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A Study of Dapagliflozin in Patients With Type 2 Diabetes on High Doses of Insulin Plus Insulin Sensitizers: Applicability of a Novel Insulin-Independent Treatment

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Objective – To determine if dapagliflozin, which selectively inhibits renal glucose reabsorption, lowers hyperglycemia in type 2 diabetes patients poorly controlled with high insulin doses plus oral antidiabetic agents (OADs).

Research Design and Methods – Randomized, double-blind, three-arm parallel group, placebo-controlled, 26-center trial (United States and Canada). Based on data from an insulin dose-adjustment setting cohort (n = 4), patients in the treatment cohort (n = 71) were randomized 1:1:1 to placebo, 10 and 20 mg dapagliflozin, plus OAD(s) and 50% of their daily insulin dose. Primary outcome was change from baseline in glycated hemoglobin (A1C) at week 12 (dapagliflozin versus placebo, LOCF).

Results – At week 12 (LOCF), dapagliflozin 10- and 20-mg groups demonstrated –0.70% and –0.78% mean differences in A1C change from baseline versus placebo. In both dapagliflozin groups, 65.2% of patients achieved a decrease from baseline in A1C ≥0.5% versus 15.8% in the placebo group. Mean changes from baseline in fasting plasma glucose (FPG) were +17.8, +2.4, and –9.6 mg/dl (placebo, 10 and 20 mg dapagliflozin). Postprandial glucose (PPG) reductions with dapagliflozin also showed dose-dependency. Mean changes in total body weight were –1.9, –4.5, and –4.3 kg (placebo, 10 and 20 mg dapagliflozin). Overall, adverse events were balanced across all groups, although more genital infections occurred in the dapagliflozin 20-mg group than placebo.

Conclusions – In patients on high insulin doses plus insulin sensitizers who had their baseline insulin reduced by 50%, dapagliflozin decreased A1C, produced better FPG and PPG levels, and lowered weight more than placebo.

Treatment of hyperglycemia in patients with type 2 diabetes remains a challenge, particularly in those who require insulin as the disease progresses (1,2). Various combinations of insulin with oral antidiabetic agents (OADs) have been investigated (2–8). Often, these combination therapies become less effective in controlling hyperglycemia over time, particularly as a result of weight gain and worsening insulin resistance as well as progressive failure of insulin secretion.

Hypoglycemia, weight gain, and subsequent increased insulin resistance are significant factors that limit optimal titration and effectiveness of insulin (2). Weight gain with insulin therapy, used alone or with OADs (7–9), is in part a consequence of reducing glucosuria (10,11). Among commonly used OADs, thiazolidinediones (TZDs) and sulfonylureas intrinsically contribute to weight gain, whereas metformin causes weight loss and dipeptidyl peptidase 4 inhibitors are weight neutral. Overall, there is need for novel agents that can be safely administered to help achieve glycemic targets without increasing the risks of weight gain or hypoglycemia.

A novel approach to treating hyperglycemia targets receptors for renal glucose reabsorption (12). Agents that selectively block sodium-glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, inhibit glucose reabsorption and induce its elimination through urinary excretion (13). Pre-clinical models have shown that SGLT2 inhibition lowers blood glucose independently of insulin (14-17). Dapagliflozin, a highly selective inhibitor of SGLT2, has demonstrated efficacy, alone or in combination with metformin, in reducing hyperglycemia in patients with type 2 diabetes (18,19), but has not been tested in patients requiring insulin.

This study was designed to determine if dapagliflozin is effective in lowering blood glucose in patients with type 2 diabetes who have not responded adequately to insulin combined with oral therapies that act through insulin-dependent mechanisms.

RESEARCH DESIGN AND METHODS

Study design: This randomized, single- and double-blind, three-arm parallel group, placebo-controlled trial was conducted in 26 study centers in the United States and Canada. Institutional review boards or independent ethics committees for each center approved the protocol. All patients provided written informed consent. The trial consisted of a 10- to 21-day qualification period, 12-week treatment phase, and 4-week follow-up phase. Starting at day -7, patients were instructed on a diet and exercise program pursuant to American Diabetes Association or similar local guidelines, to be followed throughout the study. Until day 1, patients maintained their stable dose of OADs and insulin.

We used an adaptive trial design with two cohorts. The purpose of the first cohort was to identify a reduced insulin starting dose unlikely to cause hypoglycemia after adding dapagliflozin. Four patients received single-blind dapagliflozin 20 mg after having their daily insulin dose decreased by 50%. If at least one patient recorded a glucose value ≤100 mg/dL in this cohort, lesser dose reductions (i.e., 30% or 10%) would not be tested, and the daily insulin dose reduction for patients in the larger second cohort would be set at 50%. This was the case, and in the second treatment cohort, patients were randomized 1:1:1 on day 1 to double-blind placebo, 10 or 20 mg dapagliflozin once daily, on top of open-label therapy with 50% of their usual daily insulin dose and their OAD(s)

Patients performed SMBG five times daily during the 3–5 days prior to clinic visits at weeks 1, 2, 4, 6, 8, 10, and 12. No dose

modifications of blinded study medication or OAD(s) were allowed during the treatment phase. In patients with or at risk of hypoglycemia, insulin could be down-titrated for SMBG levels <54 mg/dl, mean daily glucose <100 mg/dl, or when clinically necessary as determined by the investigator. Patients experiencing major hypoglycemia were discontinued. For any fasting plasma glucose (FPG) level >240 mg/dl at weeks 4 and 6, >220 mg/dl at week 8, or >200 mg/dl at week 10, the insulin dose could be increased after a retest. Patients lacking glycemic control despite up-titration, or whose modified insulin dose exceeded baseline, were discontinued.

Patient population : Men and women with type 2 diabetes, aged 18–75 years, with BMI ≤45 kg/m^2 and A1C 7.5%–10%, were enrolled between October 2006 and November 2007. Patients were on stable-dose insulin-sensitizer therapy (metformin ≥1000 mg and/or pioglitazone ≥30 mg or rosiglitazone 4 mg) for ≥6 weeks and insulin therapy for ≥12 weeks before enrollment (insulin dose must have been ≥50 units of U100 daily, and stable for ≥6 weeks). Laboratory criteria included fasting C-peptide ≥ 0.8 ng/ml; serum creatinine <1.5 mg/dl (men)/<1.4 mg/dl (women); and urine microalbumin/creatinine ratio <300 mg/g, or if exceeded on spot check, a 24-h urine total protein <3 g/24 h. Major exclusion criteria were history of type 1 diabetes; aspartate transaminase and/or alanine transaminase >2.5 × upper limits of normal (ULN); creatine kinase ≥ 3 × ULN; symptoms of severely uncontrolled diabetes; history of severe hypoglycemia; and unstable or serious cardiovascular, renal or hepatic disease.

Trial outcomes (dapagliflozin versus placebo): The primary efficacy measure was change from baseline in A1C at week 12, last observation carried forward (LOCF). Secondary efficacy measures at week 12 (LOCF) included changes from baseline in FPG and total daily dose of insulin (TDDI), the proportion of patients achieving a decrease in A1C ≥0.5% from baseline, and the proportion of patients achieving A1C <7%. Tertiary end points included changes from baseline in total body weight and in postprandial glucose (PPG) measured by an oral glucose tolerance test (OGTT). Safety outcomes were assessed by treatment-emergent adverse events, vital signs, and laboratory measurements, including 24-h urine collections for volume and electrolytes.

Statistical analysis : For the treatment cohort, the sample size target of 22 patients per treatment group was chosen to allow for the calculation of 95% CI for the primary end point with a half-width of 0.42% for each treatment group, assuming a 1% standard deviation; the half-width of a 95% CI for differences between mean treatment changes was estimated to be 0.59%. The primary efficacy data set consisted of all randomized patients who took ≥1 dose of double-blind study medication. Analyses of efficacy variables (except change from baseline in insulin dose) excluded data after insulin up-titration. Analyses for change from baseline in A1C, FPG, insulin dose, and total body weight at week 12 (LOCF) were performed using an analysis of covariance (ANCOVA) model with treatment group as effect and baseline value as a covariate. No statistical hypothesis testing was planned for this study designed for exploratory analysis.

RESULTS

Patient population: Of 163 patients screened for the treatment cohort, 71 were randomized (Fig. 1). Demographic and baseline characteristics are reported in Table 1.

Efficacy outcomes: Fig. 2 shows A1C, FPG, and change from baseline in body weight over time. In the 10 and 20 mg dapagliflozin groups, A1C decreased from baseline to week 12 (LOCF), resulting in

differences in mean changes versus placebo of –0.70% and –0.78% (Table 2). At week 12 (LOCF), 65.2% of patients in both dapagliflozin groups achieved a ≥0.5% decrease from baseline A1C versus 15.8% in the placebo group. Five patients (one each in the dapagliflozin 20-mg and placebo groups, and three in the dapagliflozin 10-mg group) showed a therapeutic response defined as A1C <7%. At week 12 (LOCF), mean change in total body weight was –1.9 kg (placebo), –4.5 kg (10 mg dapagliflozin), and –4.3 kg (20 mg dapagliflozin).

The effect of dapagliflozin on FPG was dose-dependent. PPG, measured at 120 min by OGTT, also showed dose-response characteristics. There was no appreciable change from baseline in TDDI. Four patients in the placebo arm required insulin up-titration, compared with one in the dapagliflozin 10-mg arm and three in the dapagliflozin 20-mg arm.

Vital signs and laboratory outcomes: The placebo group experienced a slight increase in standing blood pressure at week 12, whereas both dapagliflozin groups demonstrated mean improvements in standing systolic and diastolic blood pressure (–7.2 systolic/–1.2 diastolic mm Hg [10 mg dapagliflozin], –6.1 systolic/–3.9 diastolic mm Hg [20 mg dapagliflozin]). In the 20-mg dapagliflozin group, supine blood pressure decreased (mean change of –5.5 systolic/–5.8 diastolic mm Hg), while there was little or no change in the 10-mg group (see Appendix Table 1, available online at http://care.diabetesjournals.org).

Mean changes from baseline in urinary glucose excretion at week 12 were –1.5 g/24 h (placebo), 83.5 g/24 h (dapagliflozin 10 mg), and 85.2 g/24 h (dapagliflozin 20 mg). Mean 24-h urine output increased from 1870 to 2125 ml (placebo), 1921 to 2286 ml (dapagliflozin 10 mg), and 1809 to 2253 ml (dapagliflozin 20 mg). Compared with baseline, MDRD-estimated glomerular filtration rates at the end of treatment were normal, with minor changes of –0.58, –0.84, and 1.45 ml/min/1.73 m^2 in the respective placebo and dapagliflozin 10- and 20-mg groups. Generally, there were no remarkable changes from baseline in key laboratory parameters. Median change from baseline in serum uric acid was –0.30 mg/dl in both dapagliflozin groups. There were no marked abnormalities for serum Na+ and liver function tests. Median increases from baseline in serum hematocrit at week 12 were 2.5% and 3.05% in the dapagliflozin 10- and 20-mg groups, respectively.

Safety and adverse events: Adverse events were balanced across all groups (Table 3). Three patients who received placebo, seven who received 10 mg dapagliflozin, and six who received 20 mg dapagliflozin experienced episodes of hypoglycemia. Of these, one patient who received placebo experienced major hypoglycemia. There were no deaths. Two patients, one with placebo and one with 20 mg dapagliflozin, experienced a serious adverse event. One patient in each treatment arm experienced adverse events that led to discontinuation.

Six patients experienced genital tract infections during the double-blind period; five of these received 20 mg dapagliflozin. One patient in the dapagliflozin 20-mg group reported a urinary tract infection. Events of pollakiuria were reported across all treatment groups, including placebo. One patient in each dapagliflozin arm reported polyuria. One case of microalbuminuria in the dapagliflozin 20-mg arm resulted in discontinuation.

One event of renal failure occurred during treatment with 10 mg dapagliflozin. The patient was being chronically treated with multiple antihypertensive agents, including enalapril, carvedilol, and furosemide. Eleven days after starting study medication, the patient was discontinued from the study due to dehydration and pre-renal azotemia. Furosemide and enalapril therapy were

withheld, and the pre-renal azotemia resolved with oral rehydration.

CONCLUSIONS

Disease progression in type 2 diabetes is frequently accompanied by a cycle of deteriorating glycemic control due to declining β-cell function. Therapies that depend on insulin supplementation or secretion entail the risk of hypoglycemia, weight gain, decreased insulin sensitivity, and eventual loss of effectiveness. This frustrating clinical setting is exemplified most dramatically by patients with late-stage type 2 diabetes who require escalating insulin doses, often with oral agents such as metformin and/or TZDs to maintain glycemic control. Ultimately, more than 25% of patients are treated with insulin-based regimens, often in combination with OADs (6). A novel strategy for controlling glycemia independently of insulin involves limiting glucose reabsorption in the proximal tubule of the kidney, where glucose is reabsorbed via SGLT2 receptors. Dapagliflozin selectively inhibits SGLT2, thereby limiting glucose reabsorption.

Patients recruited for this study had inadequate glycemic control despite aggressive regimens of insulin plus OADs. After reducing the insulin dose by 50%, patients in the placebo arm experienced weight loss, little change in A1C, and a mean 17.8 mg/dl increase in FPG, an outcome that probably reflects the relatively severe insulin resistance in these patients and perhaps improved compliance with diet and lifestyle as a result of study participation. Treatment with dapagliflozin, with its insulin-independent mechanism of action, was associated with additional weight loss of ≈2.5 kg, and with improvements in glycemic control compared with placebo. Although total hypoglycemic events were more frequently reported with dapagliflozin than placebo, there were no major hypoglycemia episodes on dapagliflozin. The effect of dapagliflozin in this insulin-treated population was similar to that observed in treatment-naïve diabetic patients (19).

Improvements in glycemic outcome measures were dose-dependent, as was the potential safety signal of genital tract infections, more frequently seen in the 20-mg dose arm. However, the main pharmacodynamic measure, 24-h urinary glucose, increased by ≈85 g/day at week 12 in both the 10-mg and 20-mg dapagliflozin groups. A plausible explanation is that 20 mg dapagliflozin may have caused greater glucosuria earlier in the study, as has been seen in other settings (18–20), but that the resulting greater declines in glycemia in the 20-mg dose group led to a lower filtered load of glucose at the kidney, such that by week 12, the point at which glucosuria was measured, the amount of glucose in the urine had equalized between the dapagliflozin dose groups.

Reductions in standing blood pressure in both dapagliflozin groups, and in supine blood pressure in the dapagliflozin 20-mg group, are noteworthy. The decrease in blood pressure and slight increase in hematocrit are effects consistent with the glucose-induced osmotic diuresis caused by SGLT2 inhibition. A dramatic presentation of this effect was seen in the 10-mg dose arm in an event of dehydration and pre-renal azotemia in a volume-sensitive patient. Otherwise, there were no further reports of dizziness or dehydration associated with dapagliflozin in this study. The diuretic property of dapagliflozin warrants further evaluation.

Conclusions that can be drawn from this study are limited by its size and relatively short duration. Nevertheless, these results establish the proof of concept that SGLT2 inhibition can improve glycemic control and weight in patients poorly controlled on high insulin doses and oral insulin sensitizer therapy, despite a 50% insulin dose reduction. These results further suggest the hypothesis

that this therapeutic approach may lend itself to reducing the weight gain that otherwise might occur when insulin therapy is intensified in this population.

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Table 1—Demographic and baseline characteristics of randomized patients in the treatment cohort

	Placebo + Insulin (n = 23)	Dapagliflozin 10 mg + Insulin (n = 24)	Dapagliflozin 20 mg + Insulin (n = 24)
Age, y , mean (SD)	58.4 (6.5)	55.7 (9.2)	56.1 (10.6)
Sex, n (%)			
Male	16 (69.6)	13 (54.2)	13 (54.2)
Female	7 (30.4)	11 (45.8)	11 (45.8)
Race, n (%)			
White	22 (95.7)	22 (91.7)	23 (95.8)
Black/African American	0	1 (4.2)	1 (4.2)
Asian	0	1 (4.2)	0
Other	1 (4.3)	0	0
Ethnicity,[*] n (%)			
Hispanic/Latino	5 (21.7)	3 (12.5)	2 (8.3)
Non-Hispanic/Latino	12 (52.2)	14 (58.3)	16 (66.7)
Not reported	6 (26.1)	7 (29.2)	6 (25.0)
Weight, kg, mean (SD)	101.8 (16.5)	103.4 (10.2)	101.2 (15.3)
BMI, kg/m^2, mean (SD)	34.8 (4.6)	35.5 (3.6)	36.2 (4.6)
Duration of type 2 diabetes, y, mean (SD)	13.8 (7.3)	11.8 (5.8)	11.3 (5.6)
Background antihyperglycemic medication, n (%)			
MET + Insulin	18 (78.3)	19 (79.2)	16 (66.7)
MET + Insulin + TZD	4 (17.4)	2 (8.3)	6 (25.0)
TZD + Insulin	1 (4.3)	3 (12.5)	2 (8.3)
Total daily insulin dose[†], U, median, (IQR)	90.0 (70.0–136.0)	93.0 (67.5–136.0)	84.5 (58.0–135.5)
A1C, %, mean (SD)	8.4 (0.9)	8.4 (0.7)	8.5 (0.9)
Fasting plasma glucose, mg/dl, mean (SD)	165.9 (51.5)	156.0 (39.0)	161.6 (55.0)

[*]Ethnicity data collected for sites in the United States only.
[†]Prior to 50% insulin dose reduction on day 1 of double-blind period.
Abbreviations: A1C, glycated hemoglobin; IQR, interquartile range; MET, metformin; TZD, thiazolidinedione.

Table 2—Baseline, on-treatment, and change from baseline in efficacy parameters for randomized patients in the treatment cohort (n = 71)

	Baseline	Week 12 (LOCF)	Change from Baseline and Differences in Change vs Placebo + Insulin
	Mean (SD)*	Mean (SD)*	Mean (95% CI)*,†
A1C, %			
Placebo + Insulin (n = 19‡)	8.3 (0.8)	8.5 (0.8)	0.09 (–0.2 to 0.4)
DAPA 10 mg + Insulin (n = 23‡)	8.4 (0.7)	7.8 (0.7)	–0.61 (–0.9 to –0.4)
Difference in change vs Placebo + Insulin			–0.70 (–1.1 to –0.3)
DAPA 20 mg + Insulin (n = 23‡)	8.5 (0.9)	7.8 (0.6)	–0.69 (–0.9 to –0.4)
Difference in change vs Placebo + Insulin			–0.78 (–1.2 to –0.4)
FPG, mg/dl			
Placebo + Insulin (n = 22‡)	166.8 (52.6)	180.8 (56.9)	17.8 (1.4 to 34.2)
DAPA 10 mg + Insulin (n = 23‡)	155.7 (39.8)	160.5 (38.7)	2.4 (–13.6 to 18.3)
Difference in change vs Placebo + Insulin			–15.4 (–38.4 to 7.5)
DAPA 20 mg + Insulin (n = 23‡)	157.9 (53.0)	149.4 (32.0)	–9.6 (–25.6 to 6.3)
Difference in change vs Placebo + Insulin			–27.4 (–50.3 to –4.6)
Body weight, kg			
Placebo + Insulin (n = 22‡)	101.3 (16.7)	99.4 (16.7)	–1.9 (–2.9 to –0.9)
DAPA 10 mg + Insulin (n = 23‡)	102.8 (9.9)	98.2 (9.4)	–4.5 (–5.5 to –3.5)
Difference in change vs Placebo + Insulin			–2.6 (–4.0 to –1.2)
DAPA 20 mg + Insulin (n = 23‡)	102.1 (15.0)	97.8 (14.1)	–4.3 (–5.3 to –3.3)
Difference in change vs Placebo + Insulin			–2.4 (–3.8 to –1.0)
TDDI, U			
Placebo + Insulin (n = 22‡)	54.1 (27.3)	55.7 (26.5)	1.7 (–3.8 to 7.2)
DAPA 10 mg + Insulin (n = 24‡)	52.4 (24.4)	51.3 (20.1)	–1.4 (–6.6 to 3.9)
Difference in change vs Placebo + Insulin			–3.1 (–10.7 to 4.6)
DAPA 20 mg + Insulin (n = 24‡)	54.5 (36.3)	53.5 (32.1)	–0.8 (–6.1 to 4.5)
Difference in change vs Placebo + Insulin			–2.5 (–10.2 to 5.1)
PPG, mg/dl			
Placebo + Insulin (n = 15‡)	312.6 (82.2)	331.3 (46.8)	18.7 (–13.5 to 50.9)
DAPA 10 mg + Insulin (n = 19‡)	320.2 (51.4)	286.0 (55.1)	–34.3 (–67.5 to –1.1)
DAPA 20 mg + Insulin (n = 18‡)	314.5 (71.8)	272.6 (51.2)	–41.9 (–74.8 to –8.9)

*Excludes data after insulin up-titration, except for TDDI.

†Adjusted change from baseline based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.

‡Number of subjects with a non-missing baseline and a Week 12 LOCF value.

A1C, glycated hemoglobin; FPG, fasting plasma glucose; TDDI, total daily dose of insulin after 50% down-titration on day 1; PPG, postprandial glucose measured at 120 min by oral glucose tolerance test.

Table 3. Adverse and special interest events, double-blind treatment period for patients in the treatment cohort

		No. (%)	
	Placebo + Insulin	**Dapagliflozin 10 mg + Insulin**	**Dapagliflozin 20 mg + Insulin**
	(n = 23)	(n = 24)	(n = 24)
Overall adverse events[*]			
At least one adverse event	15 (65.2)	18 (75.0)	16 (66.7)
At least one serious adverse event	1 (4.3)[†]	0	1 (4.2)[‡]
Adverse event leading to discontinuation of study medication	1 (4.3)[§]	1 (4.2)[‖]	1 (4.2)[#]
Most common adverse events (frequency >5% in any treatment group)			
Nausea	1 (4.3)	1 (4.2)	3 (12.5)
Pollakiuria	4 (17.4)	2 (8.3)	3 (12.5)
Vomiting	0	0	3 (12.5)
Vulvovaginal mycotic infection	0	0	3 (12.5)
Anxiety	0	0	2 (8.3)
Back pain	2 (8.7)	3 (12.5)	2 (8.3)
Dry mouth	0	0	2 (8.3)
Nasopharyngitis	2 (8.7)	2 (8.3)	2 (8.3)
Edema, peripheral	0	0	2 (8.3)
Abdominal pain, upper	2 (8.7)	0	1 (4.2)
Fatigue	0	2 (8.3)	1 (4.2)
Influenza	2 (8.7)	1 (4.2)	1 (4.2)
Pain in extremity	1 (4.3)	2 (8.3)	1 (4.2)
Thirst	1 (4.3)	2 (8.3)	1 (4.2)
Upper respiratory tract infection	2 (8.7)	2 (8.3)	1 (4.2)
Headache	2 (8.7)	3 (12.5)	0
Pharyngolaryngeal pain	0	2 (8.3)	0
Procedural pain	2 (8.7)	0	0
Adverse events of special interest			
Urinary tract infection	0	0	1 (4.2)
Genital tract infection (total patients with an event)	1 (4.3)	0	5 (20.8)
Vulvovaginal mycotic infection	0	0	3 (12.5)
Balanitis candida	0	0	1 (4.2)
Vaginal candidiasis	0	0	1 (4.2)
Genital infection, fungal	1 (4.3)	0	0
Events of hypoglycemia			
Total patients with hypoglycemia	3 (13.0)	7 (29.2)	6 (25.0)
Major episode of hypoglycemia[**]	1 (4.3)	0	0
Discontinuation due to lack of glycemic control			
Overall	2 (8.7)	1 (4.2)	0
Prior to up-titration of insulin	1 (4.3)	0	0
On or after day of up-titration of insulin	1 (4.3)	1 (4.2)	0

[*] Events of hypoglycemia were evaluated separately from adverse events.
[†] Loss of consciousness.
[‡] Noncardiac chest pain.
[§] Blood creatine phosphokinase increased.

‖Renal failure. Other adverse events reported when patient was "discontinued" included increased blood creatinine, increased blood urea, dehydration, and dizziness.
#Microalbuminuria.
**Major hypoglycemic episode defined as: (1) plasma blood glucose values <54 mg/dl, (2) at least one of the following symptoms: confusion/disorientation, abnormal behavior, or unconsciousness, and (3) external treatment provided.

Figure legends

Figure 1—*Patient disposition*

Figure 2–Mean A1C (A), mean FPG (B), and mean change from baseline in total body weight (C) over time

Data are for randomized patients who took at least one dose of the double-blind study medication. Mean value based on LOCF, excluding data after up-titration of insulin. Error bars represent 95% CIs.

Figure 1.

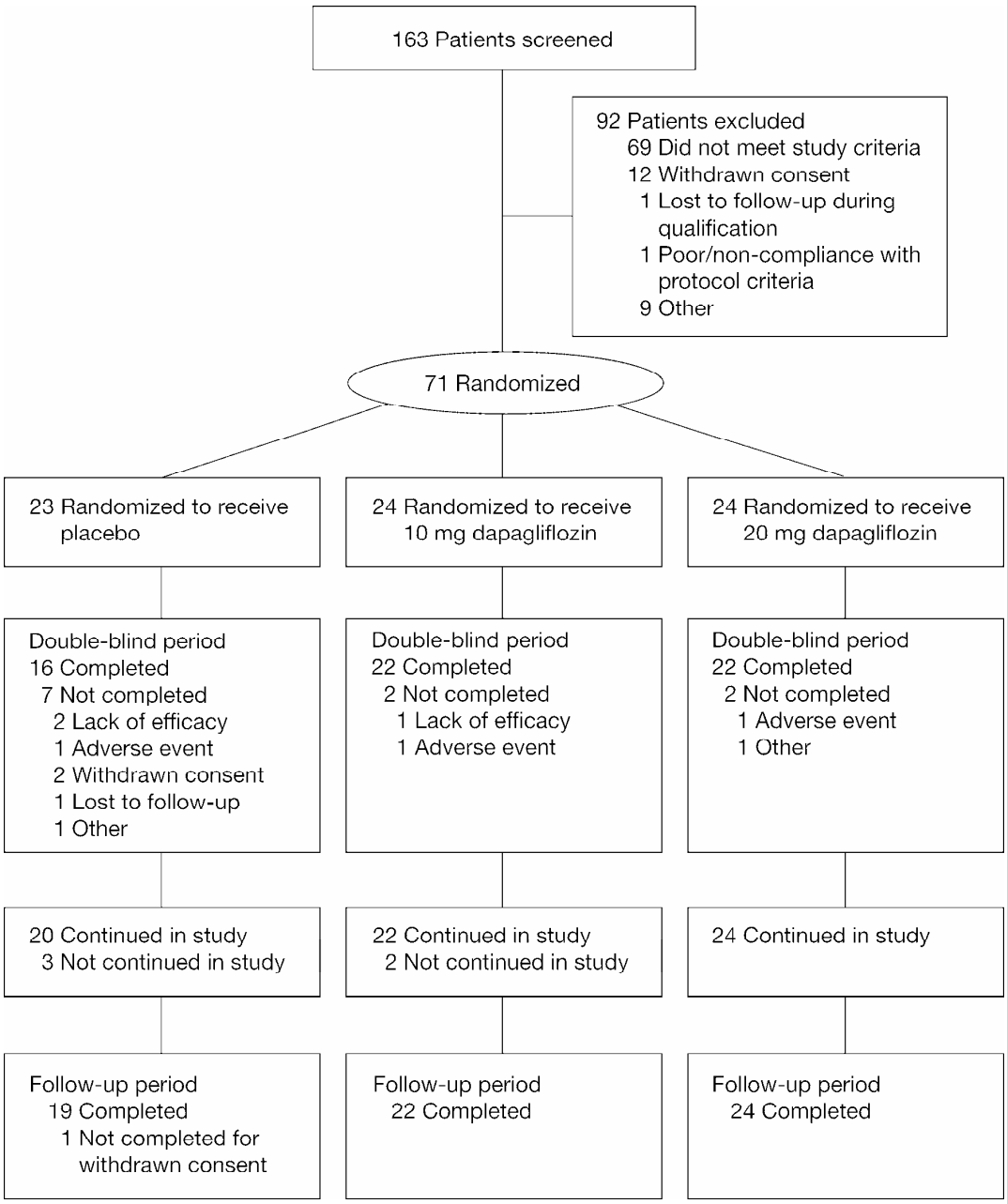
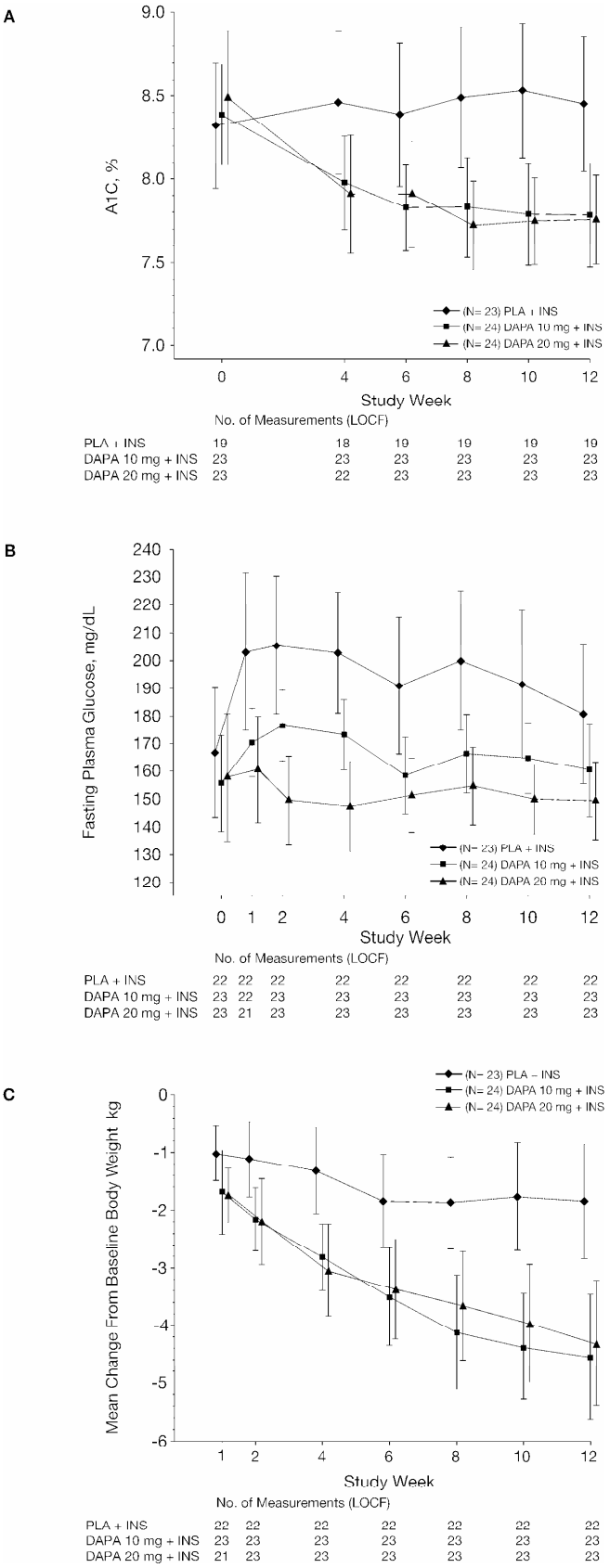

163 Patients screened
92 Patients excluded
69 Did not meet study criteria
12 Withdrawn consent
1 Lost to follow-up during qualification
1 Poor/non-compliance with protocol criteria
9 Other
71 Randomized
23 Randomized to receive placebo
24 Randomized to receive 10 mg dapagliflozin
24 Randomized to receive 20 mg dapagliflozin
Double-blind period
16 Completed
7 Not completed
2 Lack of efficacy
1 Adverse event
2 Withdrawn consent
1 Lost to follow-up
1 Other
Double-blind period
22 Completed
2 Not completed
1 Lack of efficacy
1 Adverse event
Double-blind period
22 Completed
2 Not completed
1 Adverse event
1 Other
20 Continued in study
3 Not continued in study
22 Continued in study
2 Not continued in study
24 Continued in study
Follow-up period
19 Completed
1 Not completed for withdrawn consent
Follow-up period
22 Completed
Follow-up period
24 Completed

Figure 2.


A
A1C, %
9.0
8.5
8.0
7.5
7.0
(N= 23) PLA + INS
(N= 24) DAPA 10 mg + INS
(N= 24) DAPA 20 mg + INS
0 4 6 8 10 12
Study Week
No. of Measurements (LOCF)
PLA + INS 19 18 19 19 19 19
DAPA 10 mg + INS 23 23 23 23 23 23
DAPA 20 mg + INS 23 22 23 23 23 23
B
Fasting Plasma Glucose, mg/dL
240
230
220
210
200
190
180
170
160
150
140
130
120
(N= 23) PLA + INS
(N= 24) DAPA 10 mg + INS
(N= 24) DAPA 20 mg + INS
0 1 2 4 6 8 10 12
Study Week
No. of Measurements (LOCF)
PLA + INS 22 22 22 22 22 22 22 22
DAPA 10 mg + INS 23 22 23 23 23 23 23 23
DAPA 20 mg + INS 23 21 23 23 23 23 23 23
C
Mean Change From Baseline Body Weight kg
0
-1
-2
-3
-4
-5
-6
(N= 23) PLA + INS
(N= 24) DAPA 10 mg + INS
(N= 24) DAPA 20 mg + INS
1 2 4 6 8 10 12
Study Week
No. of Measurements (LOCF)
PLA + INS 22 22 22 22 22 22 22
DAPA 10 mg + INS 23 23 23 23 23 23 23
DAPA 20 mg + INS 21 23 23 23 23 23 23