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Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial

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Original Paper

Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial**<<Short Title>>**

Saxagliptin non-inferior to glipizide as add-on therapy to metformin

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Disclosures:

Drs Göke and Eriksson declare no conflicts of interest. Dr Gallwitz has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly and Company, Novartis, Novo Nordisk, Merck & Co., Inc., Hoffman-La Roche Inc., and Takeda Pharmaceutical, and received honoraria for speaking engagements from these companies. Åsa Hellqvist, MSc, and Dr Gause-Nilsson are employees of AstraZeneca Research & Development.

Key Words: add-on therapy, dipeptidyl peptidase-4, DPP-4, HbA_{1c}, incretin, non-inferiority, sulphonylurea, glipizide, saxagliptin, type 2 diabetes mellitus, T2DM

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SUMMARY (Current word count: 262 exclusive of headers and trial reg info)

Aim: Assess the efficacy and safety of saxagliptin vs. glipizide, as add-on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone.

Methods and patients: A total of 858 patients (age ≥ 18 years; glycated haemoglobin [HbA_{1c}] > 6.5 –10.0%; on stable metformin doses ≥ 1500 mg/day) were randomised 1:1 to saxagliptin 5mg/day or glipizide up-titrated as needed from 5–20mg/day for 52 weeks. The primary objective was to assess if the change from baseline HbA_{1c} achieved with saxagliptin plus metformin was non-inferior to glipizide plus metformin.

Results: The per-protocol analysis demonstrated non-inferiority of saxagliptin vs. glipizide; adjusted mean changes from baseline HbA_{1c} were -0.74% vs. -0.80% , respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16%). Treatment with saxagliptin vs. glipizide was associated with significantly fewer proportion of patients with hypoglycaemic events (3.0% vs. 36.3% ; $p < 0.0001$) and a divergent impact on body weight (adjusted mean change from baseline -1.1 kg with saxagliptin vs. 1.1 kg with glipizide; $p < 0.0001$). There was a significantly smaller rise in HbA_{1c} (%/wk) from week 24 to 52 with saxagliptin vs. glipizide (0.001% vs. 0.004% ; $p = 0.04$) indicating a sustained glycaemic effect beyond week 24. Excluding hypoglycaemic events, the proportion of patients experiencing adverse events (AEs) was similar (60.0% saxagliptin vs. 56.7% glipizide); treatment-related AEs were less common with saxagliptin vs. glipizide (9.8% vs. 31.2%), attributable to the higher frequency of hypoglycaemia in glipizide patients. Discontinuation rates due to AEs were similar ($\sim 4\%$).

Conclusion: Saxagliptin plus metformin provided a sustained HbA_{1c} reduction over 52 weeks and was non-inferior to glipizide plus metformin, with reduced body weight and significantly lower risk of hypoglycaemia.

Trial Registration ClinicalTrials.gov ID No.: NCT00575588.

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What's known (70 words max; current word count: 57 words)

- Due to insulin resistance and the progressive beta-cell failure that characterises type 2 diabetes mellitus, most patients will eventually require combination therapy to achieve and maintain adequate glycaemic control.
- Combination therapy with metformin and a sulphonylurea is a common therapeutic strategy; however, sulphonylureas are associated with treatment-limiting side effects, such as weight gain and hypoglycaemia.

What's new (70 words max; current word count without data slug: 68 words)

- This non-inferiority trial assessed the efficacy and safety of saxagliptin 5 mg vs. glipizide, as add-on therapy to metformin for 52 weeks in patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone.
- Saxagliptin provided a sustained HbA_{1c} reduction over 52 weeks and was non-inferior to glipizide in lowering HbA_{1c} with reduced body weight and significantly lower risk of hypoglycaemia compared with glipizide.

Introduction

Failure to achieve and maintain adequate glycaemic control is due to the progressive nature of type 2 diabetes mellitus (T2DM) (1) and the limitations of current therapies (2-4). Achieving glycaemic goals can substantially reduce morbidity, making effective treatment of hyperglycaemia a high priority (5). Insulin resistance and a decreasing number of functional insulin-producing beta-cells contribute to the pathophysiology of T2DM and, thus, most patients eventually require combination therapy (6-8). Treatments targeting the beta-cell dysfunction that characterises T2DM, as well as other underlying disease mechanisms are necessary to achieve and maintain normal glucose levels over time (7). Moreover, some current therapies have treatment-limiting side effects, including hypoglycaemia and weight gain (9). Combining therapeutic agents that differ in their mechanism of action and tolerability profiles can address some of these treatment challenges (10).

Metformin is standard first-line pharmacotherapy for patients with T2DM (3,10). Metformin is inexpensive, generally well tolerated and infrequently associated with hypoglycaemia, though dosing may be limited by transient gastrointestinal effects (1,3). The major non-glycaemic benefit of metformin is weight stability or modest weight loss, in contrast with many other blood glucose-lowering medications, such as sulphonylurea or insulin (3,9). As monotherapy, metformin typically results in glycated haemoglobin (HbA_{1c}) reductions of 1.0% to 2.0% depending on baseline HbA_{1c} (1,11,12); however, metformin alone is frequently insufficient to maintain glycaemic goals over time (8,13).

Sulphonylureas are commonly used as add-on therapy in patients with inadequate glycaemic control on metformin alone and represent current standard therapy in most T2DM treatment algorithms (3,14,15). Sulphonylureas are also inexpensive and initially demonstrate strong HbA_{1c}-lowering effects (3,14). Their use, however, is associated with limitations, which include multiple titration steps, the potential for beta-cell failure (6,16), weight gain (15) and increased risk of hypoglycaemia (17). Hypoglycaemia in

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2 particular affects morbidity and quality of life for patients with T2DM and is a major obstacle to
3 medication adherence (18,19).
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7 Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of oral antidiabetic agents (OADs)
8 and augment glucose homeostasis by preventing degradation of the incretin hormones, glucagon-like
9 peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (1,4). The former hormone
10 accounts for the majority of the incretin effect and is a key component in regulating both fasting plasma
11 glucose (FPG) and postprandial glucose (PPG) by stimulating glucose-dependent insulin secretion, and
12 attenuating glucagon secretion by the pancreatic alpha-cells to decrease glucose production by the liver
13 (1,4,20). DPP-4 inhibitors demonstrate a low propensity for hypoglycaemia and are generally weight
14 neutral, making them suitable candidates for combination therapy (4,19). Further, metformin works
15 through pathways complementary to DPP-4 inhibitors, and combination therapy may improve glycaemic
16 control by targeting multiple mechanisms (21) without increasing the risk of hypoglycaemia or inducing
17 weight gain.
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19

20
21 Saxagliptin is a selective DPP-4 inhibitor approved as an adjunct to diet and exercise for the management
22 of glycaemic control in adults with T2DM (22,23). Saxagliptin, either as add-on therapy to metformin or
23 given with metformin as initial therapy for 24 weeks was well tolerated and led to statistically significant
24 improvements in glycaemic indices vs. placebo and metformin, respectively, in patients with T2DM and
25 inadequate glycaemic control (24,25). Hypoglycaemic events were comparable across treatment groups
26 and there were no increases in weight observed in the saxagliptin plus metformin groups in either study
27 (24,25). Additionally, saxagliptin and metformin combination therapy improved indices of beta-cell
28 function (24). Combination therapy with saxagliptin and metformin may offer several advantages
29 compared with the current standard practice of metformin-sulphonylurea combination therapy.
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2 This 52-week trial assessed the efficacy and safety of saxagliptin vs. the sulphonylurea, glipizide, as add-
3 on therapy to metformin in patients with T2DM and inadequate glycaemic control on a stable dose of
4 metformin alone. [A non-inferiority trial design was chosen to investigate the clinical equivalence of](#)
5 [saxagliptin plus metformin therapy as compared with the current standard treatment of sulphonylurea plus](#)
6 [metformin.](#)
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11 **Patients and methods**

12 **Patients**

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14
15 Eligible study participants were men and women age ≥ 18 years with T2DM and $HbA_{1c} > 6.5\% - 10.0\%$
16 on a stable dose of metformin monotherapy ≥ 1500 mg/day for at least 8 weeks prior to enrollment. Key
17 exclusion criteria included type 1 diabetes; history of diabetic ketoacidosis or hyperosmolar non-ketotic
18 coma; insulin therapy within 1 year of enrollment; treatment with a thiazolidinedione within the 12 weeks
19 prior to enrollment; treatment with systemic glucocorticoids other than replacement therapy; previous
20 DPP-4 inhibitor treatment; donation of blood, plasma or platelets within the 3 months prior to enrollment;
21 congestive heart failure defined as New York Heart Association class III or IV and/or known left
22 ventricular ejection fraction $\leq 40\%$; significant cardiovascular (CV) history within the past 6 months
23 defined as myocardial infarction, coronary angioplasty or bypass graft(s), valvular disease or repair,
24 unstable angina pectoris, transient ischaemic attack or cerebrovascular accident; history of
25 haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrollment; treatment
26 with human immunodeficiency virus/antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers;
27 serum creatinine ≥ 1.5 mg/dL [≥ 133 $\mu\text{mol/L}$ (men)]; ≥ 1.4 mg/dL [≥ 124 $\mu\text{mol/L}$ (women)]; active liver
28 disease and/or significant abnormal liver function [aspartate aminotransferase (AST) $> 2 \times$ upper limit of
29 normal (ULN) and/or alanine aminotransferase (ALT) $> 2 \times$ ULN and/or total bilirubin > 2.0 mg/dL (> 34
30 $\mu\text{mol/L}$)] or any clinically significant laboratory abnormality upon screening.
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2 The study protocol was approved by the Institutional Review Board/Independent Ethics Committee for
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4 each participating site, and carried out in accordance with the Declaration of Helsinki and International
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6 Conference on Harmonisation/Good Clinical Practice guidelines. Patients were informed of the study
7
8 purpose and potential risks, and gave written informed consent.
9

11 Study design

13 This was a 52-week, phase 3b, international, multicenter, randomised, parallel-group, active-controlled,
14
15 double-blind, non-inferiority trial, with a 52-week extension period (ongoing). Eligible patients enrolled
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17 in a 2-week, single-blind, placebo-controlled lead-in period that included advice on diet and exercise. All
18
19 patients received open-label metformin at 1500, 2000, 2500 or 3000 mg daily based on individual
20
21 metformin dose at enrollment for the duration of the study; the dose remained stable throughout the study.
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23 Patients were assigned a glucometer and patient diary for the course of the initial 52-week treatment
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25 period and instructed to monitor their fingerstick glucose level regularly. Information about
26
27 hypoglycaemic events (list of symptoms, fingerstick value if obtained) was to be entered into the patient
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29 diary.
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31 At screening, patients were assigned a unique identifier to be used throughout the study. Following the
32
33 lead-in period, eligible patients were randomised (1:1) via an interactive Web-response system using a
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35 balanced block randomisation schedule to 1 of 2 treatment groups: saxagliptin 5 mg/day plus open-label
36
37 metformin or glipizide up-titrated as needed from 5 to 20 mg/day plus open-label metformin. Blinding
38
39 was ensured using a double-dummy technique. Study medication was taken orally, immediately before or
40
41 with a meal.
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44 Patients assigned to saxagliptin plus metformin remained on saxagliptin 5 mg throughout the study. For
45
46 patients assigned glipizide plus metformin, glipizide was titrated to an optimal effect (FPG \leq 110 mg/dl
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48 [\leq 6.1 mmol/l]) or the highest tolerated dose during an 18-week titration period. Glipizide was initiated at
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2 5 mg/day (morning dose) and titrated in 3-week intervals to a maximum of 20 mg/day using a double-
3
4 dummy technique to ensure blinding. Titration steps were 10 mg/day (morning dose), followed by 15
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6 mg/day (10 mg morning dose, 5 mg evening dose) and 20 mg/day (10 mg morning dose, 10 mg evening
7
8 dose). Initial titration assessment was at week 3; subsequent re-assessment for titration occurred at weeks
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10 6, 9, 12, 15 and 18. During the titration period, glipizide could be down-titrated once if hypoglycaemic
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12 events occurred and could thereafter be up-titrated once. Evaluation at each titration visit and final
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14 decision by the investigator on dose increase or decrease took into account patient glucose measurements
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16 made before visits, hypoglycaemic events recorded in the patient diary and investigator's measurements
17
18 at titration visits. Following the titration period, medication doses remained stable except for instances of
19
20 glipizide down-titration to mitigate recurrent hypoglycaemia at the discretion of the study investigator; no
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22 up-titration was allowed. Patients were instructed to monitor their fingerstick glucose levels at least once
23
24 a week and continue documenting hypoglycaemic events in their patient diaries.

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26 Throughout the study, patients were discontinued if they failed to meet prespecified, progressively more
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28 stringent glycaemic control criteria. Patients with FPG > 270 mg/dl (> 15.0 mmol/l), > 240 mg/dl (> 13.3
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30 mmol/l), > 220 mg/dl (> 12.2 mmol/l) or > 200 mg/dl (11.1 mmol/l) at weeks 3, 12, 18 or 24,
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32 respectively, or HbA_{1c} > 8.0% at week 30 or 39 were discontinued. Assessments took place at each visit
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34 to determine if study discontinuation criteria were met.

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Study end-points

The primary efficacy end-point was change from baseline to week 52 in HbA_{1c} and was used to assess if saxagliptin plus metformin was non-inferior to glipizide plus metformin. Key secondary end-points were the proportion of patients reporting ≥ 1 event of hypoglycaemia over 52 weeks, the change from baseline body weight at week 52 and the mean slope of regression of change from week 24 to week 52 in HbA_{1c}. Other secondary end-points included change from baseline FPG, fasting insulin, C-peptide, glucagon and proinsulin; the proportion of patients achieving a therapeutic glycaemic response defined as HbA_{1c} $\leq 6.5\%$; HbA_{1c} change from baseline in patients with baseline HbA_{1c} $\geq 7.0\%$; the proportion of patients achieving a therapeutic glycaemic response defined as HbA_{1c} $< 7.0\%$ in patients with baseline HbA_{1c} $\geq 7.0\%$, and change from baseline beta-cell function (as measured by homeostasis model assessment [HOMA-2 β]). Change from baseline to week 52 in 120-minute PPG during an oral glucose tolerance test (OGTT) was also assessed in a subset of patients.

Safety and tolerability assessments included adverse events (AEs), serious AEs (SAEs), related AEs, discontinuations from study medication due to AEs and deaths, as well as AEs of special interest, specifically hypoglycaemia, lymphopenia, thrombocytopenia, skin disorders, localised oedema, infections and CV AEs. Laboratory values, electrocardiograms, vital signs, physical examination and body weight were also assessed.

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Statistical analyses

The primary efficacy analysis and key secondary efficacy analyses involving HbA_{1c} were conducted on a per-protocol (PP) analysis set. The PP analysis set included patients who completed the 52-week randomised treatment period, had both a baseline and week 52 HbA_{1c} measurement and no significant protocol deviations. The full analysis set, which included all patients who received at least 1 dose of randomised study medication and had at least 1 non-missing baseline and 1 post-baseline efficacy data assessment, was used for confirmatory analysis of the primary end-point and for all other efficacy analyses.

Efficacy analyses for continuous variables were performed using an analysis of covariance (ANCOVA) model, with treatment as an effect and baseline HbA_{1c} as the covariate. Within the framework of the ANCOVA model, point estimates and 95% confidence intervals (CIs) for the mean change within each treatment group, as well as for the differences in mean change between the saxagliptin plus metformin group and the glipizide plus metformin group were estimated. Saxagliptin plus metformin was considered non-inferior to glipizide plus metformin if the upper limit of the 95% CI of the difference in change in HbA_{1c} from baseline to week 52 between the 2 treatment groups was < 0.35%. A fixed-sequence test was employed for primary and key secondary efficacy end-points to control the overall type I error rate of the study. All comparisons were 2-sided at the 5% significance level. The proportion of patients reporting ≥ 1 hypoglycaemic event and the percentage of patients achieving a targeted glycaemic response were analysed using the Fisher exact test. A mixed model with patient-specific slopes using observed values assessed the durability of the HbA_{1c} effect.

Demographic and other baseline characteristics were summarised using descriptive statistics. Secondary end-point analyses and analysis by categorical baseline HbA_{1c} subgroup was prespecified. A conversion chart of conventional to Système International d'Unités is provided in Supplementary Table 1.

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2 All patients who received at least 1 dose of study medication during the 52-week treatment period were
3 included in the safety analysis (safety analysis set). Patients were assessed for safety according to the
4 actual treatment taken. AEs were tabulated; other safety-related variables were summarized using
5 descriptive statistics, tabulations and/or listings. AEs were classified according to the Medical Dictionary
6 for Regulatory Activities (MedDRA) version 12.0 at the preferred term (PT) level and grouped by system
7 organ class (SOC). AEs of special interest were identified by matching reported AEs to a predefined list
8 of PTs or lowest level terms (localised oedema only) reflective of that particular diagnosis. AE intensity
9 was defined as mild (awareness of event but easily tolerated), moderate (discomfort enough to cause some
10 interference with usual activity), severe (inability to carry out usual activity) or very severe (debilitating,
11 significantly incapacitates patient despite symptomatic therapy). Reported hypoglycaemia events were a
12 combination of reports of either signs or symptoms consistent with hypoglycaemia with or without
13 documented glucose levels or reported low glucose levels without any symptoms. Confirmed
14 hypoglycaemia was defined as fingerstick glucose value ≤ 50 mg/dl (≤ 2.8 mmol/l) with associated
15 symptoms.

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29 With 419 patients per treatment group, there was a 95% power to establish the non-inferiority comparison
30 on change from baseline to week 52 in HbA_{1c} at the 5% level, assuming that the standard deviation (SD)
31 of change from baseline in HbA_{1c} was 1.1%, with a non-inferiority limit set at 0.35% and a zero true
32 difference between the 2 randomised treatments. The sample size assumed that 35% of randomised
33 patients would be excluded from the PP analysis set.

34 35 36 37 38 39 40 **Results**

41 42 *Disposition, baseline demographics, clinical characteristics, and drug exposures*

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44 A total of 858 patients were randomised and treated with double-blind therapy; 633 (73.8%) completed
45 the 52-week treatment period, with comparable completion percentages between groups (72.9% for
46 saxagliptin plus metformin, 74.7% for glipizide plus metformin) (Figure 1). Demographic and baseline
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2 clinical characteristics were generally well balanced across treatment groups in both the randomised and
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4 PP analysis sets and representative of patients with uncontrolled T2DM treated with metformin
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6 monotherapy (Table 1). For the overall study population, mean age, HbA_{1c}, weight, body mass index
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8 (BMI), metformin dose and duration of T2DM were 57.6 years, 7.7%, 88.7 kg, 31.4 kg/m², 1910 mg/day
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10 and 5.4 years, respectively. Mean final glipizide total daily dose (TDD) was 14.7 mg/day (range, 0–20
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12 mg); more than two-thirds of patients in the glipizide plus metformin group underwent 2 or more dose
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14 titrations, and approximately 50% of the patients in the glipizide plus metformin group reached a final
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16 glipizide TDD of 20 mg/day. Median exposure to study medication was 363 days for the saxagliptin plus
17
18 metformin group and 364 days for the glipizide plus metformin group.

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21 A total of 59 patients were enrolled for an OGTT; however, the number of evaluable OGTT results was
22
23 low (35 patients).

24 25 26 *Primary end-point*

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28 At 52 weeks, saxagliptin plus metformin was non-inferior to glipizide plus metformin in lowering HbA_{1c}
29
30 (primary analysis of the PP analysis set). Adjusted mean changes from baseline HbA_{1c} were –0.74% vs. –
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32 0.80% with saxagliptin vs. glipizide, respectively; the between-group difference was 0.06% (95% CI, –
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34 0.05% to 0.16%) (Figure 2A, Table 2). Confirmatory analysis of the full analysis set yielded consistent
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36 results (adjusted mean change from baseline HbA_{1c} –0.57% vs. –0.66% for saxagliptin plus metformin vs.
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38 glipizide plus metformin, respectively). Mean HbA_{1c} values over time for the PP analysis set are shown in
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40 Figure 2B.

41 42 *Key secondary end-points*

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44 The proportion of patients reporting ≥ 1 hypoglycaemic event over 52 weeks was low in the saxagliptin
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46 plus metformin group (3.0%), and was significantly lower compared with the glipizide plus metformin
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2 group (36.3%) (difference vs. glipizide plus metformin -33.2% (95% CI, -38.1% to -28.5% ; $p < 0.0001$)

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4 (Figure 3).

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7 Treatment with saxagliptin vs. glipizide was associated with a divergent impact on body weight at week
8 52; mean body weight decreased in the saxagliptin plus metformin group and increased in the glipizide
9 plus metformin group. Adjusted mean changes from baseline were -1.1 kg vs. 1.1 kg, with saxagliptin vs.
10 glipizide respectively; the between-group difference was -2.2 kg (95% CI, -2.7 to -1.7 ; $p < 0.0001$)

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12 (Figure 4).

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18 The PP analysis demonstrated a small rise per week in HbA_{1c} during weeks 24 to 52 in both treatment
19 groups (mean changes per week 0.001% for saxagliptin and 0.004% for glipizide). The rise per week was
20 statistically significantly smaller with saxagliptin vs. glipizide (-0.002% difference, 95% CI, -0.0046% to
21 -0.0001% ; $p = 0.04$) indicating a more sustained effect on glycaemic control beyond week 24.
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27 *Other secondary end-points*

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29 Changes in other secondary efficacy variables from baseline to week 52 are listed in Table 2. Both
30 treatment groups demonstrated improved glycaemic control as assessed by decreases from baseline FPG,
31 with a numerically greater decrease with glipizide plus metformin vs. saxagliptin plus metformin. There
32 were small and generally similar increases from baseline in both treatment groups in mean values for
33 fasting insulin and fasting C-peptide. Numerical reductions in fasting proinsulin and numerically smaller
34 increases in fasting glucagon were demonstrated for saxagliptin vs. glipizide.
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42 The proportion of patients achieving HbA_{1c} $\leq 6.5\%$ was similar (35.9% vs. 34.3% for saxagliptin vs.
43 glipizide, respectively). The proportion of patients achieving HbA_{1c} $< 7.0\%$ (with or without
44 hypoglycaemic events) in patients whose baseline HbA_{1c} $\geq 7.0\%$ was similar (42.6% vs. 47.8% for
45 saxagliptin vs. glipizide, respectively). When patients with hypoglycaemic events were excluded, 41.4%
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2 (saxagliptin) vs. 30.9% (glipizide) of patients achieved $HbA_{1c} < 7.0\%$. Greater decreases were associated
3
4 with categories of higher baseline HbA_{1c} in each treatment group. Adjusted mean changes from baseline
5
6 for saxagliptin vs glipizide, respectively, were -0.32 vs. -0.30 for $HbA_{1c} < 7.0\%$; -0.45 vs. -0.58 for
7
8 $HbA_{1c} \geq 7.0\%$ to $< 8.0\%$; -0.84 vs. -0.81 for $HbA_{1c} \geq 8.0\%$ to $< 9.0\%$; and -1.05 vs. -1.72 for $HbA_{1c} \geq$
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10 9.0% . An interaction of treatment with baseline category was observed ($p = 0.0179$). The smallest
11
12 subgroup analysed, ie, those with baseline $HbA_{1c} \geq 9.0\%$, ($n = 79$) demonstrated numerically greater
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14 reductions with glipizide plus metformin vs. saxagliptin plus metformin (between-group difference 0.67%
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16 [95% CI, 0.31% to 1.04%]). and is likely to be the source of the significant interaction.

17
18 Patients treated with glipizide plus metformin had a greater mean increase in HOMA-2 β vs. saxagliptin
19
20 plus metformin. For the small OGTT patient subset, the saxagliptin plus metformin group demonstrated
21
22 numerically greater decreases from baseline in 120-minute PPG vs. the glipizide plus metformin group
23
24 (data not shown).

Deleted: Table 2

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26
27 Fifty-nine (13.8%) patients in the saxagliptin plus metformin group and 47 (10.9%) patients in the
28
29 glipizide plus metformin group met prespecified glycaemic discontinuation criteria and discontinued from
30
31 the study by week 52. A small but greater number of patients in the saxagliptin plus metformin group
32
33 discontinued due to high FPG up to week 24 vs. the glipizide plus metformin group (3.5% vs. 1.2%,
34
35 respectively). Post 24 weeks, when criteria were based on HbA_{1c} levels, discontinuation rates were similar
36
37 (10.3% for the saxagliptin group vs. 9.8% for the glipizide group).

38 39 40 *Safety and tolerability*

41
42 Overall, saxagliptin plus metformin was generally well tolerated (Table 3). Excluding hypoglycaemia, the
43
44 proportion of patients with AEs was similar between groups (60.0% saxagliptin vs. 56.7% glipizide).
45
46 Treatment-related AEs were less common with saxagliptin vs. glipizide (9.8% vs. 31.2%) due to the
47
48 higher frequency of hypoglycaemia in patients receiving glipizide. The majority of AEs in both treatment
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1
2 groups were mild or moderate in intensity and discontinuation rates due to AEs were similar for
3
4 saxagliptin vs. glipizide. Four deaths occurred during the study period (cardiac failure and head injury in
5
6 the saxagliptin plus metformin group; ischaemic stroke and myocardial infarction in the glipizide plus
7
8 metformin group), none of which was considered by study investigators to be treatment related.
9

10
11 Hypoglycaemic events are listed in Table 4. A total of 13 (3.0%) patients in the saxagliptin plus
12
13 metformin group experienced 19 hypoglycaemic events and 156 (36.3%) patients in the glipizide plus
14
15 metformin group experienced 750 hypoglycaemic events over the 52-week treatment period. No patients
16
17 (0%) experienced a hypoglycaemic event with fingerstick glucose ≤ 50 mg/dL [2.8 mmol/l] or a
18
19 confirmed hypoglycaemic event (defined as fingerstick glucose value ≤ 50 mg/dl [2.8 mmol/l] with
20
21 associated symptoms) in the saxagliptin plus metformin group vs. 38 (8.8%) and 35 (8.1%) of the patients
22
23 in the glipizide plus metformin group, respectively. Most hypoglycaemic events were mild in intensity.
24
25 One (0.2%) patient in the saxagliptin plus metformin group and 62 (14.4%) patients in the glipizide plus
26
27 metformin group had hypoglycaemic events that were moderate in intensity. No (0%) patients in the
28
29 saxagliptin plus metformin group and 7 (1.6%) patients in the glipizide plus metformin group had
30
31 hypoglycaemic events that were severe. No patients in the saxagliptin plus metformin group required
32
33 medical assistance for a hypoglycaemic event; 4 (0.9%) patients experienced a non-serious
34
35 hypoglycaemic AE requiring medical assistance in the glipizide plus metformin group.
36

37
38 Two or fewer patients in either treatment group had AEs of lymphopenia, thrombocytopenia, skin
39
40 disorders or localised oedema. The proportion of patients with CV AEs was comparable for saxagliptin
41
42 vs. glipizide (8 [1.9%] vs 9 [2.1%], respectively). A total of 3 patients had hypersensitivity AEs: 1 patient
43
44 in the saxagliptin plus metformin group (SAE of hypersensitivity) and 2 patients in the glipizide plus
45
46 metformin group (AE of drug hypersensitivity [ciprofloxacin] and SAE of laryngeal oedema). There were
47
48 no AEs of pancreatitis in the saxagliptin plus metformin group; 1 (0.2%) patient in the glipizide plus
49
50 metformin group had 2 SAEs of pancreatitis. Small mean decreases from baseline in systolic and diastolic
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2 blood pressure, respectively, occurred in the saxagliptin plus metformin (-4.1 and -2.7 mm Hg) and
3
4 glipizide plus metformin (-1.2 and -1.1 mm Hg) treatment groups. There were no apparent differences
5
6 between the saxagliptin plus metformin and glipizide plus metformin groups in change from baseline in
7
8 mean values for fasting lipid parameters. There were no clinically relevant changes in electrocardiograms
9
10 or clinically meaningful drug effects on any laboratory safety parameter.

11 12 13 Discussion

14
15 This study demonstrated that in patients with T2DM not achieving glycaemic control on stable doses of
16
17 metformin, the addition of saxagliptin 5 mg/day to metformin provided HbA_{1c} reduction that was
18
19 sustained over 52 weeks. The HbA_{1c} reduction at week 52 was non-inferior to adding glipizide to
20
21 metformin, with a decrease in body weight and statistically significantly lower proportion of patients with
22
23 hypoglycaemia vs. glipizide. Both saxagliptin and titrated dosages of glipizide added to metformin
24
25 improved glycaemic control, as assessed by decreases from baseline HbA_{1c} and FPG, as well as the
26
27 proportion of patients achieving a therapeutic response. As is frequently observed with
28
29 antihyperglycaemic agents, greater reductions in HbA_{1c} were seen in patients with higher HbA_{1c} values at
30
31 baseline. Although both treatment groups showed a small rise in HbA_{1c} from week 24 to week 52, a
32
33 smaller rise per week in HbA_{1c} during this time period was observed for saxagliptin plus metformin vs.
34
35 glipizide plus metformin indicating a longer period of sustained glycaemic control with saxagliptin
36
37 treatment. The findings that glipizide-treated patients had a transient greater decrease in HbA_{1c} at some
38
39 time points in the first half of the study as well as a greater mean increase in HOMA-2 β may be explained
40
41 by the mechanism of action of a sulphonylurea agent to directly stimulate insulin secretion and is in
42
43 agreement with findings in other studies (26,27).

44
45 While the importance of long-term glycaemic control has been repeatedly demonstrated, achievement of
46
47 treatment goals may be limited by adverse drug effects, most notably hypoglycaemia and weight gain
48
49 associated with some OADs used to treat T2DM (17). The increased number of patients experiencing
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2 hypoglycaemia is particularly relevant for treatment combinations that include sulphonylureas and/or
3
4 insulin; however, treatment with saxagliptin provided added efficacy without safety issues
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6 (hypoglycaemia or weight gain). Specifically, treatment with glipizide resulted in 12 times as many
7
8 patients with hypoglycaemic events relative to saxagliptin-treated patients.
9

10
11 Despite the fact that weight gain has been observed with intensive glycaemic control (9), saxagliptin
12
13 treatment resulted in a small weight loss, compared to weight gain with sulphonylurea therapy. Results
14
15 from 24-week studies of saxagliptin and metformin combination therapy have also demonstrated
16
17 reductions from baseline body weight from -0.87 kg to -1.8 kg (24,25). Because a majority of patients
18
19 with T2DM are overweight or obese, therapeutic regimens that have a neutral or beneficial impact on
20
21 weight are important in clinical practice.
22
23

24 Although firm conclusions cannot be drawn from comparisons between studies performed in different
25
26 patient populations with different designs, the present results were comparable to those of a similar 52-
27
28 week study by Nauck et al using a DPP-4 inhibitor (sitagliptin) added to metformin compared with
29
30 glipizide added to metformin. Sitagliptin 100 mg/day plus metformin was noninferior to glipizide plus
31
32 metformin (HbA_{1c} change from baseline -0.67%, both groups); proportion of patients experiencing
33
34 hypoglycaemia was significantly higher with glipizide vs. sitagliptin. Sitagliptin also demonstrated a
35
36 small decrease in weight compared with with glipizide (26). Two-year study results were recently
37
38 published and demonstrated similar glucose-lowering efficacy between completers in the 2 treatment
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40 groups, but with lower risk of hypoglycaemia and weight loss compared with weight gain with sitagliptin
41
42 vs glipizide (28). Another DPP-4 inhibitor, vildagliptin, was also studied as an add-on to metformin
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44 therapy vs. the sulphonylurea glimepiride added on to metformin. Two year results indicated vildagliptin
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46 50 mg twice daily was noninferior to glimepiride (HbA_{1c} change from baseline -0.1%, both groups), with
47
48 fewer patients experiencing hypoglycaemia and a beneficial effect on body weight for vildagliptin vs
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50 glimepiride, respectively (29). In all studies, a greater proportion of patients treated with a DPP-4
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1
2 inhibitor achieved target HbA_{1c} goals. These results, in addition to those of the current study, support the
3 utility of DPP-4 inhibitor therapy added to metformin and suggest greater tolerability with comparable
4 efficacy vs. the current standard practice of metformin-sulphonylurea combination therapy.
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9 Given the common and increasing use of OADs, the relative impact on CV health is also of critical
10 importance and a matter of much debate. Studies assessing the association of combination therapy of
11 metformin and sulphonylureas on all-cause and/or cardiovascular mortality risk in T2DM are not
12 consistent. There has been reported both a neutral CV risk (30,31), a decreased CV risk (32), and an
13 increased CV risk (33-36). A recent evaluation of total CV death/myocardial infarction/stroke events in
14 the pooled phase 2/3 clinical trials of saxagliptin demonstrated no evidence of increased risk (37).
15 Retrospective studies of other DPP-4 inhibitors (sitagliptin, vildagliptin) as monotherapy or in
16 combination treatment suggest no increased risk of CV events (38-40). This favourable tolerability profile
17 suggests that the addition of DPP-4 inhibitors to metformin may be appropriate and preferable for certain
18 patients, including those who are overweight or at higher risk of hypoglycaemia.
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29 There were some limitations to this study; it included mostly patients with uncomplicated T2DM at the
30 time of metformin failure, thus limiting the ability to generalise safety findings across the broad range of
31 patients with T2DM. However, the characteristics of the patient population recruited as well as the degree
32 of HbA_{1c} reduction are well in line with other studies in patients with failure on metformin monotherapy
33 and support the external validity of the study findings (41). The small sample size of the OGTT patient
34 subset precluded definitive conclusions about PPG effects in this study. Reduction of PPG with
35 saxagliptin in combination with metformin has been demonstrated in other studies (24,25).
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44 In summary, achieving specific glycaemic goals can substantially reduce diabetes-related morbidity,
45 making the effective treatment of hyperglycaemia a high priority. By using agents that differ in their
46 mechanism of action and side effect profiles, combination regimens can better address the numerous
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2 pathophysiologic abnormalities that characterise T2DM while reducing safety and tolerability issues.
3
4 Combination therapy with saxagliptin and metformin provided similar HbA_{1c} lowering efficacy with a
5
6 reduction in weight compared with weight gain and a lower proportion of hypoglycaemia vs. glipizide
7
8 plus metformin. Based on this overall profile, saxagliptin plus metformin may be preferable to adding a
9
10 sulphonylurea to metformin in patients with inadequate glycaemic control with metformin monotherapy.
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Author Contributions

14 Drs Göke, Gallwitz and Eriksson contributed to the data acquisition, drafting and critical revision of the
15 manuscript content. Dr Gause-Nilsson and Åsa Hellqvist, MSc, contributed to the study design, data
16 analysis/interpretation, drafting and critical revision of the manuscript content. All authors approved the
17 final manuscript.
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APPENDIX

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Table 1 Demographic and baseline clinical characteristics*

	SAXA + MET	GPZ + MET
Characteristic	(n = 428)	(n = 430)
Age, years, mean (SD)	57.5 (10.26)	57.6 (10.37)
Aged ≥ 65 years, n (%)	106 (24.8)	113 (26.3)
Aged ≥ 75 years, n (%)	21 (4.9)	21 (4.9)
Gender, n (%)		
Male	212 (49.5)	232 (54.0)
Female	216 (50.5)	198 (46.0)
Race, n (%)		
Asian	73 (17.1)	65 (15.1)
Black/African American	1 (0.2)	0
White	352 (82.2)	362 (84.2)
Other	2 (0.5)	3 (0.7)
Geographical region, n (%)		
Asia	68 (15.9)	63 (14.7)
Europe	360 (84.1)	367 (85.3)
Weight, kg, mean (SD)	88.7 (18.61)	88.6 (19.64)
BMI, kg/m ² , mean (SD)	31.5 (5.70)	31.3 (6.17)
Duration of diabetes, years, mean (SD)	5.5 (4.5)	5.4 (4.7)
HbA _{1c} , %, mean (SD)	7.7 (0.9)	7.7 (0.9)
< 7.0%, n (%)	99 (23.1)	105 (24.4)
≥ 7.0% to < 8.0%, n (%)	190 (44.4)	186 (43.3)
≥ 8.0% to < 9.0%, n (%)	93 (21.7)	105 (24.4)
≥ 9.0%, n (%)	46 (10.7)	34 (7.9)
FPG, mg/dl, mean (SD)	163 (41.2)	161 (39.2)
MET dose, mg, mean (SD) [†]	1938 (484.8)	1883 (453.7)
≥ 1500 to < 2000, n (%) [†]	193 (45.1)	209 (48.6)
≥ 2000 to < 2500, n (%) [†]	131 (30.6)	143 (33.3)
≥ 2500 to < 3000, n (%) [†]	66 (15.4)	48 (11.2)
≥ 3000, n (%) [†]	37 (8.6)	30 (7.0)
Not reported, n (%) [†]	1 (0.2)	0

BMI, body mass index; FPG, fasting plasma glucose; GPZ, glipizide; HbA_{1c}, glycated haemoglobin; MET, metformin; SAXA, saxagliptin.

* Randomized analysis set.

[†]At randomization.

Table 2 Changes in efficacy variables from baseline to week 52

	SAXA + MET (n = 428)	GPZ + MET (n = 430)
Efficacy end-point (week 52)		
HbA_{1c} (%)*		
N	293	293
BL mean (SE)	7.46 (0.045)	7.53 (0.045)
Adjusted mean change from BL (SE)	-0.74 (0.038)	-0.80 (0.038)
Mean difference vs. GPZ + MET (SE)	0.06 (0.053)	
95% CI	-0.05 to 0.16	
FPG (mg/dl)		
N	420	420
BL mean (SE)	162 (2.0)	161 (1.9)
Adjusted mean change from BL (SE)	-9 (1.6)	-16 (1.6)
Mean difference vs. GPZ + MET (SE)	6 (2.2)	
95% CI	1.7 to 10.5	
Fasting insulin (μU/ml)		
N	374	375
BL mean (SE)	13.3 (0.72)	13.1 (0.47)
Adjusted mean change from BL (SE)	1.0 (0.54)	1.2 (0.54)
Mean difference vs. GPZ + MET (SE)	-0.2 (0.76)	
95% CI	-1.7 to 1.3	
Fasting C-peptide (ng/ml)		
N	357	358
BL mean (SE)	3.17 (0.076)	3.15 (0.081)
Adjusted mean change from BL (SE)	0.10 (0.065)	0.25 (0.064)
Mean difference vs. GPZ + MET (SE)	-0.15 (0.091)	
95% CI	-0.33 to 0.03	
Fasting glucagon (pg/ml)		
N	384	374
BL mean (SE)	71.6 (1.52)	74.0 (1.56)
Adjusted mean change from BL (SE)	1.8 (1.32)	6.6 (1.34)
Mean difference vs. GPZ + MET (SE)	-4.9 (1.88)	
95% CI	-8.6 to -1.2	
Fasting proinsulin (pmol/l)		
N	393	389
BL mean (SE)	26.1 (1.24)	28.0 (1.54)
Adjusted mean change from BL (SE)	-1.1 (1.18)	4.4 (1.19)
Mean difference vs. GPZ + MET (SE)	-5.5 (1.67)	
95% CI	-8.8 to -2.2	
HbA_{1c} ≤ 6.5%		
N	423	423
n (%)	152 (35.9)	145 (34.3)
Mean difference in proportion vs. GPZ + MET (%)	1.7	
95% CI	-4.8 to 8.1	
HbA_{1c} change from BL with BL HbA_{1c} ≥ 7.0%		
N	324	320

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BL mean (SE)	7.96 (0.045)	7.96 (0.041)
Adjusted mean change from BL (SE)	-0.65 (0.049)	-0.77 (0.050)
Mean difference in proportion vs. GPZ + MET (SE)	0.12 (0.070)	
95% CI	-0.01 to 0.26	
HbA_{1c} < 7.0% with BL HbA_{1c} ≥ 7.0%		
<i>N</i>	324	320
<i>n</i> (%)	138 (42.6)	153 (47.8)
Difference vs. GPZ + MET (%)	-5.2	
95% CI	-12.9 to 2.5	
HOMA-2β (%)		
<i>N</i>	341	336
BL mean (SE)	66.7 (1.72)	68.3 (2.08)
Adjusted mean change from BL (SE)	7.4 (2.54)	21.7 (2.56)
Mean difference vs. GPZ + MET (SE)	-14.3 (3.60)	
95% CI	-21.4 to -7.2	

BL, baseline; CI, confidence interval; FPG, fasting plasma glucose; GPZ, glipizide; HbA_{1c}, glycated haemoglobin; MET, metformin; SAXA, saxagliptin; SE, standard error; PPG, postprandial glucose.

*Per-protocol analysis set.

Deleted: PPG at 120 min† (mg ... [1]

Deleted: †Oral glucose tolerance test (OGTT) patient subset.¶

Table 3 Safety and tolerability during the 52-week treatment period

	SAXA + MET	GPZ + MET
Adverse events, n (%)^{*†‡}	(n = 428)	(n = 430)
≥ 1 AE	260 (60.7)	293 (68.1)
≥ 1 related AE	42 (9.8)	134 (31.2)
Deaths	2 (0.5)	2 (0.5)
≥ 1 SAE§¶	39 (9.1)	32 (7.4)
≥ 1 related SAE	0	1 (0.2)
Discontinuation from study medication due to AE	18 (4.2)	19 (4.4)
Discontinuation from study medication due to SAEs	8 (1.9)	8 (1.9)
Adverse events (≥ 5%)^{**}		
Nasopharyngitis	41 (9.6)	37 (8.6)
Diarrhoea	22 (5.1)	16 (3.7)

AE, adverse event; GPZ, glipizide; MET, metformin; SAE, serious adverse event; SAXA, saxagliptin.

*AE defined as any new or worsening illness, sign, symptom or clinically significant laboratory test abnormality as noted by the investigator during the course of the study, regardless of the investigator's attribution of the event to study treatment.

†AEs are included up to the last of: 1) the last treatment day +1 day or, 2) the last visit day in the 52-week treatment period.

‡Includes hypoglycaemia events.

§SAE defined as an AE that was fatal, life threatening, required in-patient hospitalisation or prolonged an existing hospitalisation, resulted in persistent or significant disability or incapacity, a cancer, a congenital anomaly/birth defect, resulted in the development of drug dependency or drug abuse or was an important medical event that jeopardised the patient or required intervention to prevent a serious outcome.

¶SAEs are included up to the last of: 1) the last treatment day +30 days or 2) the last visit day +30 days in the 52-week treatment period.

**Excludes hypoglycaemia events.

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Table 4 All reported hypoglycaemic events by fingerstick plasma glucose concentration during 52-week treatment period*†

		Plasma Glucose Level (mg/dL) [mmol/L]				No fingerstick value obtained	Total
		≤ 50 [≤ 2.8]	> 50 – < 63 [> 2.8 – < 3.5]	≥ 63 – < 70 [≥ 3.5 – < 3.9]	≥ 70 [≥ 3.9]		
Treatment group							
SAXA + MET, N = 428	Events, n (%)‡,§	0 (0.0)	5 (26.3)	2 (10.5)	3 (15.8)	9 (47.4)	19 (100.0)
	Patients, n (%)‡,¶	0 (0.0)	4 (0.9)	2 (0.5)	2 (0.5)	6 (1.4)	13 (3.0)
GPZ + MET, N = 430	Events, n (%)‡,§	66 (8.8)	283 (37.7)	146 (19.5)	151 (20.1)	104 (13.9)	750 (100.0)
	Patients, n (%)‡,¶	38 (8.8)	103 (24.0)	72 (16.7)	51 (11.9)	44 (10.2)	156 (36.3)

GPZ, glipizide; MET, metformin; SAXA, saxagliptin.

*Safety analysis set.

†Reported hypoglycaemia events is a combination of reports of either signs or symptoms consistent with hypoglycaemia or reported low glucose levels.

‡In patient and event incidences, a patient could contribute to more than 1 column. In event incidences, a patient could experience more than 1 event corresponding to the same column.

§Event percent = 100*(number of events of the column)/total number of events.

¶Patient percent = 100*(number of patients with events of the column)/N.

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FIGURE LEGENDS

Figure 1 Patient disposition. Recruitment period ran from December 11, 2007 through August 5, 2008, and the last visit in the 52-week treatment period was August 28, 2009. *The category of “No longer met study criteria” corresponds to the category of “Development of study specific discontinuation criteria.”

†Patients were only included in this category if the study investigator checked adverse event (AE) as the primary reason for discontinuation. A patient may have experienced an AE that resulted in discontinuation and was summarised as an AE leading to discontinuation that was not counted here as a reason for discontinuation if the study investigator checked an alternative primary reason for discontinuation. ‡Per study investigator’s opinion. GPZ, glipizide; MET, metformin; SAXA, saxagliptin.

Figure 2 Composite figure. (A) Primary end-point: Adjusted mean change from baseline HbA_{1c} at week 52: SAXA + MET vs. GPZ + MET. (B) Mean HbA_{1c} values over time: SAXA + MET vs. GPZ + MET.

*Per-protocol analysis set GPZ, glipizide; MET, metformin; SAXA, saxagliptin.

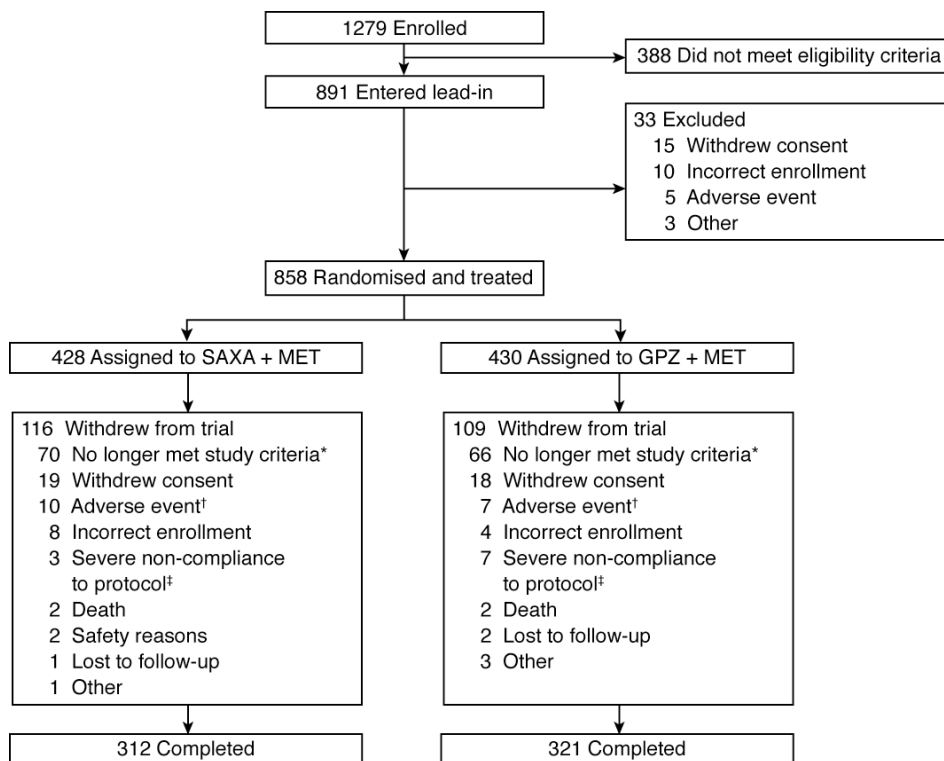
Figure 3 Proportion of patients with at least 1 hypoglycaemic episode over 52 weeks. *Safety analysis set. †p < 0.0001.

Figure 4 Adjusted mean change from baseline body weight (kg) to week 52. *Safety analysis set. †p < 0.0001.

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FIGURES

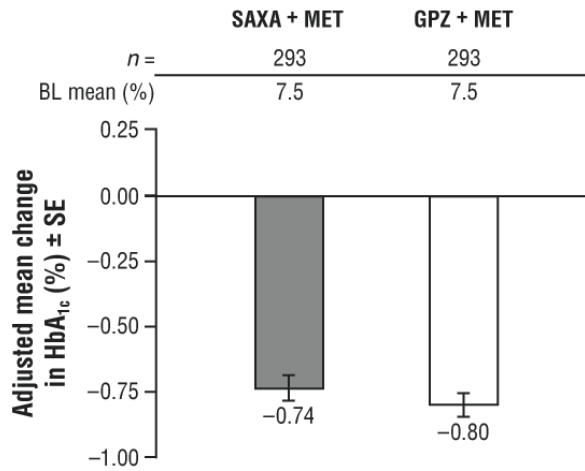
Figure 1 Patient disposition



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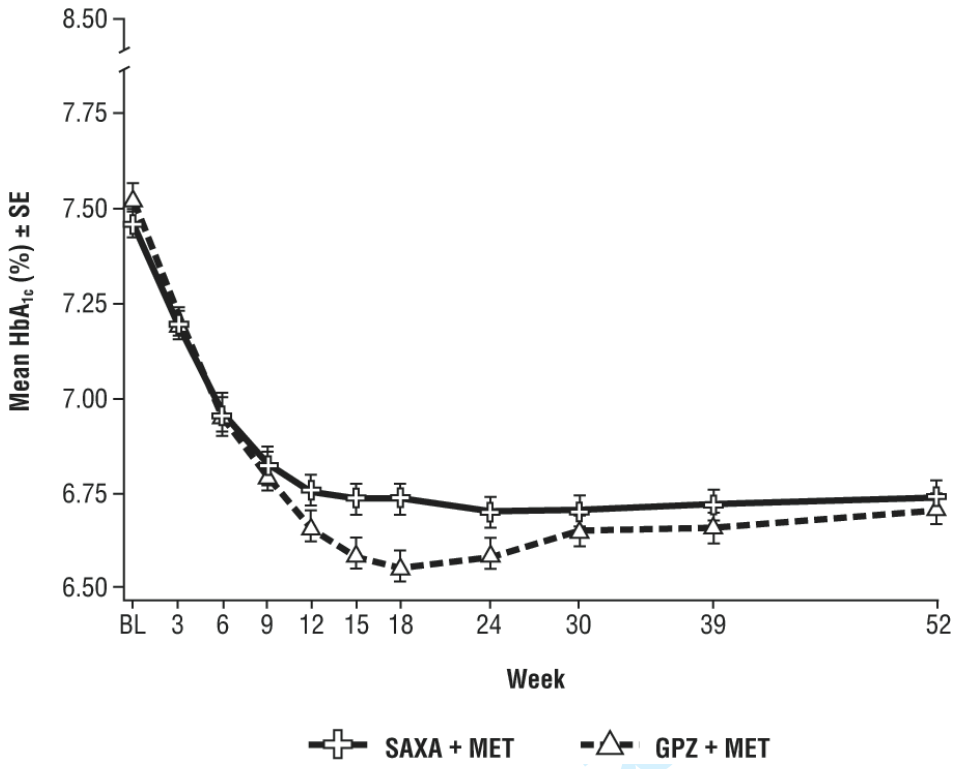
Figure 2 Composite figure

(A) Primary end-point: Adjusted mean change from baseline HbA_{1c} at week 52*: SAXA + MET vs. GPZ + MET



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(B) Mean HbA_{1c} values over time*: SAXA + MET vs. GPZ + MET



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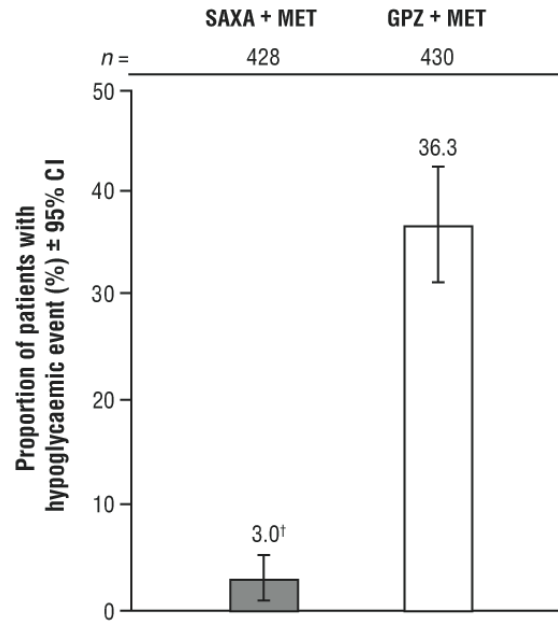
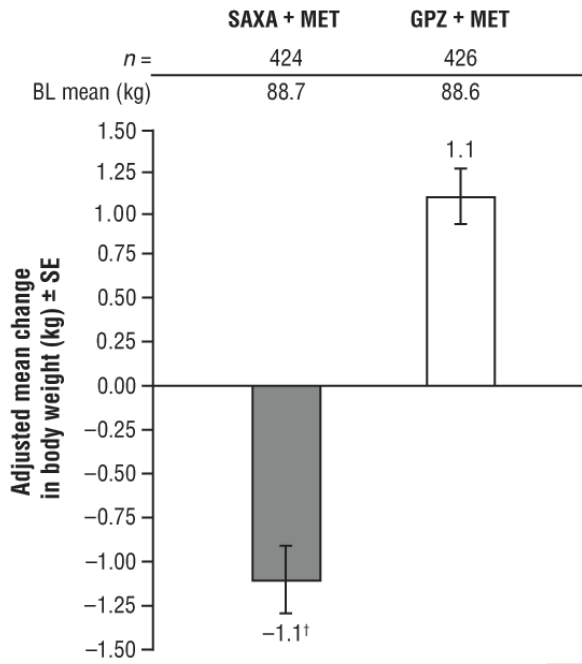
Figure 3 Proportion of patients with at least 1 hypoglycaemic episode over 52 weeks*

Figure 4 Adjusted mean change from baseline body weight to week 52*: SAXA + MET vs. GPZ + MET



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SUPPLEMENTARY MATERIAL**Table 1** Conversion chart: conventional to SI units*

Component	Conventional Unit	Conversion Factor	SI Unit
Glucose	mg/dl	0.0555	mmol/l
Insulin	μIU/ml	6.945	pmol/l
Glucagon	pg/ml	1.0	ng/l
C-peptide	ng/ml	0.333	nmol/l

*To convert from the conventional unit to the SI unit, multiply by the conversion factor.

SI, Système International d'Unités.

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PPG at 120 min[†] (mg/dl)		
<i>N</i>	18	17
BL mean (SE)	285 (11.7)	280 (16.1)
Adjusted mean change from BL (SE)	-49 (16.6)	-28(17.1)
Mean difference vs. GPZ + MET (SE)	-21 (23.8)	
95% CI	-69.3 to 27.8	

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