Efficacy and Safety of Saxagliptin Compared with Acarbose in Chinese Patients with Type 2 Diabetes Mellitus Uncontrolled on Metformin Monotherapy: Results of a Phase IV Open-Label Randomized Controlled Study (The SMART Study)

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Abstract

Aim: To investigate the efficacy, safety and tolerability of saxagliptin compared with acarbose in Chinese patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin monotherapy.

Materials and Methods: SMART was a 24-week, multicentre, randomized, parallel-group, open-label Phase IV study conducted at 35 sites in China (24/09/2014–29/09/2015). The primary outcome was change from baseline in HbA1c at Week 24. Secondary efficacy outcomes assessed at Week 24 included the proportion of patients achieving HbA1c<7.0%, the proportion of patients with gastrointestinal adverse events (GI AEs), and the proportion of patients achieving HbA1c<7.0% without GI AEs. Safety and tolerability were also assessed in all patients who received ≥1 dose of study medication.

Results: 488 patients were randomized (1:1) to saxagliptin or acarbose via a central randomization system (interactive voice/web response system); 241 and 244 patients received saxagliptin and acarbose, respectively, and 238 and 243 of these had ≥1 pre- and ≥1 post-baseline efficacy values recorded. Saxagliptin was non-inferior to acarbose for glycaemic control (Week 24 HbA1c change: –0.82 and –0.78%, respectively; difference [95%
confidence interval]: –0.04 [–0.22, 0.13]%) with similar proportions of patients in both
treatment groups achieving HbA1c<7.0%. However, fewer GI AEs were reported with
saxagliptin compared with acarbose and a greater number of patients who received
saxagliptin achieved HbA1c<7.0% without GI AEs compared with those receiving acarbose.

**Conclusion:** Both therapies had similar efficacy profiles. However saxagliptin was
associated with fewer GI AEs, suggesting it might be preferential for clinical practice.

**Clinical trial registration number:** NCT02243176, clinicaltrials.gov.

**Introduction**
Diabetes is epidemic in China, with an estimated 11.6% of adults having type 2 diabetes
mellitus (T2DM) and 50.1% having prediabetes.\(^1, 2\) Poor diet and lack of physical activity are
considered the main causes of T2DM in the Chinese population, with adiposity being an
important risk factor for diabetes. Furthermore, Chinese people are more susceptible to
developing T2DM at a lower body mass index (BMI; 25 vs 30 kg/m\(^2\)).\(^1, 3\) An increasing
number of Chinese individuals are overweight (body mass index [BMI] ≥25 kg/m\(^2\)) or obese
(BMI ≥30 kg/m\(^2\)),\(^1, 3\) and there has been an increased prevalence of central obesity.\(^3, 8\) In
addition, Chinese people with T2DM have been observed to have worse β-cell deterioration
in the early stages of diabetes compared with Western populations.\(^9\) These differences in the
characteristics of Chinese patients with T2DM highlight the need for clinical trials
specifically in the Chinese population.\(^10\)

In China, metformin is the recommended first-line therapy for patients with T2D\(^11\), and α-
glucosidase inhibitors (including acarbose) are the most-widely used class of second-line oral
antihyperglycaemic drugs (OADs).\(^10, 11\) They act in the brush border of the small intestine to
reduce the digestion of carbohydrates in the first half of the small intestine.\(^12\) This reduces
postprandial glucose (PPG) levels, HbA1c, fasting plasma glucose (FPG) and body weight,
without significantly increasing the risk of hypoglycaemia.\(^10-13\) However, gastrointestinal (GI)
side effects are common, with flatulence occurring in ≥1/10 patients, and diarrhoea and GI and abdominal pain in ≥1/100 to <1/10 patients.\textsuperscript{14} 

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that has been demonstrated to improve glycaemic control with a low risk of hypoglycaemia, as well as being body weight-neutral.\textsuperscript{15-18} DPP-4 inhibitors prevent the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), resulting in increased glucose-dependent insulin secretion and suppression of glucagon secretion.\textsuperscript{19} Previous data have shown that DPP-4 inhibitors have a similar efficacy profile to α-glucosidase inhibitors but with better GI tolerability,\textsuperscript{14, 15, 20, 21} and so may be a more attractive choice of second-line therapy than acarbose for some patients. The SMART Study investigated the efficacy, safety and tolerability of saxagliptin compared with acarbose in Chinese patients with T2DM inadequately controlled with metformin monotherapy.

**Materials and Methods**

**Study design and participants**

The SMART study (NCT02243176) was a 24-week, multicentre, randomized, parallel-group, open-label Phase IV study comparing saxagliptin with acarbose in patients with T2DM inadequately controlled with metformin monotherapy that was conducted at 35 sites in China. The study included patients (≥18 years) treated with stable metformin monotherapy (≥1500 mg/day or individually maximally tolerated dose, but not more than the maximum dose specified on the label) for at least 8 weeks with an HbA1c between 7.5 and 11.0% at screening, and an HbA1c between 7.0 and 11.0% and an FPG ≤13.3 mmol/L at the pre-randomization visit.
Exclusion criteria included: diagnosis of type 1 diabetes, diabetes resulting from pancreatic injury or secondary forms of diabetes; history of acute metabolic complications of diabetes (including ketoacidosis or hyperosmolar coma) within 6 months of screening; previous treatment with any DPP-4 inhibitor or GLP-1 receptor agonists within 1 year of screening; history of hypersensitivity reaction to either a DPP-4 inhibitor or acarbose; treatment with any anti-hyperglycaemic agent other than metformin for more than 7 consecutive days in the 8 weeks before screening; triglycerides >4.5 mmol/L at screening or within 4 weeks prior to screening; moderate/severe renal impairment or end-stage renal disease at screening or within 4 weeks prior to screening; congestive heart failure defined as New York Heart Association (NYHA) class III or IV; significant cardiovascular history within 3 months prior to screening; or a history of chronic pancreatitis or idiopathic acute pancreatitis or gastrointestinal disease.

Patients were randomized (1:1) via a central randomization system to receive either saxagliptin (Onglyza®, AstraZeneca, Möndal, Sweden) 5 mg once daily for 24 weeks or acarbose (Glucobay®, Bayer AG, Leverkusen, Germany) 50 mg three-times daily for the first 7 days following randomization, and then titrated to 100 mg three-times daily if appropriate. All patients also continued on their existing dose and regimen of metformin throughout the study; metformin dose could be reduced in response to hypoglycaemia, but otherwise could not be adjusted. In addition, all patients received a diet and exercise plan that was implemented from the lead-in period to the end of the study. Patients were randomized by a central randomization system (interactive voice/web response system), stratified according to HbA1c (<8.0% and ≥8.0%). Those receiving acarbose had an additional telephone consultation on Day 7 to monitor for adverse events (AEs) and to titrate the dose to 100 mg, if appropriate. The study design is shown in Supplementary Figure 1.
Patients were discontinued if FPG was >13.3 mmol/L at Visit 6 (Week 4; confirmed by a second measurement within 1 week) or if FPG was >12.2 mmol/L at Visit 7 (Week 12; confirmed by a second measurement within 1 week). Although the study was open label, investigators were blinded to key efficacy parameters (HbA1c, FPG and 2-hour PPG) during the course of the study (randomization to Week 24) with the exception of the screening and pre-randomization visits. If a patient met one of the FPG discontinuation criteria the investigator was alerted so that the confirmation test could be scheduled.

The study was performed in accordance with the clinical trial protocol, the International Conference on Harmonization–Good Clinical Practice guidelines, ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements. The study protocol was approved by the institutional review board or independent ethics committee at each site and all patients provided written informed consent.

**Study objectives and outcomes**

The primary efficacy outcome was absolute change from baseline in HbA1c at Week 24 with saxagliptin compared with acarbose. Secondary efficacy outcomes were the proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7.0%) at Week 24, the proportion of patients with any GI AEs, the proportion of patients achieving therapeutic glycaemic response at Week 24 without GI AEs, and the change from baseline in FPG, 2-h PPG, β-cell function and body weight at Week 24. β-cell function was measured by HOMA-β (homeostasis model assessment-β).

The safety and tolerability of saxagliptin and acarbose were evaluated according to the frequency of AEs and serious AEs (SAEs), as well as monitoring of vital signs, clinical...
chemistry and haematology parameters. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) 18.0, summarized by system organ class and preferred term, and sorted by frequency according to treatment group. Common AEs were defined as those that occurred in at least 2% of patients in either treatment group. Hypoglycaemic events were defined as either a symptomatic event with blood glucose level <2.9 mmol/L and no need for external assistance, or an asymptomatic blood glucose measurement <2.9 mmol/L. Severe hypoglycaemic events were defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour. Compliance was assessed based on returned tablet counts. The change from baseline in the European Quality of Life – 5 Dimensions (EQ-5D) at Week 24 with saxagliptin compared with acarbose was also evaluated.

**Statistical analysis**

A total of 480 patients were planned to be enrolled (240 patients per study arm) to provide 90% power to establish non-inferiority of saxagliptin compared with acarbose for the primary endpoint at a one-sided $\alpha$ level of 0.025, with a non-inferiority margin of 0.4% and based upon an expected drop-out rate of 20%. This assumed that the true effects would be the same between treatments and that the standard deviation (SD) for the change in HbA1c was 1.2%. A study population of 480 would also provide approximately 85% power to detect a difference in the incidence of GI AEs between saxagliptin and acarbose, assuming GI AE rates of 12.5 and 25% with saxagliptin and acarbose, respectively.

The primary outcome was analysed in the full analysis set (FAS), which included all patients who received at least one dose of study medication and had at least one baseline and one
post-baseline efficacy measurement. The primary outcome was analysed using a mixed-model repeated-measures (MMRM) analysis including terms for treatment group, time, baseline measurement and time-by-treatment-group interaction. Data were analysed as observed without imputation of missing efficacy data. Point estimates and 2-sided 95% confidence intervals (CIs) were presented at each visit for the least squares mean change from baseline within each treatment group, as well as the difference in the least squares mean change from baseline (standard error [SE]) between groups. A sensitivity analysis was also conducted on the primary outcome using analysis of covariance (ANCOVA) with last observation carried forward for missing values. The ANCOVA included treatment group as a fixed effect and HbA1c value at baseline as a covariate. The primary outcome was also investigated in the per-protocol (PP) analysis set as a supportive analysis. The PP analysis set was a subset of the FAS that included all FAS patients who did not have significant protocol deviations that might affect the study outcome. The most frequent protocol deviations were premature discontinuation and poor compliance.

Secondary efficacy outcomes recorded as continuous variables were either analysed using a MMRM analysis similar to that used for the primary outcome (change from baseline in FPG and body weight) or an ANCOVA similar to that used for the sensitivity analysis of the primary outcome (change from baseline in 2-h PPG and HOMA-β). Secondary efficacy outcomes recorded as categorical variables were analysed using the Cochran–Mantel–Haenszel test with HbA1c at baseline (<8.0% or ≥8.0%) as a stratification factor. The relative risk and associated 95% CI were estimated using the Mantel–Haenszel method.

Safety outcomes were evaluated in the safety analysis set which included all patients who took at least one dose of study treatment. Analyses for safety outcomes were summarized...
using descriptive statistics for continuous variables or frequency counts and percentages for categorical variables.

Change from baseline in each individual item of the EQ-5D as well as the EQ-5D index were analysed in patients included in the FAS who completed EQ-5D questionnaires at both Week 0 and Week 24 (patient reported outcome analysis set), using an ANCOVA similar to that used for the sensitivity analysis of the primary outcome.

**Results**

**Disposition**

Overall, 689 patients were enrolled between 24 September 2014 and 29 September 2015 (Figure 1). Following screening, 488 patients were randomized (1:1) to receive saxagliptin (n=244) or acarbose (n=244). Three patients in the saxagliptin group did not take any study medication. Therefore, the safety analysis set included 241 patients in the saxagliptin group and 244 patients in the acarbose group.

Three additional patients in the saxagliptin group and one patient in the acarbose group did not have at least one post-baseline efficacy measure, meaning that the FAS included 238 and 243 patients in the saxagliptin and acarbose groups, respectively. Nineteen patients in the saxagliptin group and 39 in the acarbose group had significant protocol deviations, and the PP analysis set therefore included 219 and 204 patients in the saxagliptin and acarbose groups, respectively.

Similar numbers of patients discontinued in both groups (saxagliptin, n=14 [5.7%]; acarbose, n=15 [6.1%]), most frequently because of a patient’s decision to discontinue (Figure 1).
Baseline characteristics and demographics

Demographic and baseline characteristics for the FAS were generally well balanced between treatment groups, with the exception of 2-h PPG which was higher in the group receiving saxagliptin compared with the group receiving acarbose (Table 1). The mean BMI was 26.4 and 26.3 kg/m² in the saxagliptin and acarbose groups, respectively, with both overweight and obese individuals included in both groups, as would be expected in a population with T2DM.

Efficacy outcomes

Primary efficacy outcome

Both saxagliptin and acarbose reduced HbA1c levels rapidly (by Week 4 of treatment; Figure 2) with reductions continuing up to the end of the study (Week 24). The least squares mean (SE) change from baseline to Week 24 (MMRM analysis) in HbA1c of –0.82 (0.06)% and –0.78 (0.06)% in the saxagliptin group and acarbose group, respectively (Table 2). The least squares mean (SE) difference (MMRM analysis) between the groups (saxagliptin – acarbose) was –0.04 (0.09)%; 95% CI: –0.22% to 0.13%. The upper limit of the 95% CI was below the non-inferiority margin of 0.4% but greater than 0, indicating the non-inferiority of saxagliptin to acarbose for the primary endpoint. This was supported by the results of the sensitivity analysis (ANCOVA) in the FAS (least squares mean [SE] change from baseline to Week 24: –0.81 [0.06]% and –0.76 [0.06]% with saxagliptin and acarbose, respectively; least squares mean [SE] difference: –0.04 [0.09]%; 95% CI: –0.22% to 0.13%), as well as the MMRM analysis of the PP population (Supplementary table 1).
Secondary efficacy outcomes

At Week 24, 88 (38.3%) patients receiving saxagliptin and 95 (41.5%) patients receiving acarbose had achieved a therapeutic glycaemic response (HbA1c <7.0%). In the FAS, 13 (5.5%) patients receiving saxagliptin and 60 (24.7%) patients receiving acarbose reported GI AEs (risk ratio=0.22, p<0.0001). This lower risk of GI AEs was also observed in the PP population (saxagliptin, 11/219 [5.0%]; acarbose, 53/204 [26.0%]; risk ratio=0.19, p<0.0001). Overall, 85 (37.0%) patients and 66 (28.8%) patients receiving saxagliptin and acarbose, respectively, achieved a therapeutic glycaemic response without GI AEs.

There was no significant difference between treatment groups for change from baseline to Week 24 in FPG, 2-h PPG and HOMA-β (Table 2), however, significantly greater weight loss was observed with acarbose compared with saxagliptin (p=0.0078). Consistent results for these endpoints were also observed in the PP population (Supplementary Table 1). In addition, treatment compliance was high in both treatment groups; mean compliance to treatment was 100.2% and 99.9% for patients receiving saxagliptin and acarbose, respectively.

Safety and tolerability

The mean (SD) duration of exposure to saxagliptin and acarbose was 165.5 (21.93) and 163.2 (24.64) days, respectively. The frequency of treatment-related AEs was lower in the saxagliptin group compared with the acarbose group, occurring in 8 (3.3%) and 50 (20.5%) patients in each group, respectively (Table 3). The most frequently occurring treatment-related AEs were GI events, occurring in three (1.2%) patients treated with saxagliptin and 49 (20.1%) patients treated with acarbose. Commonly occurring treatment-related AEs (occurring in ≥2% of the safety analysis set) were abdominal distension and flatulence which

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occurred in 23 (9.4%) and 17 (7.0%) patients, respectively, treated with acarbose, and two (0.8%) and zero patients, respectively, treated with saxagliptin.

The incidence of AEs leading to discontinuation was also low in both groups with one (0.4%) patient discontinuing in each group. One patient treated with saxagliptin had an SAE potentially related to the treatment, experiencing moderate oedema of both lower limbs after taking the drug for 106 days. The oedema resolved following symptomatic treatment. This SAE did not lead to discontinuation of saxagliptin. There were no unexpected observations with saxagliptin or acarbose in terms of haematology, clinical chemistry or vital signs (Supplementary Table 2). The incidence of hypoglycaemia was low and similar in both groups; 3 (1.2%) patients receiving saxagliptin and 4(1.6%) patients receiving acarbose.

**Patient reported outcomes**

At Week 24, the changes from baseline in all items of the EQ-5D were similar in both treatment groups (Supplementary Table 3), with no overall apparent difference between saxagliptin and acarbose.

**Discussion**

This study in a population typical of patients with T2DM in China demonstrated that saxagliptin was non-inferior to acarbose for reduction in HbA1c, as add-on to metformin in patients with inadequate glycaemic control. Furthermore, there was no significant difference between the effects of saxagliptin and acarbose on FPG, 2-h PPG or HOMA-β. Similar proportions of patients in both treatment groups achieved a therapeutic glycaemic response (HbA1c <7.0%). However, fewer GI AEs were reported with saxagliptin compared with acarbose, and a greater number of patients who received saxagliptin achieved a therapeutic glycaemic response without GI AEs. Despite this difference in the proportion of patients with GI AEs there was no significant difference between treatment groups in the change from
baseline to Week 24 in EQ-5D items, including pain/discomfort. In addition, there were no unexpected safety findings with saxagliptin or acarbose and a low incidence of hypoglycaemia over 24 weeks was observed in this study.

The current Chinese treatment guidelines for T2DM recommend that, unless contraindicated, patients with T2DM poorly controlled with diet and exercise are initiated on metformin. However, once patients can no longer maintain glycaemic control with metformin the current guideline recommend the addition of a second-line treatment, which could be an alpha-glucosidase inhibitor, insulin secretagogue, thiazolidinedione or DPP-4 inhibitor. Head-to-head studies of these treatment choices are, therefore, important for clinical practice as they enable any potential differences, advantages and disadvantages to be identified for consideration, thereby facilitating selection of the optimum second-line treatment for each individual patient.

Saxagliptin has been studied in the Chinese population as monotherapy and as combination therapy with other OADs, and has been shown to provide antihyperglycemic efficacy with a low risk of AEs. In addition to its good tolerability, there are a number of other theoretical benefits with the use of saxagliptin. It is given once-daily, whereas acarbose is generally initiated at 50 mg three-times daily, increased to 100 mg three-times daily, if required. The use of saxagliptin, therefore, reduces the pill burden for patients compared with acarbose. This is important as patients have a preference for less burdensome treatment regimens, which has also been observed to improve compliance. No difference in compliance between treatment arms was observed in the SMART study, however, this may be related to the clinical trial setting. In addition, the daily cost of acarbose at a dose of 300 mg/day is currently higher than the daily cost of saxagliptin.
DPP-4 inhibitors act by inhibiting the degradation of the incretins GLP-1 and GIP, which are produced physiologically in response to eating.\textsuperscript{27, 28} The incretins stimulate insulin secretion and inhibit glucagon release, both of which contribute to a reduction in blood glucose levels. Owing to their mechanism of action they predominantly act on PPG and this may be beneficial for Asian patients in a similar manner to acarbose, as it has been suggested that PPG levels have a larger impact on hyperglycaemia than FPG levels in Asian patients.\textsuperscript{12, 18, 29-31} This might be related to the Asian diet, which includes food with high glycaemic load (e.g. rice) resulting in larger PPG excursions in Asian people.\textsuperscript{31}

This study has a number of limitations that should be kept in mind when considering the results. The EQ-5D was only evaluated at baseline and Week 24 and, as most GI AEs are likely to have occurred during the first weeks following treatment initiation (before treatment with symptomatic medication), patients might not have registered them on the EQ-5D assessment at 24 weeks. In addition, the study duration was only 24 weeks and so does not provide long-term efficacy or safety data for the use of saxagliptin compared with acarbose. However, longer-term studies in non-Chinese populations have shown that the glycaemic efficacy of saxagliptin is maintained beyond 2 years, without any significant changes in its safety profile.\textsuperscript{32, 33}

In conclusion, this study demonstrated that saxagliptin and acarbose have similar efficacy profiles, including their effects on PPG and β-cell function, but saxagliptin is associated with fewer GI AEs. This suggests that it may be preferable to acarbose for second-line use following failure of metformin.
**Author contributions**
Yiming Mu led the study design, trial operation, data analysis and manuscript preparation.

All authors were involved in the study design, trial operation, data collection, and preparation, review and final approval of the manuscript.

**Acknowledgements**
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**Role of the funding source**
AstraZeneca was involved in the study design, the collection, analysis and interpretation of data, and the writing of the report.

**Conflicts of Interest**
JD has received lecture fees from Novo Nordisk and Sanofi. YM has attended advisory boards for Novo Nordisk, Eli Lilly, and AstraZeneca; received research grants from Novartis; and been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis, and Bayer.

WL has participated in the clinical trials of Novo Nordisk, Eli Lilly and Sanofi Aventis; has been a speaker for these companies. XW has been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis and Bayer. HF had been a speaker for Novo Nordisk, AstraZeneca, Sanofi Aventis, Bayer and Eli Lilly. CX has received lecture fees from Novo Nordisk. FX has received lecture fees from Novo Nordisk and Eli Lilly, and been a speaker for Eli Lilly and Bayer. LL has attended advisory boards for Novo Nordisk, Eli Lilly, and AstraZeneca; and been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis.
and Bayer. FB has received research grants and lecture fees from Novo Nordisk. LS has participated in the clinical trials of Novartis and Takeda; has been a speaker for Novo Nordisk, Boehringer Ingelheim, Novartis, Takeda, Sanofi Aventis, MSD.

References

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http://www.zjpi.gov.cn/main/html/2014/CT10046/dd72e4240a7e4c1da820a849642f7b37.htm


Figure legends

**Figure 1.** Patient disposition throughout the study

**Figure 2.** Change from baseline in HbA1c over time

Tables

**Table 1.** Demographic and baseline characteristics (full analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin (n=238)</th>
<th>Acarbose (n=243)</th>
<th>Overall (n=481)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean [SD])</td>
<td>54.7 (10.51)</td>
<td>56.5 (10.81)</td>
<td>55.6 (10.69)</td>
</tr>
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<table>
<thead>
<tr>
<th></th>
<th>Female (n [%])</th>
<th>105 (43.2)</th>
<th>196 (40.7)</th>
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<tr>
<td>Weight, kg (mean [SD])</td>
<td>73.3 (12.61)*</td>
<td>72.6 (12.27)</td>
<td>72.9 (12.43)†</td>
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<tr>
<td>BMI, kg/m² (mean [SD])</td>
<td>26.4 (3.47)*</td>
<td>26.3 (3.49)</td>
<td>26.3 (3.48)†</td>
</tr>
<tr>
<td>Duration of T2DM diagnosis, years (Mean [SD])</td>
<td>5.1 (4.40)*</td>
<td>5.3 (4.76)</td>
<td>5.2 (4.58)†</td>
</tr>
<tr>
<td>HbA1c, % (mean [SD])</td>
<td>8.23 (0.85)</td>
<td>8.16 (0.81)</td>
<td>8.20 (0.83)</td>
</tr>
<tr>
<td>FPG, mmol/L (mean [SD])</td>
<td>9.01 (2.14)‡</td>
<td>8.81 (1.95)</td>
<td>8.90 (2.04)§</td>
</tr>
<tr>
<td>2-h PPG, mmol/L (mean [SD])</td>
<td>11.17 (2.82)‡</td>
<td>10.25 (2.89)</td>
<td>10.70 (2.89)§</td>
</tr>
</tbody>
</table>

*n=237; †n=480; ‡n=235; §n=478.

2-h PPG, 2-hour postprandial glucose; BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; T2DM, type 2 diabetes mellitus.
Table 2. Change from baseline to Week 24 in HbA1c, fasting plasma glucose, 2-hour postprandial glucose, HOMA-β and body weight (full analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin (n=238)</th>
<th>Acarbose (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (MMRM analysis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n at BL / 24 Weeks</td>
<td>238 / 230</td>
<td>243 / 229</td>
</tr>
<tr>
<td>Baseline, % (Mean [SD])</td>
<td>8.23 (0.85)</td>
<td>8.16 (0.81)</td>
</tr>
<tr>
<td>Week 24, % (Mean [SD])</td>
<td>7.38 (1.03)</td>
<td>7.34 (1.04)</td>
</tr>
<tr>
<td>LS means change (SE)</td>
<td>–0.82 (0.06)</td>
<td>–0.78 (0.06)</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>–0.04 (0.09)</td>
<td>0.6236</td>
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<tr>
<td><strong>FPG (MMRM analysis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n at BL / 24 Weeks</td>
<td>235 / 227</td>
<td>243 / 229</td>
</tr>
<tr>
<td>Baseline, mmol/L (Mean [SD])</td>
<td>9.01 (2.14)</td>
<td>8.81 (1.95)</td>
</tr>
<tr>
<td>Week 24, mmol/L (Mean [SD])</td>
<td>7.87 (1.98)</td>
<td>7.76 (1.92)</td>
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<tr>
<td>LS means change (SE)</td>
<td>–0.99 (0.13)</td>
<td>–1.01 (0.13)</td>
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<td>Difference (SE)</td>
<td>0.02 (0.18)</td>
<td>0.8915</td>
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<td><strong>2-h PPG (ANCOVA analysis)</strong></td>
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<td>n at BL / 24 Weeks</td>
<td>235 / 227</td>
<td>243 / 232</td>
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<td>Baseline, mmol/L (Mean [SD])</td>
<td>11.17 (2.82)</td>
<td>10.25 (2.89)</td>
</tr>
<tr>
<td>Week 24, mmol/L (Mean [SD])</td>
<td>10.04 (2.79)</td>
<td>9.38 (2.75)</td>
</tr>
<tr>
<td>LS means change (SE)</td>
<td>–0.77 (0.176)</td>
<td>–1.07 (0.174)</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>0.30 (0.249)</td>
<td>0.2248</td>
</tr>
<tr>
<td><strong>HOMA-β (ANCOVA analysis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n at BL / 24 Weeks</td>
<td>235 / 227</td>
<td>240 / 225</td>
</tr>
<tr>
<td>Baseline, mU/mmol (Mean [SD])</td>
<td>55.4 (54.5)</td>
<td>55.6 (59.5)</td>
</tr>
<tr>
<td>Week 24, mU/mmol (Mean [SD])</td>
<td>75.6 (118.5)</td>
<td>68.3 (66.7)</td>
</tr>
<tr>
<td>LS means change (SE)</td>
<td>20.56 (5.932)</td>
<td>13.08 (5.958)</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>7.48 (8.407)</td>
<td>0.3739</td>
</tr>
<tr>
<td><strong>Body weight (MMRM analysis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n at BL / 24 Weeks</td>
<td>237 / 227</td>
<td>243 / 226</td>
</tr>
<tr>
<td>Baseline, kg (Mean [SD])</td>
<td>73.3 (12.6)</td>
<td>72.6 (12.3)</td>
</tr>
<tr>
<td>Week 24, kg (Mean [SD])</td>
<td>71.6 (12.5)</td>
<td>70.4 (12.6)</td>
</tr>
<tr>
<td>LS means change (SE)</td>
<td>–1.36 (0.18)</td>
<td>–2.05 (0.18)</td>
</tr>
<tr>
<td>Difference (SE)</td>
<td>0.69 (0.26)</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

2-h PPG, 2-hour postprandial glucose; ANCOVA, analysis of covariance; BL, baseline; FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment-β; LS, least squares; MMRM, mixed-model repeated-measures; SD, standard deviation; SE, standard error.

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Table 3. Adverse events over 24 Weeks (safety analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin (n=231)</th>
<th>Acarbose (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>78 (32.4)</td>
<td>109 (44.7)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>8 (3.3)</td>
<td>50 (20.5)</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other significant AE*</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Hypoglycaemia†</td>
<td>3 (1.2)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>AE leading to permanent treatment discontinuation</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

All data are reported as number (%) of patients. *Other significant AEs were identified by a medically qualified expert in consultation with the appropriate Global Patient Safety Physician during the evaluation of safety data. †Hypoglycaemic events were defined as either a symptomatic event with blood glucose level <2.9 mmol/L and no need for external assistance, or an asymptomatic blood glucose measurement <2.9 mmol/L. Severe hypoglycaemic events were defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour. AE, adverse event; SAE, severe adverse event.
Figures

Figure 1

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Figure 2

![Graph showing the change from baseline in HbA1c (%) for Saxagliptin and Acarbose over time.]

- **Saxagliptin**
  - Week 10: -0.80 (0.98)
  - Week 20: -0.86 (0.99)

- **Acarbose**

<table>
<thead>
<tr>
<th>Sample size per time point</th>
<th>Week 10</th>
<th>Week 20</th>
<th>BL value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>237</td>
<td>236</td>
<td>230</td>
</tr>
<tr>
<td>Acarbose</td>
<td>242</td>
<td>237</td>
<td>229</td>
</tr>
</tbody>
</table>

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