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BRIEF REPORT

Characterization of the Open-Label Lead-In Period of Two Randomized Controlled Phase 3 Trials Evaluating Dapagliflozin, Saxagliptin, and Metformin in Type 2 Diabetes

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ABSTRACT

Introduction: To examine the utility of sequential versus dual add-on approaches in patients who have type 2 diabetes and inadequate glycemic control with metformin therapy alone, we characterized the efficacy and safety of dual therapy with dapagliflozin or saxagliptin added to metformin in the open-label lead-in periods of two phase 3 trials (study 1, NCT01619059; study 2, NCT01646320) that evaluated triple therapy in patients with inadequately controlled type 2 diabetes.

Methods: During the lead-in periods of each trial, patients [glycated hemoglobin (HbA1c) 8.0–11.5%] who had been receiving metformin ≥ 1500 mg/day for ≥ 8 weeks received metformin immediate release at an equivalent dose plus dapagliflozin 10 mg/day (study 1; $N = 482$) or saxagliptin 5 mg/day (study 2; $N = 349$) for 16 weeks. Efficacy end points were assessed at week − 2 before randomization.

Results: Mean change in HbA1c [95% confidence interval (CI)] from lead-in baseline (study 1, 9.3%; study 2, 9.4%) was − 1.6% (− 1.7, − 1.5) in study 1 and − 1.3% (− 1.5, − 1.2) in study 2. Mean changes (95% CI) from lead-in baseline in weight and fasting plasma glucose were − 2.4 kg (− 2.6, − 2.1) and − 47.5 mg/dL (− 52.8, − 42.3) for study 1 and − 0.5 kg (− 0.8, − 0.2) and − 28.5 mg/dL (− 35.8, − 21.2) for study 2. At the end of the lead-in period, 22.0% of patients achieved HbA1c < 7.0% in study 1 and 17.5% in study 2. Dual therapy was well tolerated, with hypoglycemia incidence < 1% in both studies.

Conclusion: Dual therapy improved glycemic control and was well tolerated; however, most patients required additional therapy to further

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improve HbA1c towards target, suggesting that an early move to triple therapy with oral glucose-lowering drugs rather than a stepwise approach may be beneficial for patients with high HbA1c levels on metformin therapy.
Trial Registration: ClinicalTrials.gov NCT01619059, NCT01646320.
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Keywords: Dapagliflozin; Dual therapy; Saxagliptin; Triple therapy; Type 2 diabetes

INTRODUCTION

Type 2 diabetes is a progressive disease characterized by a decline in β-cell function and loss of glycemic control [1]. Achieving control of glucose levels is a major focus of treatment [2]. Current guidelines recommend metformin as first-line glucose-lowering therapy in people with type 2 diabetes, with stepwise addition of other antidiabetes agents as glycemic control deteriorates [3, 4]. A wide range of second- and subsequent-line therapies are available for this purpose, each targeting various aspects of the disease pathophysiology; however, there is no clear consensus on the optimal treatment regimen for patients with type 2 diabetes that is inadequately controlled with metformin alone [2]. A key consideration is the need to balance efficacy with the potential risks of adverse effects, and guidelines recommend transition to triple therapy if glycemic targets are not reached or maintained after 3 months of dual therapy [4]. However, treatment intensification in patients with inadequately controlled type 2 diabetes is often delayed [5].

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are potential options for add-on therapy in patients whose glycemic control is inadequate with metformin alone [6]. Both classes of agent have demonstrated good efficacy, safety, and tolerability as monotherapy and as add-on to metformin in patients with type 2 diabetes [7–11]. Furthermore, in a phase 3 study, dual addition of dapagliflozin (an SGLT-2 inhibitor) plus saxagliptin (a DPP-4 inhibitor) to metformin provided greater improvements in glycemic control than adding either dapagliflozin or saxagliptin alone [7]. Both agents are associated with low incidence of hypoglycemia; dapagliflozin therapy is associated with weight loss and saxagliptin therapy is weight neutral [4].

Two randomized, double-blind, placebo-controlled, 24-week studies showed improved glycemic control with triple therapy of dapagliflozin and saxagliptin sequential add-on to metformin compared with dual therapy of either dapagliflozin or saxagliptin plus metformin [8, 9]. The studies were similar in design and both included an open-label lead-in period (16 weeks) during which patients received dual therapy with metformin plus dapagliflozin or saxagliptin. The aim of the current analysis was to characterize efficacy and safety in the open-label lead-in periods of these studies to examine the utility of sequential versus dual add-on approaches for oral glucose-lowering drugs in patients who have type 2 diabetes and inadequate glycemic control with metformin alone. We hypothesized that patients with high HbA1c levels on metformin therapy would be unlikely to achieve a therapeutic glycemic target with dual therapy over 16 weeks of treatment, and that safety and tolerability findings from the lead-in periods would be similar to those reported with triple therapy.

METHODS

Study Design and Study Participants

This report analyzes data from the lead-in periods of two phase 3 trials that evaluated the efficacy, safety, and tolerability of sequential add-on therapy with saxagliptin plus dapagliflozin to metformin in patients with inadequately controlled type 2 diabetes [8, 9]. In study 1, saxagliptin was added to dapagliflozin plus metformin (ClinicalTrials.gov NCT01619059) [8]. In study 2, dapagliflozin was added to saxagliptin plus metformin (NCT01646320) [9]. Both studies consisted of an open-label lead-in period, during which patients received dual therapy, followed by a 24-week double-blind triple therapy treatment

period and a 28-week long-term extension. The studies were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, and the Declaration of Helsinki. The protocols were approved by the relevant institutional review boards or ethics committees at each study site and all patients provided written informed consent to participate.

Study 1: Dapagliflozin Plus Metformin Lead-In

Patients with type 2 diabetes and inadequate glycemic control [glycated hemoglobin (HbA1c) 8.0–11.5% (64–102 mmol/mol)] who had been receiving stable metformin immediate release (IR) or extended release (XR) $\geq$ 1500 mg/day for $\geq$ 8 weeks at screening were eligible for enrollment in study 1. Enrollment of patients with HbA1c 8.0–9.0% (64–75 mmol/mol) was capped at approximately 50% of participants. Patients also had C-peptide concentration of $\geq$ 1.0 ng/mL, body mass index (BMI) of $\leq$ 45.0 kg/m^2, and estimated glomerular filtration rate (eGFR) of $\geq$ 60 mL/min/1.73 m^2. Patients underwent 16 weeks of open-label treatment with the nearest multiple of metformin IR 500 mg to their usual dose and dapagliflozin 10 mg/day (Fig. 1). Patients discontinued from the study if their fasting plasma glucose (FPG) was $>$ 270 mg/dL (15 mmol/L) at week $-$ 10 or week $-$ 2. To be eligible for randomization and continuation to the double-blind treatment period, patients were required to have HbA1c 7.0–10.5% (53–91 mmol/mol) at week $-$ 2 before randomization.

Study 2: Saxagliptin Plus Metformin Lead-In

In study 2, patients with type 2 diabetes were stratified into two groups, depending on their use of DPP-4 inhibitors. Stratum A had HbA1c 8.0–11.5% (64–102 mmol/mol) at screening and had been receiving stable metformin IR or XR $\geq$ 1500 mg/day for $\geq$ 8 weeks at screening. Stratum B had HbA1c 7.5–10.5% (59–91 mmol/mol) at screening and had been receiving stable metformin IR or XR $\geq$ 1500 mg/day and any DPP-4 inhibitor at the maximum dose for $\geq$ 8 weeks before screening. Only the patients in stratum A, who had not previously been receiving DPP-4 inhibitor therapy, are included in this analysis of the lead-in period.

Eligible patients had C-peptide concentration of $\geq$ 1.0 ng/mL, BMI of $\leq$ 45.0 kg/m^2 and eGFR of $\geq$ 60 mL/min/1.73 m^2. Enrollment of patients with HbA1c 8.0–9.0% (64–75 mmol/mol) was capped at approximately 50% of participants. Patients received the nearest multiple of metformin IR 500 mg to their usual dose and saxagliptin 5 mg/day for 16 weeks of open-label treatment (Fig. 1). Patients were discontinued from the study if their FPG was $>$ 270 mg/dL (15 mmol/L) at week $-$ 10 or week $-$ 2. To be eligible for randomization and continuation to the double-blind treatment period, patients were required to have HbA1c 7.0–10.5% (53–91 mmol/mol) at week $-$ 2 before randomization.

Study Assessments

The following efficacy assessments were performed during the lead-in periods for both

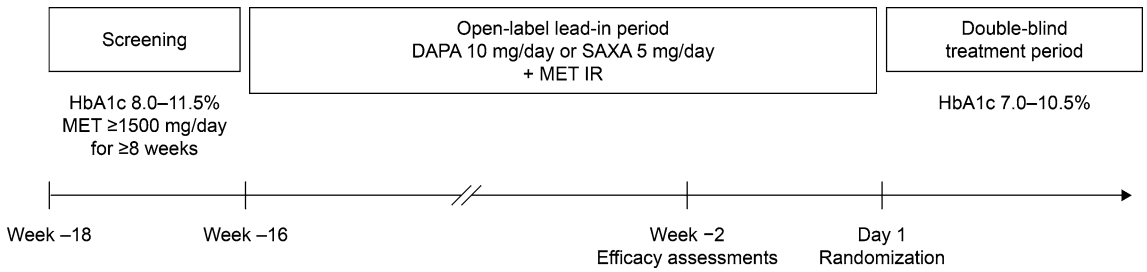

Fig. 1 Design for the lead-in periods of the sequential add-on triple therapy studies. *DAPA* dapagliflozin, *HbA1c* glycated hemoglobin, *IR* immediate release, *MET* metformin, *SAXA* saxagliptin

studies: change in HbA1c, FPG, and body weight from lead-in baseline to week − 2 before randomization, and the proportion of patients with HbA1c < 7.0%, 7.0–10.5%, and > 10.5% (< 53, 53–91, and > 91 mmol/mol, respectively) at week − 2 before randomization. Safety assessments during the lead-in period (week − 16 to randomization at study day 1) included adverse events (AEs), serious AEs (SAEs), hypoglycemia, and other AEs of special interest.

Statistical Analysis

Analyses for this study were conducted for all patients who entered the lead-in period. Data collected during this period were analyzed and presented using descriptive statistics only. Full statistical methodology for the randomized double-blind studies has been described previously [8, 9].

RESULTS

Patient Disposition and Baseline Characteristics

Patient disposition during the lead-in period for each study is shown in Fig. S1. Most patients who entered the lead-in period completed the open-label treatment phase in each study (study 1, 89.4%; study 2, 81.9%). The most common reasons for discontinuation in both studies were not meeting study criteria, loss to follow-up, and withdrawal of consent. Baseline characteristics of patients entering the lead-in period of each study are displayed in Table 1. At lead-in baseline, mean HbA1c was 9.3% (79 mmol/mol) in study 1 and 9.4% (79 mmol/mol) in study 2.

Table 1 Demographics and baseline characteristics for patients entering the lead-in period

	DAPA + MET *N* = 482	SAXA + MET *N* = 349
Age, years	54 (9.7)	54 (9.0)
Gender, *n* (%)		
Men	244 (50.6)	147 (42.1)
Women	238 (49.4)	202 (57.9)
Race, *n* (%)		
White	419 (86.9)	330 (94.6)
Black/African American	32 (6.6)	16 (4.6)
Asian	23 (4.8)	1 (0.3)
Other	8 (1.7)	2 (0.6)
HbA1c (%)	9.3 (1.0)	9.4 (0.9)
HbA1c subcategories, *n* (%)		
< 8.0%	0	1 (0.3)
8.0 to < 9.0%	193 (40.0)	128 (36.7)
≥ 9.0%	286 (59.3)	219 (62.8)
Not reported	3 (0.6)	1 (0.3)
T2D duration, years	7.2 (6.2)	6.8 (6.0)
BMI (kg/m^2)	32.1 (5.2)	31.5 (5.1)
Weight (kg)	89.9 (17.9)	85.5 (18.6)
FPG (mg/dL)	203 (53.4)	201 (61.4)
Fasting C-peptide, ng/mL	2.5 (1.1)	2.5 (1.0)

Data are mean (SD) unless otherwise stated
BMI body mass index, *DAPA* dapagliflozin, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *MET* metformin, *SAXA* saxagliptin, *SD* standard deviation, *T2D* type 2 diabetes

Efficacy

The mean change in HbA1c [95% confidence interval (CI)] from lead-in baseline to end of lead-in was − 1.6% (− 1.7, − 1.5) [− 17.5 mmol/mol (− 18.6, − 16.4)] in patients in study 1 receiving dapagliflozin plus metformin therapy (Fig. 2). In patients in study 2 receiving saxagliptin plus metformin therapy, the mean change in HbA1c from lead-in baseline to end of lead-in was − 1.3% (− 1.5, − 1.2) [− 14.2 mmol/mol (− 16.4, − 13.1)] (Fig. 2). Mean FPG and body weight decreased in both studies (Table 2). The proportion of patients achieving HbA1c < 7.0% at the end of lead-in was 22.0% in study 1 and 17.5% in study 2 (Table 2).

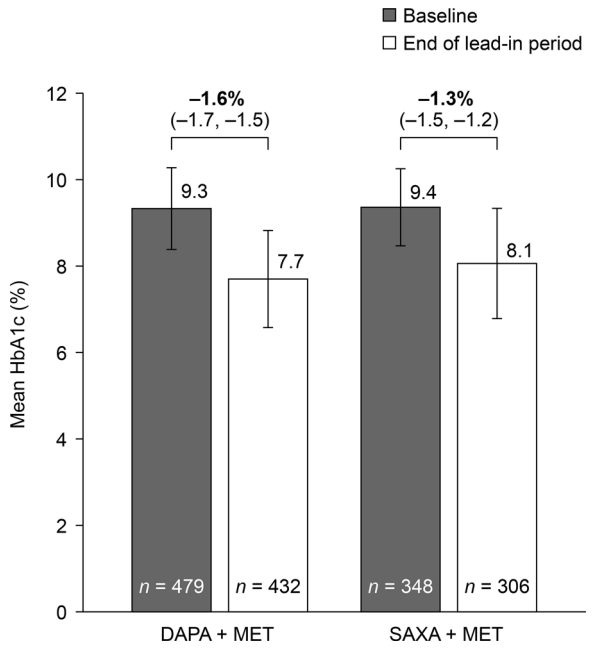

Fig. 2 HbA1c levels at lead-in baseline and the end of the lead-in period. Efficacy end points were assessed at week − 2 before randomization (treatment duration 14 weeks). Data are mean with SD shown as error bars. Mean change from baseline (95% CI) is shown above the bars. *n* is the number of patients with baseline and week − 2 results. CI confidence interval, DAPA dapagliflozin, HbA1c glycated hemoglobin, MET metformin, SAXA saxagliptin, SD standard deviation

Safety and Tolerability

During the lead-in period, AEs were reported by 120 (24.9%) patients in study 1 receiving dapagliflozin plus metformin and by 113 (32.4%) patients in study 2 receiving saxagliptin plus metformin (Table 3). Few AEs led to treatment discontinuation and the incidence of SAEs was low in both studies, with no SAEs considered to be treatment related. There was one patient death in study 1 (pulmonary embolism), which was not considered to be related to treatment. Hypoglycemia was reported infrequently during the lead-in period of both studies; it was reported by only two patients, both receiving dapagliflozin plus metformin. The incidence of cardiovascular events was also low. The most common AEs in patients receiving dapagliflozin plus metformin were genital infections and urinary tract infections. In patients receiving saxagliptin plus metformin, the most common AEs were diarrhea and influenza (Table 3).

DISCUSSION

The guidelines of several international associations suggest that initial combination therapies should be considered for patients with high HbA1c [2, 3]. In this report, we scrutinized the open-label lead-in periods of two studies that evaluated sequential add-on triple therapy with metformin, an SGLT-2 inhibitor (dapagliflozin), and a DPP-4 inhibitor (saxagliptin) in patients with type 2 diabetes and inadequate glycemic control with metformin therapy [8, 9]. During the lead-in periods, data were gathered on the efficacy and safety of dual therapy in patients with high baseline HbA1c levels. The data presented indicate that adding an SGLT-2 inhibitor or a DPP-4 inhibitor to metformin therapy in the setting of a clinical study succeeds in reducing HbA1c substantially over a 16-week period. However, as we hypothesized, the proportion of patients who achieved the HbA1c target (< 7.0%) was relatively low (22.0% with dapagliflozin and 17.5% with saxagliptin). In the subsequent double-blind studies, 35% (dapagliflozin lead-in) and 38% (saxagliptin lead-in) of randomized patients receiving triple therapy reached their HbA1c targets [8, 9]. Together, these findings suggest that in patients with high baseline HbA1c levels, early triple therapy may be more effective in achieving glycemic control than dual therapy. These findings are particularly relevant considering the clinical inertia that is observed in the intensification of glucose-lowering therapy in people living with type 2 diabetes in real-world settings [5].

The magnitude of the reduction in HbA1c observed in these lead-in periods exceeds the effects typically seen with the introduction of an SGLT-2 inhibitor or a DPP-4 inhibitor in patients receiving metformin therapy outside of the clinical trial setting, even in people with similarly high HbA1c levels to those of the patients who were included in this study. This points to a study effect [12], most likely owing

Table 2 Additional efficacy assessments during the lead-in period

	DAPA + MET *N* = 482	SAXA + MET *N* = 349
FPG (mg/dL)		
Mean change from baseline (95% CI)	− 47.5 (− 52.8, − 42.3)	− 28.5 (− 35.8, − 21.2)
FPG (mmol/L)		
Mean change from baseline (95% CI)	− 2.6 (− 2.9, − 2.4)	− 1.6 (− 2.0, − 1.2)
Weight (kg)		
Mean change from baseline (95% CI)	− 2.4 (− 2.6, − 2.1)	− 0.5 (− 0.8, − 0.2)
HbA1c, *n* (%)		
< 7.0%	106 (22.0)	61 (17.5)
7.0–10.5%	320 (66.4)	234 (67.0)
> 10.5%	8 (1.7)	12 (3.4)
No available data[a]	48 (10.0)	42 (12.0)

Efficacy end points were assessed at week − 2 before randomization (treatment duration 14 weeks)
CI confidence interval, *DAPA* dapagliflozin, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *MET* metformin, *SAXA* saxagliptin
[a] Patients not completing the lead-in period who had no available data at week − 2

to the impact of intensified contact with health care workers (e.g., dieticians and diabetes educators) during the clinical trial on treatment outcomes. A potential effect of intensified attention on the patient and increased diabetes education is of utmost importance and should encourage clinicians to accompany initiations of novel glucose-lowering therapies in their patients with close follow-up and in-depth advice from dieticians and diabetes educators.

When comparing the relative efficacies of dapagliflozin and saxagliptin, reductions in HbA1c during the lead-in period were greater with the SGLT-2 inhibitor than with the DPP-4 inhibitor (− 1.6% vs − 1.3%), and treatment with dapagliflozin was also associated with greater weight loss (− 2.4 kg vs − 0.5 kg). Both treatments were well tolerated, although the expected genital infections in the dapagliflozin-treated patients were observed [13]. The safety and tolerability profiles in the lead-in periods were similar to those reported during the 24-week double-blind treatment periods [8, 9] and the 28-week extensions [10, 11], indicating that progression to triple therapy was not associated with increased risk of side effects in these studies.

This analysis has several limitations. The lead-in periods were open-label and the mean baseline HbA1c levels were high in both study 1 (9.3%) and study 2 (9.4%), reflecting the difficulty in maintaining glycemic control experienced by many individuals with type 2 diabetes. The study also only investigated the effects of add-on therapy with oral glucose-lowering drugs, and the findings may not be applicable for add-on therapy with injectable drugs. The duration of the lead-in period was only 16 weeks (14 weeks at assessment of efficacy outcomes), and it is possible that with longer treatment more patients might have achieved the HbA1c target of < 7.0% within the controlled setting of the clinical study. However, intensification of treatment after the lead-in period was consistent with current guidelines that recommend transition to triple therapy for patients with type 2 diabetes if HbA1c targets are not reached or maintained after 3 months of dual therapy [4].

Table 3 Summary of adverse events during the lead-in period

	DAPA + MET *N* = 482	SAXA + MET *N* = 349
≥ 1 AE	120 (24.9)	113 (32.4)
≥ 1 SAE	4 (0.8)	5 (1.4)
SAE related to treatment	0	0
AE leading to discontinuation	5 (1.0)	4 (1.1)
SAE leading to discontinuation	1 (0.2)	2 (0.6)
Death	1 (0.2)	0
Hypoglycemia	2 (0.4)	0
Adjudicated CV events	0	3[a] (0.9)
Most common AEs (≥ 2% of patients)		
Diarrhea	7 (1.5)	10 (2.9)
Genital infections	12 (2.5)	0
Headache	10 (2.1)	4 (1.1)
Influenza	2 (0.4)	8 (2.3)
Urinary tract infections	11 (2.3)	4 (1.1)

From lead-in baseline to randomization at study day 1 (treatment duration 16 weeks)
Data are number of patients (%)
AE adverse event, *CV* cardiovascular, *DAPA* dapagliflozin, *MET* metformin, *SAE* serious adverse event, *SAXA* saxagliptin
[a] One case each of unstable angina, atrial fibrillation, and ischemic stroke

CONCLUSIONS

Approximately 20% of patients with type 2 diabetes and high baseline HbA1c achieved a treatment goal of HbA1c < 7.0% during the dual therapy lead-in periods. Most patients, however, required further add-on therapy to achieve glycemic control. Safety and tolerability findings during the lead-in periods were similar to those from the 24-week double-blind treatment period of the triple therapy studies. These results suggest that type 2 diabetes is often inadequately controlled with add-on of a single oral agent to metformin and that an early move to triple therapy may allow patients with type 2 diabetes to achieve HbA1c goals efficiently without additional risk of AEs or hypoglycemia.

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Compliance with Ethics Guidelines. The studies reported here were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, and the Declaration of Helsinki. The protocols were approved by the relevant institutional review boards or ethics committees at each study site and all patients provided written informed consent to participate.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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