend toward greater reduction from baseline in A1C with increasing baseline A1C levels observed in both treatment groups (Table 2). The treatment effect on A1C with SITA/MET was generally consistent for subgroups defined by demographic/anthropometric characteristics, including age (<65 vs. ≥65 years; ≤median vs. > median), gender, race (Asian, Black, White or other), ethnicity (Hispanic vs. non-Hispanic) and body mass index (BMI) (≤median vs. >median) (data not shown). Significantly greater mean changes from baseline were observed with SITA/MET vs. PIO for FPG and 2-h PMG (Table 2; Figures 3B and 3C). The SITA/MET group exhibited

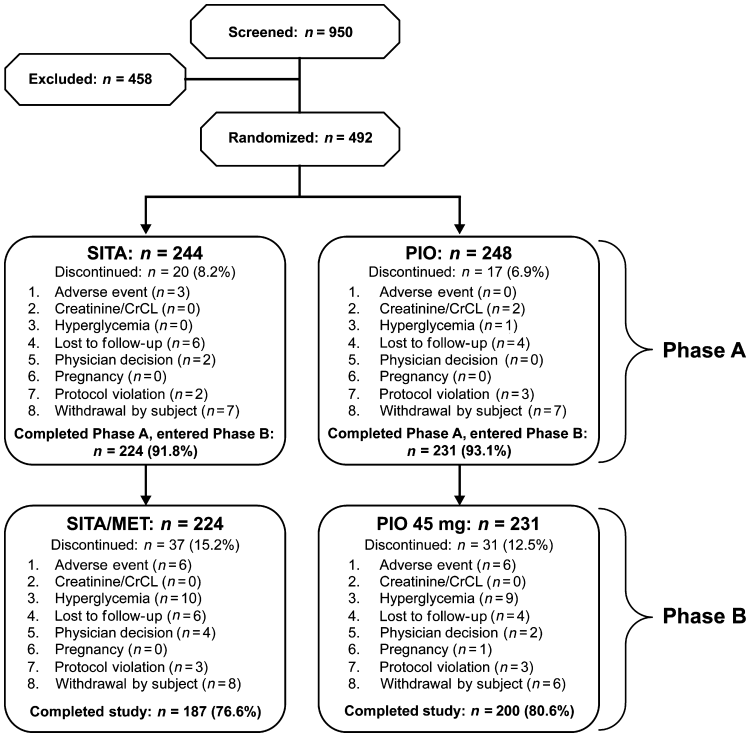


**Figure 2** Patient disposition. The denominator for all percentages is the number randomised within each group

little change in total cholesterol and LDL-C relative to baseline compared with an increase in the PIO group, resulting in statistically significant between-group differences ($p < 0.001$) (Table 2). For TG and HDL-C, between-group differences were not statistically significant (Table 2). The SITA/MET group exhibited an increase in HOMA-β compared with little change in the PIO group, resulting in a significant between-group difference (Table 2). Both groups exhibited decreases in HOMA-IR (Table 2). Both treatment groups exhibited a decrease from baseline in fasting proinsulin-to-insulin ratio, with a significantly larger decrease in the SITA/MET group compared with the PIO group (Table 2).

**Table 1** Baseline characteristics

| Parameter | SITA/MET (*n* = 244) | PIO (*n* = 248) |
|---|---|---|
| Age, years, mean ± SD | 50.5 ± 10.9 | 51.7 ± 10.1 |
| Gender, male, *n* (%) | 152 (62.3) | 148 (59.7) |
| **Race, *n* (%)** | | |
| White | 125 (51.2) | 137 (55.2) |
| American Indian/Alaska Native | 57 (23.4) | 47 (19.0) |
| Asian | 33 (13.5) | 32 (12.9) |
| Multi-racial | 25 (10.2) | 21 (8.5) |
| Black | 4 (1.6) | 11 (4.4) |
| **Ethnicity, *n* (%)** | | |
| Hispanic | 119 (48.8) | 112 (45.2) |
| Not Hispanic | 125 (51.2) | 136 (54.8) |
| Body weight (kg), mean ± SD | 83.4 ± 19.0 | 82.2 ± 19.0 |
| BMI ($kg/m^2$), mean ± SD | 30.3 ± 5.2 | 29.4 ± 5.2 |
| A1C (%), mean ± SD (range) | 9.0 ± 1.4 (6.0–13.7) | 9.1 ± 1.4 (6.4–13.3) |
| FPG, mg/dl, mean ± SD | 185.1 ± 58.1 | 185.2 ± 54.0 |
| 2-h PMG, mg/dl, mean ± SD | 261.0 ± 96.3 | 265.5 ± 92.6 |
| Duration of T2DM, years, mean ± SD (range) | 2.9 ± 2.8 (1.0–18.0) | 3.5 ± 3.7 (1.0–26.0) |

**Table 2** Summary of efficacy analyses at week 12 and week 40

| Endpoint | Estimate (95% CI) | | | |
|---|---|---|---|---|
| **LS mean change from baseline at week 12** | | | | |
| | ***N*** | **SITA** | ***N*** | **PIO** |
| A1C, % | 231 | −1.0 (−1.2, −0.9)* | 240 | −0.9 (−1.0, −0.7)* |
| Baseline A1C <8% | 58 | −0.45 (−0.75, 0.15) | 63 | −0.56 (−0.85, −0.27) |
| Baseline A1C ≥8% to <9% | 75 | −0.94 (−1.20, −0.67) | 64 | −0.66 (−0.95, −0.38) |
| Baseline A1C ≥9% to <10% | 44 | −1.33 (−1.67, −0.98) | 50 | −1.11 (−1.49, −0.78) |
| Baseline A1C ≥10% | 54 | −1.49 (−1.80, −1.18) | 63 | −1.24 (−1.53, −0.95) |
| 2-h PMG, mg/dl | 202 | −52.8 (−62.4, −43.3)* | 210 | −50.1 (−59.4, −40.7)* |
| FPG, mg/dl | 235 | −26.6 (−31.7, −21.5)* | 245 | −28.0 (−33.0, −23.0)* |
| HOMA-β | 199 | 22.9 (9.8, 35.9)* | 204 | 19.3 (6.4, 32.2)** |
| HOMA-IR | 199 | −0.7 (−1.4, −0.1)** | 204 | −1.8 (−2.4, −1.2)* |
| Proinsulin:insulin | 200 | −0.166 (−0.236, −0.096)* | 204 | −0.120 (−0.190, −0.051)* |
| **LS mean change from baseline at week 40†** | | | | |
| | ***N*** | **SITA/MET** | ***N*** | **PIO** | **SITA/MET minus PIO** |
| A1C, % | 218 | −1.7 (−1.9, −1.6) | 222 | −1.4 (−1.5, −1.2) | −0.4 (−0.6, −0.1)** |
| Baseline A1C <8% | 56 | −0.68 (−1.01, −0.36) | 58 | −0.76 (−1.08, −0.45) | 0.08 (−0.37, 0.53) |
| Baseline A1C ≥8% to <9% | 74 | −1.61 (−1.89, −1.33) | 61 | −1.05 (−1.36, −0.74) | −0.56 (−0.98, −0.14)** |
| Baseline A1C ≥9% to <10% | 41 | −2.26 (−2.64, −1.89) | 48 | −1.90 (−2.25, −1.55) | −0.36 (−0.87, 0.15) |
| Baseline A1C ≥10% | 47 | −2.69 (−3.04, −2.34) | 55 | −2.04 (−2.37, −1.72) | −0.65 (−1.13, −0.17)** |
| Patients with A1C <7.0% [*n* (%)] | 218 | 120 (55.0) | 222 | 90 (40.5) | Odds ratio = 1.8 (1.2, 2.7)** |
| 2-h PMG, mg/dl | 165 | −90.3 (−99.6, −81.0) | 172 | −69.1 (−78.2, −60.0) | −21.2 (−34.3, −8.2)* |
| FPG, mg/dl | 219 | −45.8 (−51.1, −40.5) | 226 | −37.6 (−42.8, −32.4) | −8.3 (15.7, −0.8)** |
| TC, mg/dl | 198 | −0.4 (−2.7, 1.9) | 209 | 6.2 (3.9, 8.4) | −6.6 (−9.8, −3.3)* |
| TG, mg/dl‡ | 198 | −4.9 (−11.2, 1.4) | 209 | −6.1 (−12.0, −0.3) | 3.9 (−3.8, 11.3) |
| HDL-C, mg/dl | 197 | 7.5 (4.8, 10.1) | 209 | 10.5 (8.0, 13.1) | −3.0 (−6.7, 0.6) |
| LDL-C, mg/dl | 197 | −2.4 (−6.1, 1.4) | 209 | 11.0 (7.4, 14.6) | −13.4 (−18.5, −8.2)* |
| HOMA-β | 166 | 46.6 (33.5, 59.6) | 170 | 5.7 (−7.2, 18.6) | 40.9 (22.5, 59.3)* |
| HOMA-IR | 166 | −1.9 (−2.6, −1.2) | 170 | −2.3 (−3.0, −1.7) | 0.4 (−0.5, 1.4) |
| Proinsulin: Insulin | 164 | −0.240 (−0.300, −0.181) | 167 | −0.134 (−0.193, −0.075) | −0.106 (−0.191,−0.022)** |

*p ≤ 0.001 **p < 0.05. †Unless otherwise noted. ‡Expressed as median change from baseline. A1C, glycosylated haemoglobin; CI, confidence interval; FPG, fasting plasma glucose; HOMA- β, homeostatic model assessment – beta cell function; HOMA-IR, homeostatic model assessment – insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol, LS, least squares; PMG, post-meal glucose; TC, total cholesterol; TG, triglycerides.

## Safety and tolerability

During weeks 0–12 (Phase A), both SITA and PIO were generally well tolerated, with similar incidences of adverse events observed in both treatment groups (22.5% and 23.8%, respectively). There was a numerically higher incidence of drug-related adverse events in the PIO group (5.2%) compared with the SITA group (2.0%), which was primarily because of higher incidences of oedema (1.2% vs. 0%, respectively) and increased body weight (1.6% vs. 0%, respectively). The incidences of the adverse events of abdominal pain, nausea, vomiting and hypoglycaemia were similar in both treatment groups.

During weeks 0–40 (Phase A + Phase B), a numerically higher incidence of serious adverse events was observed in the SITA/MET treatment group compared with the PIO group, which were the result of small differences across a range of specific adverse events with no discernable pattern (Table 3). No serious drug-related adverse events occurred in the SITA/MET group (Table 3). One patient in the PIO group had a serious adverse event of spontaneous abortion, which was considered by the investigator to be drug-related. One death occurred during the study; a patient in the SITA/MET group died from sudden cardiac death, which was considered by the investigator as not related to study drug.

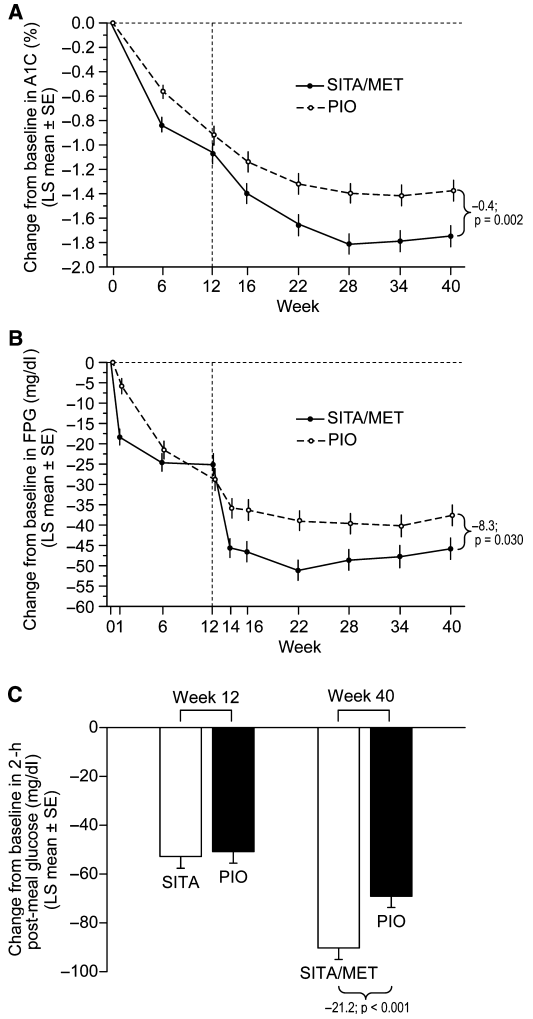


**Figure 3** Changes from baseline in (A) A1C (%); (B) FPG (mg/dl); and (C) 2-h PMG (mg/dl). The dotted line in panels A and B represents the transition point from Phase A to Phase B of the study

**Table 3** Adverse event summary, weeks 0–40†

| | SITA/MET *N* = 222 | PIO *N* = 230 |
|---|---|---|
| **Overview** | | |
| Patients with one or more | | |
| Adverse event | 101 (45.5) | 99 (43.0) |
| Drug-related adverse event‡ | 22 (9.9) | 20 (8.7) |
| Serious adverse event | 8 (3.6) | 3 (1.3) |
| Serious drug-related adverse event | 0 (0.0) | 1 (0.4) |
| Patients discontinued because of adverse event | 5 (2.3) | 6 (2.6) |
| **Prespecified adverse events of interest** | | |
| Gastrointestinal | | |
| Diarrhea | 6 (2.7) | 7 (3.0) |
| Nausea | 6 (2.7) | 2 (0.9) |
| Vomiting | 2 (0.9) | 0 (0.0) |
| Abdominal pain | 7 (3.2) | 2 (0.9) |
| Oedema* | 2 (0.9) | 14 (6.1) |
| Symptomatic hypoglycaemia | | |
| Any type | 5 (2.3) | 5 (2.2) |
| Severe¶ | 0 (0.0) | 0 (0.0) |

*$p < 0.05$ for the between-group difference in percentages. †Data displayed are the number (%) of patients with one or more occurrence of the respective endpoint. ‡Determined by the investigator to be related to the drug. ¶Defined as episode requiring medical or non-medical assistance, or exhibiting marked severity (defined as markedly depressed level of consciousness, loss of consciousness, or seizure).

The incidence of hypoglycaemia was low and similar in both treatment groups (Table 3). No hypoglycaemia episode required medical or non-medical assistance, and no episode exhibited marked severity (defined as markedly depressed level of consciousness, loss of consciousness, or seizure).

A significantly higher incidence of oedema was observed in the PIO group compared with the SITA/MET group (Table 3). Over the 40-week treatment period, patients treated with PIO gained weight (3.4 kg), whereas patients treated with SITA/MET lost weight (−1.1 kg), resulting in a clinically meaningful between-group difference of 4.5 kg (Figure 4).

Numerically higher incidences of abdominal pain, nausea and vomiting in the SITA/MET group were observed compared with the PIO group, but the between-treatment group differences were not significant (Table 3). The incidence of the adverse event of diarrhea was similar in both treatment groups (Table 3).

Higher incidences of the adverse event of increased alanine aminotransferase [ALT; 2.7% ($n = 6$) for SITA/MET vs. 0% ($n = 0$) for PIO] and a higher proportion of patients meeting predefined limits of change for aspartate aminotransferase (AST) or ALT [last value > upper limit of normal and with an increase > 200%; 2.7% ($n = 6$) for SITA/MET vs. 0% ($n = 0$) for PIO] were observed in the SITA/MET group compared with the PIO group. For the adverse events of ALT increased, the relative day of onset ranged from 85 to 290 days postrandomisation. The patients were taking SITA (2 of 6) or SITA/MET (4 of 6) at the time of onset of the reported adverse event. All of the reported adverse events of ALT increased were considered mild (4 of 6) or moderate (2 of 6) in intensity. Two adverse events resolved while the patients continued study drug, and the other events were continuing at the time the patient completed the study. None of the episodes resulted in interruption or discontinua-

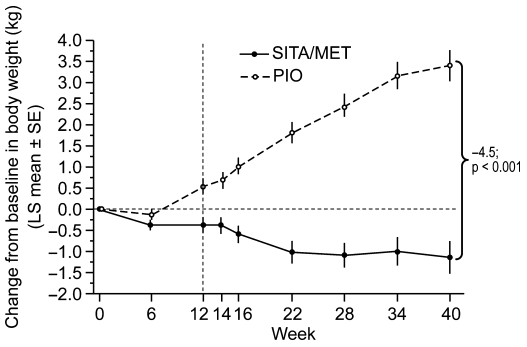


**Figure 4** Changes from baseline by treatment group in body weight. The dotted line represents the transition point from Phase A to Phase B of the study

tion of treatment, and none was considered as related to study drug by the investigator. For 2 of the 6 patients, the investigator suspected increased alcohol consumption as a precipitating factor for the increase in ALT. For both of these patients, the event did not resolve while continuing in the study. For mean ALT and AST levels, no meaningful changes were observed in the SITA/MET group (mean change from baseline at week 40: ALT 0.5 IU/l, AST 0.3 IU/l), whereas for PIO, modest decreases were observed for both parameters (mean change from baseline at week 40: ALT −4.7 IU/l, AST −1.4 IU/l).

## Discussion

The efficacy, safety and tolerability of SITA monotherapy (Phase A, weeks 0–12) and the fixed-dose combination of SITA/MET (Phase B, weeks 12–40) were assessed in this multinational, randomised, double-blind, active-controlled, parallel-group study in drug-naïve patients with T2DM and inadequate glycaemic control. SITA monotherapy provided statistically significant and clinically meaningful reductions in A1C after 12 weeks of treatment. The magnitude of mean improvement in glycaemic control observed with SITA after 12 weeks (1.0%) is generally consistent with subgroup analyses from prior studies of SITA monotherapy, considering the higher A1C at baseline in this study (21,22). As expected, patients with higher A1C at baseline (≥10%) experienced larger reductions in A1C than patients with lower A1C at baseline, consistent with results from studies of other AHAs (23). The reductions in A1C with SITA were generally similar across patients with different baseline characteristics, including age, gender, race, ethnicity and BMI.

Patients taking PIO also had significant reductions in mean A1C relative to baseline. Because PIO may not reach its maximal A1C-lowering efficacy within 12 weeks (24), a formal, between-treatment comparison between SITA and PIO at this time point was not considered appropriate and hence not conducted. In a prior study, similar A1C reductions were observed with SITA and another thiazolidinedione, rosiglitazone (8 mg/day), after 18 weeks of treatment in patients with inadequate glycaemic control on a stable dose of MET (25).

In addition to the reductions in A1C in patients treated with SITA during the first 12 weeks of the study, statistically significant improvements in other glycaemic endpoints were observed. Relative to baseline, clinically meaningful reductions in FPG and 2-h PMG were observed with SITA. Favourable effects of SITA on indices of β-cell function were also observed at week 12, consistent with results from prior studies of SITA monotherapy (21,22).

Although monotherapy with SITA and PIO provided substantial improvements in glycaemic endpoints during the first 12 weeks of the study, the majority of patients did not achieve the A1C goal of <7%, suggesting that antihyperglycaemic monotherapy is not sufficient for many patients with moderate-to-severe hyperglycaemia. Similar findings have been observed with other AHAs. For example, results from a large longitudinal study showed that among patients with poor glycaemic control (A1C >8%), good glycaemic control was achieved in only 12.5% of patients initially treated with sulfonylurea monotherapy and 18% of those initially treated with MET monotherapy (26). These findings underscore the need for an alternate approach to achieve glycaemic targets in patients with T2DM and moderate-to-severe hyperglycaemia.

Compared with monotherapy, combination therapy may offer a better approach to achieve glycaemic control targets among patients with T2DM and moderate-to-severe hyperglycaemia. As at the beginning of Phase B, patients randomised to SITA were switched to SITA/MET, the present study also assessed whether combination therapy with SITA/MET would provide superior glycaemic control and A1C goal attainment (< 7%) relative to maximal-dose PIO monotherapy. The results demonstrated superior A1C improvements with SITA/MET vs. PIO at the end of Phase B. As noted for Phase A, the severity of hyperglycaemia at baseline influenced the treatment response in both treatment arms, with numerically larger reductions from baseline in A1C observed among patients with higher baseline A1C values relative to those with lower baseline A1C values. The treatment effects on A1C were generally consistent across subgroups defined by baseline age, gender, race, ethnicity and BMI. Despite a relatively high mean baseline A1C (∼9.0% in both treatment groups), a substantial and

significantly larger proportion of patients in the SITA/MET group achieved the current American Diabetes Association A1C goal of < 7% (27,28) relative to patients in the PIO group.

Superior reductions in FPG and 2-h PMG relative to baseline were observed in the STIA/MET group compared with the PIO treatment group. In addition, markers of β-cell function showed favourable results for SITA/MET compared with PIO monotherapy; however, longer-term studies are needed to determine whether this finding is associated with sustained improvements in glycaemic control.

Both SITA monotherapy and the combination of SITA/MET were generally well tolerated, with no meaningful differences in the incidence of overall adverse events compared with PIO monotherapy. There was a significantly higher incidence of oedema in the PIO group compared with the SITA group during Phase A and the SITA/MET group during Phase B, consistent with previous findings of an increased incidence of oedema with PIO therapy (24). There was a low incidence of hypoglycaemia in both treatment groups, consistent with the known profiles of SITA (16,21,22,29,30), MET (13) and PIO (26). The mean change in body weight was notably different between the treatment groups, with a decrease in the SITA/MET group vs. an increase in the PIO group, resulting in a significant between-group difference. As expected based on the MET component of the SITA/MET combination, the incidences of the adverse events of abdominal pain, nausea and vomiting were numerically higher in the SITA/MET group compared with the PIO group.

Higher incidences in the adverse events of AST/ALT and predefined limits of change for AST/ALT were observed in the SITA/MET group compared with the PIO group over the 40-week treatment period. The reason for the higher incidences in the SITA/MET group compared with the PIO group is not clear. A higher incidence of increased liver enzymes has not been observed in prior clinical studies with SITA, MET, or SITA in combination with MET (31,32). In a large pool of SITA studies including over 10,000 patients, the incidence of the adverse event of increased liver enzymes was similar in patients who were treated with SITA, alone or in combination with other AHAs including MET, and those not exposed to SITA (i.e. patients treated with placebo or an active comparator) (31). In addition, no meaningful changes from baseline in the mean AST and ALT levels were observed in the SITA/MET group in the present study, while marked decreases in ALT and AST were observed in the PIO group in this study, a finding that is consistent with prior studies with PIO in patients with T2DM (33). Thus, the difference in incidence of increased liver enzymes in the SITA/MET group compared with the PIO group observed in the present study may be related to a decrease of hepatic steatosis and, consequently, a reduction in incidence of sporadic increases in liver enzymes in the PIO group, rather than an increase of liver enzymes in the SITA/MET group.

In conclusion, SITA and PIO produced clinically meaningful improvements in glycaemic control in drug-naïve patients with T2DM. Combination therapy with SITA/MET produced a significantly greater improvement in glycaemic control compared with PIO, suggesting that antihyperglycaemic combination therapy with SITA/MET is an appropriate treatment option in drug-naïve patients with moderate-to-severe hyperglycaemia.

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## Author contributions

Armando Pérez-Monteverde collected data and analysed the results; Thomas Seck helped conceive, design and plan the study, performed analyses and interpreted the results; Lei Xu helped conceive, design the study; collected or assembled data, performed or supervised analyses and interpreted the results; Mark A. Lee helped conceive, design and plan the study and performed or supervised analyses; and provided administrative, technical or logistic support; Christine McCrary Sisk interpreted results, wrote sections of the initial draft; Debora Williams-Herman conceived, designed and planned the study; Samuel Engel helped conceive, design and plan the study and interpret the results; Keith D. Kaufman helped conceive, design and plan the study and interpreted the results; Barry J. Goldstein performed or supervised analyses and interpreted the results; and provided administrative, technical, or logistic support. All authors provided substantive suggestions for revision or critically reviewed subsequent iterations of the manuscript and reviewed and approved the final version of the manuscript.

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