Dapagliflozin as Monotherapy in Drug-Naive Asian Patients With Type 2 Diabetes Mellitus: A Randomized, Blinded, Prospective Phase III Study

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ABSTRACT

Objective: Dapagliflozin is a highly selective, orally active inhibitor of renal sodium-glucose cotransporter 2 that reduces hyperglycemia by increasing urinary glucose excretion. The goal of this study was to evaluate dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes whose disease was inadequately controlled with diet and exercise.

Methods: In this Phase III, multicenter, parallel-group, double-blind study, drug-naive patients with glycosylated hemoglobin (HbA_{1c}) levels ≥7.0% to ≤10.5% (≥53–≤91 mmol/mol) were randomized (by using an interactive voice response system) to receive placebo (n = 132), dapagliflozin 5 mg (n = 128), or dapagliflozin 10 mg (n = 133). The primary end point was mean change from baseline in HbA_{1c} level at week 24 (last-observation-carried-forward). Secondary end points included changes in fasting plasma glucose, 2-hour postprandial glucose, body weight, and other glycemic parameters.

Results: Baseline characteristics were balanced across groups. Most patients (89%) were Chinese, median disease duration was 0.2 year, and mean HbA_{1c} level was 8.26%. Most patients (87%) completed the study. At week 24, mean reductions in HbA_{1c} were −0.29% for placebo versus −1.04% and −1.11% for dapagliflozin 5 and 10 mg, respectively ($P < 0.0001$ for both doses). Changes in fasting plasma glucose were 2.5, −25.1, and −31.6 mg/dL (0.14, −1.39, and −1.75 mmol/L) for placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg. Changes in 2-hour postprandial glucose were 1.1, −46.8, and −54.9 mg/dL (0.06, −2.60, and −3.05 mmol/L). Reductions in body weight were −0.27, −1.64, and −2.25 kg. Proportions of patients achieving HbA_{1c} levels <7.0% (53 mmol/mol) were 21.3%, 42.6%, and 49.8%. Adverse events (AEs) occurred in 63.6%, 61.7%, and 60.9% of patients, and serious AEs occurred in 1.5%, 3.9%, and 3.0% of patients. No deaths occurred. Hypoglycemia was uncommon (1.5%, 0.8%, and 0.8%); no hypoglycemic event led to discontinuation. Genital infections occurred in 0.8%, 3.1%, and 4.5% of patients and urinary tract infections in 3.0%, 3.9%, and 5.3% of patients. No AEs of renal infection or pyelonephritis were reported. No changes in renal function or AEs of renal failure occurred.

Conclusions: Compared with placebo, dapagliflozin 5 and 10 mg demonstrated clinically and statistically significant improvements in HbA_{1c} levels after 24 weeks of treatment. Dose-dependent, statistically significant reductions in fasting plasma glucose, postprandial glucose, and weight were also observed for both doses compared with placebo. AEs and serious AEs were balanced across groups, with low rates of hypoglycemia and no increase in renal events. Genital infections and urinary tract infections were more common with dapagliflozin. Dapagliflozin as monotherapy in these drug-naive Asian patients was well

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tolerated, significantly improving glycemic control with the additional benefit of weight loss. (*Clin Ther.* 2014;36:84–100)

Key words: Asian, dapagliflozin, glycemic control, monotherapy, SGLT2, type 2 diabetes mellitus.

INTRODUCTION

As the global burden of diabetes increases, Asian countries in particular are experiencing a pronounced rise in the number of patients with type 2 diabetes mellitus (T2DM). As recently as 1978, diabetes was considered a rare disease in Asia, with an estimated prevalence of just 0.6% in China.[1] A large-scale, Chinese survey conducted from June 2007 to May 2008 estimated that the overall prevalence of diabetes (including both type 1 and 2 disease, diagnosed and undiagnosed cases) was now closer to 10%, translating into >90 million adults.[2] The increase in T2DM specifically is believed to be due to unhealthy lifestyle changes associated with recent and rapid socioeconomic development,[3] in addition to genetic determinants.[4] Furthermore, the ~150 million adults in China with prediabetes (ie, impaired fasting glucose) represent a substantial at-risk population for an increasing T2DM burden in Asia in the future.[2,3]

Faced with this increasing global burden of disease, the treatment of T2DM presents a number of continuing challenges.[5] Due to the progressive nature of T2DM, treatment intensification is frequently required to maintain glycemic control.[6] However, many of the currently available therapies are associated with adverse effects such as hypoglycemia and weight gain, highlighting the unmet need for novel agents with an improved risk/benefit profile.

Dapagliflozin is a novel, highly selective, orally active inhibitor of renal sodium-glucose cotransporter 2 (SGLT2) that has recently been approved for the treatment of adult patients with T2DM in several European Union countries, Australia, Brazil, Mexico, and Ukraine. Under normal physiological conditions, glucose is freely filtered in renal glomeruli and reabsorbed in the proximal tubules via SGLT2 (and to a lesser extent by SGLT1). Through its inhibition of SGLT2, dapagliflozin decreases renal glucose reabsorption, which in turn leads to a reduction in hyperglycemia, increased glycosuria, and mild diuresis.[7,8]

Dapagliflozin has demonstrated efficacy and consistent safety across a wide range of patient populations with T2DM at varying stages of disease severity and duration. Efficacy of dapagliflozin has been established in predominantly Western populations, when used as monotherapy[9–12] and as add-on therapy to metformin,[9,13] sulfonylureas,[14] pioglitazone,[15] sitagliptin,[16] or insulin regimens.[17] Previous studies in both Asian and non-Asian populations have demonstrated similar, linear pharmacokinetics with dapagliflozin over the dose range of 2.5 to 500 mg/d and dose-related excretion of glucose in the urine over 24 hours.[7,18–20] A recent Phase II study in Japanese patients demonstrated the benefits of dapagliflozin monotherapy in reducing hyperglycemia over 12 weeks, with a low risk for hypoglycemia.[21] Increased renal glucose excretion with dapagliflozin is also associated with caloric loss, resulting in decreases in weight, body fat mass, and waist circumference.[22] Both weight loss and the observed diuretic effect with treatment are consistent with findings of modest blood pressure reductions in the dapagliflozin clinical development program.[23]

Due to the lower body mass index (BMI) of Asian versus non-Asian patients with T2DM[24–26] and the observed effect of dapagliflozin on weight[22] in addition to ethnic differences in postprandial glucose (PPG) regulation,[27–29] it was important to investigate the effects of dapagliflozin therapy in a broad Asian population. The goal of the current study was to present the efficacy and safety findings of dapagliflozin as monotherapy in drug-naive, Asian (predominantly Chinese) patients with T2DM whose disease was inadequately controlled with diet and exercise.

PATIENTS AND METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, Phase III study with a 42-day lead-in period, a 24-week double-blind treatment period, and a 28-day follow-up period conducted between June 2010 and March 2012 at 40 sites (26 in China, 5 each in Korea and Taiwan, and 4 in India). The study complied with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice Guideline. It was approved by institutional review boards and independent ethics committees for participating centers, and is registered with ClinicalTrials.gov

(NCT01095653). All participants provided written informed consent.

Men and woman aged ≥18 years with inadequately controlled T2DM defined as a glycosylated hemoglobin (HbA_{1c}) levels ≥7.5% and ≤10.5% (≥58 and ≤91 mmol/mol) at the enrollment visit and ≥7.0% and ≤10.5% (≥53 and ≤91 mmol/mol) at the lead-in day −14 visit were included in this study. Patients were required to have a C-peptide level ≥1.0 ng/mL (0.34 nmol/L) and a BMI ≤45.0 kg/m^2 at the enrollment visit and be drug naive (never received prescription medication, including Chinese traditional medicines for diabetes, or have received prescription medication for diabetes for <24 weeks since original diagnosis).

Full exclusion criteria are provided in **Supplemental Table I** (available in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002). In brief, patients were excluded from enrollment if they had: aspartate aminotransferase and/or alanine aminotransferase levels >3 times the upper limit of normal (ULN), serum total bilirubin >2 mg/dL (34.2 μmol/L), serum creatinine ≥1.5 mg/dL (132.6 μmol/L) for men or ≥1.4 mg/dL (123.8 μmol/L) for women (based on guidance from the rescue therapy [metformin] prescribing information), hemoglobin ≤110 g/L for men and ≤100 g/L for women, creatine kinase ≥3 times the ULN, urine albumin: creatinine ratio >1800 mg/g, severe hypertriglyceridemia (triglyceride >800 mg/dL [9.3 mmol/L]), urinary excretion of *N*-acetyl-β-D-glucosaminidase (NAG) >84 μmol/h NAG/mmol creatinine, urinary excretion of α1 microglobulin >28 mg α1 microglobulin/g creatinine, parathyroid hormone value >1.5 times the ULN, calcium or serum phosphate values outside the normal reference range, abnormal free T4 values, and positive hepatitis B surface antigen or positive anti–hepatitis C antibodies. Patients with currently unstable or serious vascular, renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic diseases were also excluded.

Eligible patients first completed a 6-week, single-blind, placebo lead-in period in which they received diet and exercise counseling consistent with the China Diabetes Society recommendations. An interim visit at lead-in day −14 to evaluate patient safety and continued eligibility was also performed. Eligible patients from the lead-in period with HbA_{1c} levels ≥7.0% and ≤10.5% (≥53 and ≤91 mmol/mol) were then randomized sequentially by using an interactive voice response system in a blinded manner to 1 of 3 treatment groups (in a 1:1:1 ratio, stratified according to site): 5 or 10 mg of dapagliflozin or placebo taken orally once per day before the first meal of the day. Changes in the blinded study medication were not permitted during the study. The number of patients with HbA_{1c} levels ≥7.0 and ≤7.4% (≥53 and ≤57 mmol/mol) randomized to treatment was limited to 20% of the population maximum (ie, 76 patients). Visits were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24 during the double-blind period. After the initial screening visit, patients, investigators, and the study sponsors were blinded to treatment group and HbA_{1c} and urinary glucose values (including urinary glucose:creatinine ratio).

Patients with inadequate glycemic control could remain in the trial and receive open-label rescue therapy with metformin (500 mg daily, titrated to 2000 mg if necessary). Criteria for inadequate glycemic control requiring rescue therapy became progressively more stringent over time: during weeks 4 to 12, a central laboratory fasting plasma glucose (FPG) measurement (confirmed with a second measurement within 3–5 days) of >240 mg/dL (13.3 mmol/L) was required; during weeks 12 to 24, an FPG level >200 mg/dL (11.1 mmol/L) was required. Patients with FPG values consistently greater than protocol-specified values for 12 weeks despite a maximum tolerated dose of metformin were discontinued from the study.

Clinical Measures

The primary end point was the mean change from baseline in HbA_{1c} level at week 24 for each dapagliflozin group versus placebo by using the last-observation-carried-forward (LOCF) method to impute missing observations, excluding data after rescue therapy. Secondary end points were: (1) change from baseline in FPG at week 24; (2) change from baseline in 2-hour PPG (after a liquid meal challenge) at week 24; (3) change from baseline in total weight at week 24; and (4) proportion of patients achieving a therapeutic glycemic response, defined as HbA_{1c} levels <7.0% (53 mmol/mol), at week 24. A sensitivity analysis evaluated change in HbA_{1c} according to baseline HbA_{1c} subgroups (<8.0% [<64 mmol/mol], ≥8.0 to <9.0% [≥64–<75 mmol/mol], and ≥9.0% [≥75 mmol/mol]).

Exploratory end points included: change from baseline at week 24 in β-cell function and insulin resistance

(as measured by homeostasis model assessment version 2 [HOMA-2]), change from baseline in waist circumference at week 24, percent change from baseline in lipids (total cholesterol, LDL-C, HDL-C, and fasting triglyceride) at week 24, and the proportion of patients with ≥3% or ≥5% reduction in total weight at week 24. The pharmacodynamic end point was the change from baseline in spot fasting urinary glucose to creatinine ratio at week 24.

Safety and tolerability were assessed by collating data on adverse events (AEs) and serious AEs (SAEs) by using preferred terms from the Medical Dictionary for Regulatory Activities (version 15.0). (The definition of an SAE is described in **Supplemental Table I** available in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002.) Discontinuations due to AEs, laboratory tests (conducted at the central laboratory, QLabs [Beijing, China; Mumbai, India; and Singapore]), changes in vital signs, hypoglycemia, and other AEs of special interest were also assessed.

Major hypoglycemia was defined as symptomatic episodes requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose values <54 mg/dL (<3.0 mmol/L) and prompt recovery after glucose or glucagon administration. Minor hypoglycemia was defined as any episode (symptomatic or asymptomatic) with a capillary or plasma glucose measure <63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode. Other episodes of hypoglycemia were defined as episodes reported by the investigator that were suggestive of hypoglycemia but did not meet the aforementioned criteria. A prespecified list of preferred terms from the Medical Dictionary for Regulatory Activities identified AEs as genital infections, urinary tract infections (UTIs), renal AEs, and volume depletion. Patients reported safety events to investigators both spontaneously and in response to questions proactively posed by the investigator at study visits.

Statistical Analysis

Sample size calculations were conducted on the basis of anticipated differences for the primary end point. Furthermore, for registration in China, regional Asian studies are required to have at least 100 patients from China in each treatment arm or at least 90% power in the Chinese subgroup, whichever is greater. Therefore, to detect a difference of 0.6% between dapagliflozin versus placebo for changes from baseline to week 24 in HbA_{1c} level (assuming an SD of 1.1% and at a significance level of 0.027), 120 patients (100 from China) per treatment group were required to provide 97% power (94% for the Chinese population). Assuming that 5% of patients would not have a postbaseline assessment, 126 patients per group (105 from China and 21 from other countries/regions) were planned for randomization (378 patients in total).

Patients randomized to treatment who received at least 1 dose of double-blind study medication and had both a baseline and postbaseline measurement were included in the efficacy analyses. Patients who received at least 1 dose of double-blind study medication were included in the safety analyses. The primary end point was tested by using Dunnett's method at the level of $\alpha = 0.027$ for each pair-wise group comparison of dapagliflozin versus placebo (overall level of $\alpha = 0.05$). A hierarchical closed testing procedure was used to control the type I error rate across the primary and secondary end points at the level of $\alpha = 0.05$ within each treatment group. If the primary comparison between a dapagliflozin group finding versus placebo was significant, statistical tests for the secondary end points were performed for that treatment group. The statistical testing of the secondary end points proceeded in a sequential manner; only those dapagliflozin groups significantly superior to placebo for the first secondary end point had statistical inference tested versus placebo for the second secondary end point ($\alpha = 0.05$ level) and, if significant, followed by the third secondary end point, and so forth.

The continuous end points were evaluated by using ANCOVA with treatment group as a fixed effect and the baseline value as a covariate. The assessment of the primary end point according to baseline HbA_{1c} subgroups was analyzed by using an ANCOVA model with terms for treatment group, baseline HbA_{1c} category, and the interaction between treatment and baseline HbA_{1c} category. The proportion of patients achieving HbA_{1c} levels <7.0% (53 mmol/mol) was analyzed by logistic regression using methods of Zhang et al,[30] with adjustment for baseline HbA_{1c} levels. The proportion of patients with ≥3% or ≥5% reduction in total weight was analyzed by using the same method, with adjustment for baseline weight. For the efficacy analysis, observations after the initiation of rescue therapy were excluded, with these and other missing values replaced by using the LOCF method. Safety data were summarized by using

descriptive statistics and included data after the initiation of rescue therapy.

RESULTS

Patients

Demographic and baseline characteristics were balanced across treatment groups; mean age was 51.3 years, and patients had a median disease duration of 0.2 year (Table I). More male than female patients participated in the study (65.4% vs 34.6%), and the majority of patients were from China (89%). Mean weight and BMI were 70.7 kg and 25.6 kg/m^2, respectively; mean waist circumference was 90.2 cm. According to Asian definitions,[31] approximately two thirds of patients (64.9%) were overweight (BMI $\geq$24 kg/m^2) and a smaller proportion (21.4%) were obese (BMI $\geq$28 kg/m^2). Mean HbA_{1c} level was 8.26% (67 mmol/mol), and mean seated systolic blood pressure (SBP) and seated diastolic blood pressure (DBP) were 123.7 and 77.8 mm Hg, respectively, at baseline.

Table I. Demographic and baseline characteristics.

Characteristic	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg
No. of patients	132	128	133
Age, mean (SD), y	49.9 (10.87)	53.0 (11.07)	51.2 (9.89)
Sex, no. (%)			
Male	87 (65.9)	84 (65.6)	86 (64.7)
Female	45 (34.1)	44 (34.4)	47 (35.3)
Race, no. (%)			
Chinese	117 (88.6)	114 (89.1)	117 (88.0)
Asian Indian	8 (6.1)	8 (6.3)	9 (6.8)
Korean	5 (3.8)	6 (4.7)	5 (3.8)
Japanese	1 (0.8)	0	1 (0.8)*
Other Asian	1 (0.8)	0	1 (0.8)
Weight, mean (SD), kg	72.18 (13.23)	68.89 (11.43)	70.92 (11.64)
Waist circumference, mean (SD), cm	91.33 (9.65)	89.32 (8.93)	89.86 (9.02)
BMI, mean (SD), kg/m^2	25.93 (3.64)	25.17 (3.29)	25.76 (3.43)
History of dyslipidemia, no. (%)	53 (40.2)	49 (38.3)	57 (42.9)
History of hypertension, no. (%)	54 (40.9)	49 (38.3)	50 (37.6)
Duration of T2DM, y			
Mean (SD)	1.30 (2.0)	1.15 (2.3)	1.67 (2.8)
Median (range)	0.2 (0–9.9)	0.2 (0–14.7)	0.4 (0–13.0)
HbA_{1c}, mean (SD), %	8.35 (0.95)	8.14 (0.74)	8.28 (0.95)
FPG, mean (SD), mg/dL (mmol/L)	167.13 (42.79) (9.28 [2.37])	154.37 (31.68) (8.57 [1.76])	162.22 (43.30) (9.00 [2.40])
Fasting C-peptide, mean (SD), ng/mL (nmol/L)	2.63 (1.17) (0.87 [0.39])	2.39 (1.39) (0.79 [0.46])	2.47 (1.00) (0.82 [0.33])
Seated blood pressure, mean (SD), mm Hg			
Systolic	123.5 (14.7)	124.1 (13.6)	123.5 (14.7)
Diastolic	78.7 (8.2)	76.8 (9.0)	78.0 (8.5)

BMI = body mass index; T2DM = type 2 diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; FPG = fasting plasma glucose.

*After a database lock, it was determined that this patient was incorrectly entered into the study database as Japanese; the patient is actually Chinese.

In total, 40.5% of patients had a history of dyslipidemia and 38.9% had a history of hypertension. (For baseline characteristics and patient disposition of the exclusively Chinese population, see **Supplemental Figure 1** and **Supplemental Table II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002.)

Overall, the majority of randomized patients completed the study (87.3%) (**Figure 1**); the most common reasons for discontinuation were withdrawal of consent (3.0%, 3.9%, and 2.3% in the placebo, dapagliflozin 5-mg, and dapagliflozin 10-mg groups, respectively), patient request (6.1%, 2.3%, and 0.8%), and AEs (0.8%, 3.1%, and 3.0%). Median exposure to study drug was 169 days in each group. More patients discontinued or received rescue medication for failing to achieve glycemic targets for placebo (16.0% [95% CI, 9.9 to 22.0]) versus either dapagliflozin 5 mg (3.1% [95% CI, 0.6 to 5.6]) or dapagliflozin 10 mg (1.4% [95% CI, −0.7 to 3.4]).

Primary End Point

Dapagliflozin 5- and 10-mg monotherapy met the primary end point at week 24 LOCF (**Figure 2A**); adjusted mean changes from baseline in HbA_{1c} were −1.04% and −1.11%, respectively, versus −0.29% for placebo ($P < 0.0001$ for both doses). Differences versus placebo in adjusted mean reductions from baseline were −0.75% for dapagliflozin 5 mg and −0.82% for dapagliflozin 10 mg, suggesting that the effect of dapagliflozin on HbA_{1c} is dose related.

Sensitivity Analysis

When evaluated according to baseline HbA_{1c} subgroup (**Figure 2B**), the most pronounced effect was observed in the highest baseline HbA_{1c} group (≥9.0% [75 mmol/mol]); the difference versus placebo was −1.06% (95% CI, −1.54 to −0.57) for dapagliflozin 5 mg and −1.32% (95% CI, −1.72 to −0.93) for dapagliflozin 10 mg. The primary outcome and sensitivity analyses according to baseline HbA_{1c} level were similar when the exclusively Chinese population

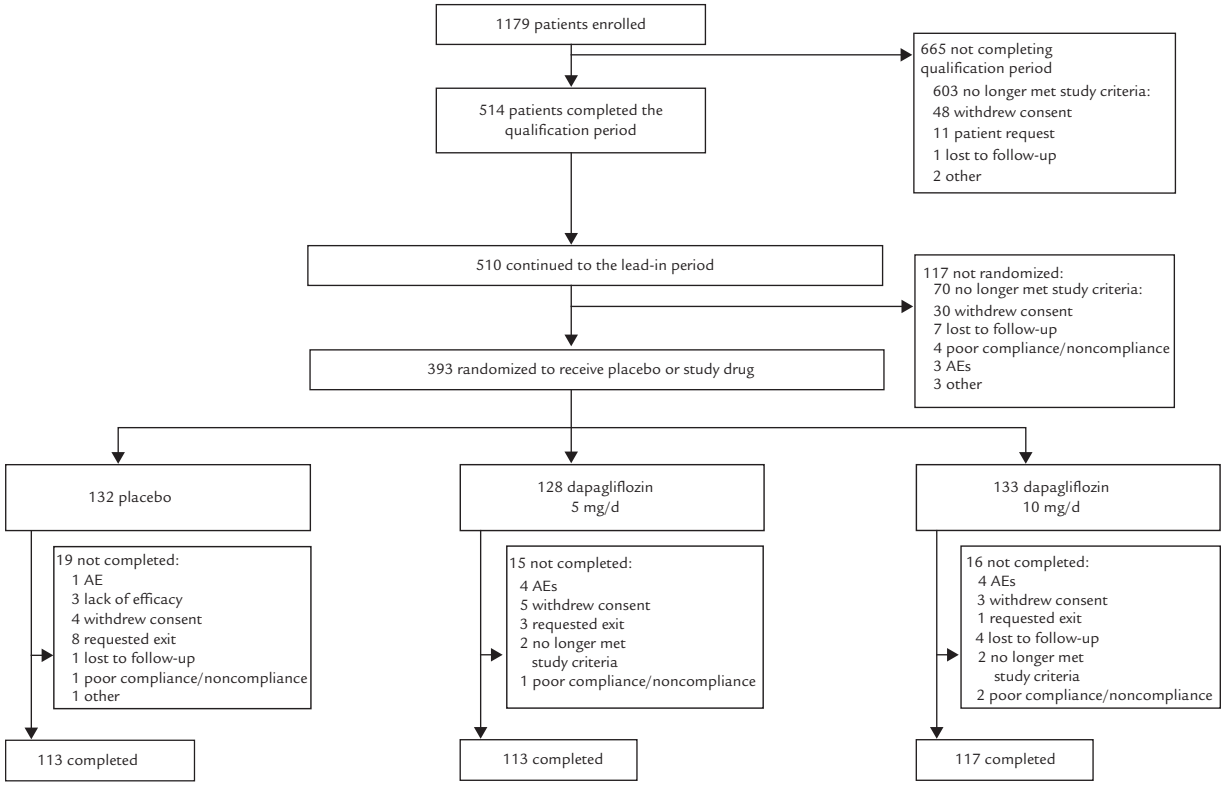
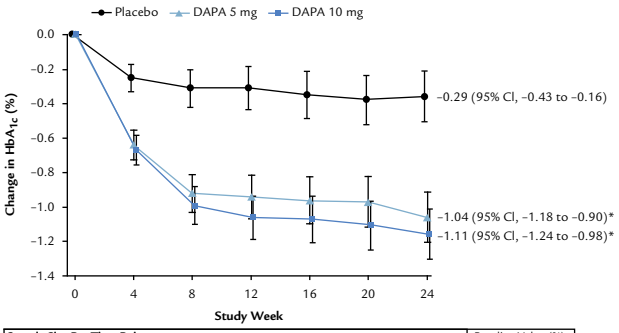


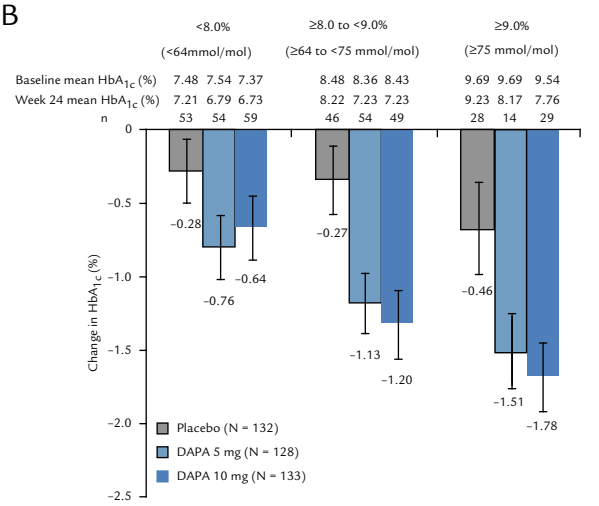
Figure 1. Trial profile.

A



Sample Size Per Time Point								Baseline Value (%)
Placebo	132	125	127	127	127	127	127	8.33
DAPA 5 mg	128	119	122	122	122	122	122	8.15
DAPA 10 mg	133	122	127	127	127	127	127	8.28

B



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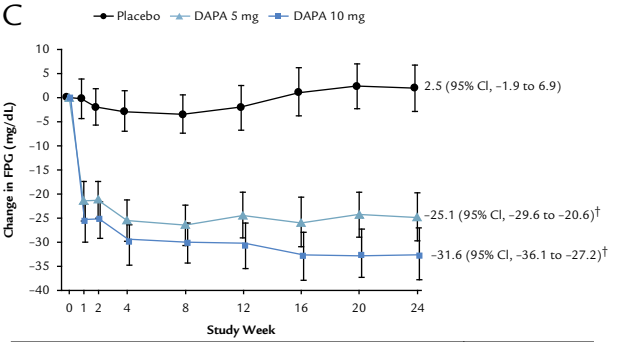
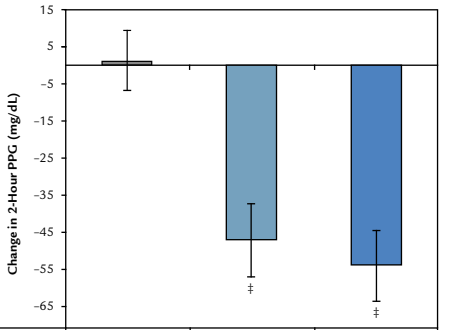


Sample Size Per Time Point										Baseline Value (mg/dL)
Placebo	132	115	129	131	131	131	131	131	131	166.6
DAPA 5 mg	128	113	125	127	127	127	127	127	127	154.2
DAPA 10 mg	133	117	127	128	128	128	128	128	128	161.8

D



Week 24 PPG	Placebo (n = 105)	DAPA 5 mg (n = 100)	DAPA 10 mg (n = 105)
Baseline 2-hour PPG (mg/dL)	250.4	224.0	230.3
Change from baseline (95% CI)	1.1 (−7.90 to 10.07)	−46.8 (−55.95 to −37.63)	−54.9 (−63.79 to −45.98)
Difference versus placebo (95% CI of difference)		−47.9 (−60.80 to −34.96)	−56.0 (−68.66 to −43.28)

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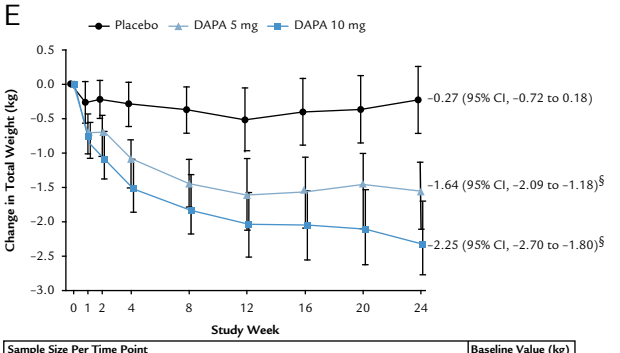
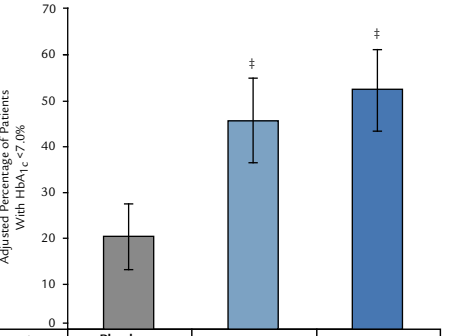


Sample Size Per Time Point										Baseline Value (kg)
Placebo	132	117	130	132	132	132	132	132	132	72.18
DAPA 5 mg	128	113	126	128	128	128	128	128	128	68.89
DAPA 10 mg	133	116	127	128	128	128	128	128	128	70.76

F



Week 24 therapeutic glycemic response	Placebo (x/n = 26/127)	DAPA 5 mg (x/n = 55/122)	DAPA 10 mg (x/n = 62/127)
Percent with HbA1c<7% (95% CI)	21.3 (14.8 to 27.8)	42.6 (34.2 to 51.1)	49.8 (41.9 to 57.7)
Difference versus placebo (95% CI of difference)		21.3 (11.1 to 31.6)	28.5 (18.6 to 38.3)

was analyzed separately (**Supplemental Figures 2A** and **2B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002).

Secondary End Points

Dapagliflozin was significantly different from placebo at week 24 (LOCF) in all the secondary end points assessed (**Figures 2C–2F**). The dapagliflozin 5- and 10-mg doses produced mean reductions from baseline in FPG, which were significantly greater (–25.1 mg/dL [–1.39 mmol/L], $P < 0.0001$ and –31.6 mg/dL [–1.75 mmol/L], $P < 0.0001$) compared with placebo (2.5 mg/dL [0.14 mmol/L]). Reduction from baseline in mean 2-hour PPG in response to a liquid meal challenge was significantly greater with dapagliflozin 5 mg (–46.8 mg/dL [–2.60 mmol/L], $P < 0.0001$) and 10 mg (–54.9 mg/dL [−3.05 mmol/L], $P < 0.0001$) compared with placebo (1.1 mg/dL [0.06 mmol/L]). Dapagliflozin also resulted in significant mean reductions from baseline in total weight (–1.64 kg for the 5-mg dose and –2.25 kg for the 10-mg dose; $P < 0.0001$ for both doses) compared with the mean reduction from baseline observed with placebo (–0.27 kg). The proportion of patients achieving an HbA_{1c} level <7.0% (53 mmol/mol) at week 24 was significantly greater with dapagliflozin 5 mg (42.6%; $P < 0.0001$) and 10 mg (49.8%; $P < 0.0001$) compared with placebo (21.3%). Secondary outcomes were similar in the exclusively Chinese subgroup (**Supplemental Figures 2C–2F** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002).

Exploratory End Points

Exploratory end points are detailed in **Table II**. Greater proportions of patients receiving dapagliflozin 10 mg and 5 mg achieved ≥3% reduction from baseline in total weight (46.0% and 42.4%, respectively) versus placebo (15.1%). This trend was also apparent when considering proportions achieving ≥5% reduction from baseline in total weight: 29.6% and 20.8%,

Figure 2. Primary and secondary end points. (A) Primary end point: change in glycosylated hemoglobin (HbA_{1c}). *Difference versus placebo (95% CI) of −0.75% (−0.94 to −0.56) and −0.82% (−1.01 to −0.63) for dapagliflozin (DAPA) 5 mg and 10 mg, respectively ($P < 0.0001$ at $\alpha = 0.027$ applying Dunnett's adjustment). (B) Sensitivity analysis: change in HbA_{1c} according to baseline HbA_{1c} subgroups. In HbA_{1c} <8.0% (<64 mmol/mol) baseline subgroup: difference versus placebo (95% CI) of −0.48% (−0.77 to −0.19) and −0.36% (−0.66 to −0.07) for DAPA 5 mg and 10 mg, respectively. In HbA_{1c} ≥8.0 to <9.0% (≥64 to <75 mmol/mol) subgroup: difference of −0.86% (−1.16 to −0.56) and −0.93% (−1.24 to −0.63), respectively. In HbA_{1c} ≥9.0% (≥75 mmol/mol) subgroup: difference of −1.06% (−1.54 to −0.57) and −1.32% (−1.72 to −0.93), respectively. (C) Change in fasting plasma glucose (FPG). †Difference versus placebo (95% CI) of −27.7 mg/dL (−34.0 to −21.4) [−1.54 mmol/L (1.89 to 1.19)] and −34.2 mg/dL (−40.4 to −27.9) [−1.90 mmol/L (2.24 to 1.55)] for DAPA 5 mg and 10 mg, respectively ($P < 0.0001$ after sequential testing procedure at $\alpha = 0.05$). (D) Change in 2-hour postprandial glucose (PPG) after a liquid meal challenge. ‡$P < 0.0001$ versus placebo after sequential testing procedure at $\alpha = 0.05$. (E) Change in total weight. §Difference versus placebo (95% CI) of −1.37 kg (−2.01 to −0.73) and −1.98 kg (−2.62 to −1.34) for DAPA 5 mg and 10 mg, respectively ($P < 0.0001$ after sequential testing procedure at $\alpha = 0.05$). (F) Adjusted proportion of patients with a therapeutic glycemic response, defined as an HbA_{1c} level <7.0% (53 mmol/mol). Analyses exclude data after rescue therapy. N is the number of patients randomized to treatment who received ≥1 dose of double-blind study medication; n is the number of patients randomized to treatment who received ≥1 dose of double-blind study medication and had nonmissing baseline and week 24 (last-observation-carried-forward) values. For A, C, and D, data are adjusted mean change from baseline ± 95% CIs derived from ANCOVA with treatment group as effect and baseline value as a covariate. For B, data are adjusted mean change from baseline ± 95% CIs derived from ANCOVA with terms for treatment group, baseline HbA_{1c} category, and interaction between treatment and baseline HbA_{1c} category. For F, data are adjusted percent with 95% CIs derived from logistic regression analysis based on the methods of Zhang et al,[30] with adjustment for baseline for baseline HbA_{1c}; x is the number of patients showing a response.

Table II. Exploratory end points at week 24. Data are last-observation-carried-forward (LOCF) excluding data after rescue therapy.

Characteristic	Placebo (N = 132)	Dapagliflozin 5 mg (N = 128)	Dapagliflozin 10 mg (N = 133)
Total cholesterol			
n	123	119	123
Baseline mean (SD), mg/dL	189.7 (41.3)	191.8 (59.9)	187.8 (34.1)
Adjusted mean percent change at week 24, % (95% CI)*	−1.43 (−4.11 to 1.33)	−2.66 (−5.34, 0.11)	2.28 (−0.50 to 5.14)
Difference versus placebo		−1.25	3.76
95% CI of difference		−5.05 to 2.71	−0.21 to 7.88
LDL-C			
n	122	119	123
Baseline mean (SD), mg/dL	106.3 (33.8)	109.7 (37.1)	103.2 (30.3)
Adjusted mean percent change at week 24, % (95% CI)*	−0.97 (−5.45 to 3.73)	−2.16 (−6.65 to 2.54)	7.20 (2.36 to 12.26)
Difference versus placebo		−1.21	8.24
95% CI of difference		−7.52 to 5.53	1.39 to 15.56
HDL-C			
n	123	119	123
Baseline mean (SD), mg/dL	44.1 (10.0)	46.7 (11.1)	45.7 (11.4)
Adjusted mean percent change at week 24, % (95% CI)*	4.24 (1.45 to 7.11)	9.55 (6.57 to 12.62)	11.52 (8.55 to 14.58)
Difference versus placebo		5.09	6.99
95% CI of difference		1.10 to 9.25	2.96 to 11.17
Triglycerides			
n	123	120	126
Baseline mean (SD), mg/dL	227.1 (262.0)	186.1 (349.2)	205.8 (150.2)
Adjusted mean percent change at week 24, % (95% CI)*	−6.95 (−13.39 to −0.03)	−19.11 (−24.81 to −12.99)	−16.47 (−22.18 to −10.33)
Difference versus placebo		−13.07	−10.23
95% CI of difference		−21.55 to −3.67	−18.82 to −0.72
Urinary glucose:creatinine ratio, g/g			
n	116	112	114
Baseline mean (SD)	3.59 (9.70)	3.48 (9.63)	3.49 (12.04)
Adjusted mean absolute change at week 24 (95% CI)†	0.79 (−3.02 to 4.60)	26.92 (23.04 to 30.79)	34.91 (31.07 to 38.76)
Difference versus placebo		26.13	34.12
95% CI of difference		20.69 to 31.56	28.71 to 39.53
Fasting C-peptide, ng/mL			
n	115	110	114
Baseline mean (SD)	2.61 (1.19)	2.35 (1.41)	2.50 (1.03)
Adjusted mean absolute change at week 24 (95% CI)†	−0.03 (−0.17 to 0.12)	−0.36 (−0.51 to −0.21)	−0.40 (−0.54 to −0.25)
Difference versus placebo		−0.34	−0.37
95% CI of difference		−0.54 to −0.13	−0.57 to −0.17
Waist circumference, cm			
n	118	114	118
Baseline mean (SD)	91.2 (9.7)	89.1 (9.1)	89.9 (8.8)
Adjusted mean absolute change at week 24 (95% CI)†	−0.72 (−1.50 to 0.06)	−2.77 (−3.56 to −1.97)	−2.20 (−2.98 to −1.42)

(continued)

Table II (continued).

Characteristic	Placebo (N = 132)	Dapagliflozin 5 mg (N = 128)	Dapagliflozin 10 mg (N = 133)
Difference versus placebo		−2.05	−1.48
95% CI of difference		−3.17 to −0.93	−2.59 to −0.38
HOMA-2 β-cell function, %			
n	114	109	113
Baseline mean (SD)	56.9 (30.5)	53.9 (25.0)	56.1 (22.9)
Adjusted mean absolute change at week 24 (95% CI)†	1.05 (−2.66 to 4.76)	10.49 (6.69 to 14.28)	12.74 (9.02 to 16.47)
Difference versus placebo		9.44	11.69
95% CI of difference		4.13 to 14.74	6.44 to 16.95
HOMA-2 insulin sensitivity, %			
n	114	109	113
Baseline mean (SD)	52.8 (24.0)	59.4 (22.5)	52.9 (20.7)
Adjusted mean absolute change at week 24 (95% CI)†	−0.16 (−4.13 to 3.82)	10.05 (5.96 to 14.13)	15.48 (11.49 to 19.48)
Difference versus placebo		10.20	15.64
95% CI of difference		4.48 to 15.92	10.01 to 21.27
Proportion of patients with ≥3% reduction in total weight, %			
n	132	128	128
Baseline mean weight, kg	72.2	68.9	70.8
Proportion (adjusted for baseline weight) at week 24, % (95% CI)‡	15.1 (9.0 to 21.3)	42.4 (33.8 to 50.9)	46.0 (37.4 to 54.6)
Difference versus placebo		27.2	30.9
95% CI of difference		16.7 to 37.8	20.3 to 41.4
Proportion of patients with ≥5% reduction in total weight, %			
n	132	128	128
Baseline mean weight, kg	72.2	68.9	70.8
Proportion (adjusted for baseline weight) at week 24, % (95% CI)‡	5.6 (1.8 to 9.4)	20.8 (13.7 to 27.9)	29.6 (21.8 to 37.5)
Difference versus placebo		15.2	24.0
95% CI of difference		7.2 to 23.2	15.3 to 32.8

N = number of patients randomized to treatment who received ≥1 dose of double-blind study medication; n = number of patients randomized to treatment who received ≥1 dose of double-blind study medication with nonmissing baseline and week 24 LOCF values; HOMA-2 = homeostasis model assessment version 2.

*Derived from ANCOVA model for (log [week 24 value] − log [baseline value]) for each end point with treatment group as an effect and log [baseline value] as a covariate.

†Derived from ANCOVA model with treatment group as an effect and baseline value as a covariate.

‡Proportion analyzed by using the methods of Zhang et al,[30] with adjustment for baseline total weight. Measures for urinary glucose:creatinine ratio were derived from a urinary spot-check performed in the morning fasting state.

respectively, versus 5.6% with placebo. The effect of treatment on patient lipid profiles was also assessed. For placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively, week 24 adjusted mean percent changes from baseline were −1.43%, −2.66%, and 2.28% for total cholesterol; −0.97%, −2.16%, and 7.20% for LDL-C; 4.24%, 9.55%, and 11.52% for HDL-C; and −6.95%, −19.11%, and −16.47% for triglycerides. Other exploratory end points, including waist circumference, HOMA-2 β-cell function, and HOMA-2 insulin sensitivity, are shown in Table II. Findings were similar when the exclusively Chinese population was considered (Supplemental Table III in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002).

Pharmacodynamic End Point

Dapagliflozin treatment produced a dose-related increase in mean urinary glucose:creatinine ratio, consistent with its mechanism of action (Table II). Adjusted absolute mean change at week 24 was 0.79 g/g for placebo, 26.92 g/g for dapagliflozin 5 mg, and 34.91 g/g for dapagliflozin 10 mg.

Safety and Tolerability

Overall, dapagliflozin was well tolerated (Table III). AEs and SAEs were balanced across treatment groups. No deaths occurred during the 24-week double-blind period, no major episodes of hypoglycemia were reported, and no patient discontinued the study due to hypoglycemia. Hypoglycemic events (minor or other) were reported in 1 patient each in the 5- and 10-mg dapagliflozin groups and 2 patients in the placebo group.

Overall, few patients experienced AEs of genital infection or UTI, although proportions were higher in the dapagliflozin versus placebo groups: 0.8%, 3.1%, and 4.5% experienced genital infections in the placebo and dapagliflozin 5- and 10-mg groups, respectively, and 3.0%, 3.9%, and 5.3% experienced UTIs. All reported events were of mild or moderate intensity. One patient (in the dapagliflozin 5-mg group) discontinued the study due to a genital infection and UTI, both of moderate intensity. Both events resolved after antibiotic treatment. One patient (in the dapagliflozin 10-mg group) experienced an SAE (urethritis of moderate intensity). The event resolved after treatment with an antibiotic and an antifungal agent, and the patient continued in the study. No patient experienced kidney infection or pyelonephritis. An SAE of pancreatic carcinoma was observed in 1 patient in the dapagliflozin 5-mg group; no other neoplasms were observed in this study.

Events of renal impairment occurred in 6 patients overall (1.5%); 2 patients in the placebo group, 1 patient in the dapagliflozin 5-mg group, and 3 patients in the dapagliflozin 10-mg group. There were no episodes of renal failure reported during the 24-week double-blind period. All the renal impairment events were of mild intensity, and none were serious or resulted in discontinuation. Five of 6 of these AEs were reported due to asymptomatic, transient NAG increases that did not meet protocol-specified criteria for either retesting or study discontinuation. None of these patients had findings outside of normal limits for any of the traditional markers of renal function (serum creatinine, cystatin C, blood urea nitrogen, and estimated glomerular filtration rate). Mean estimated glomerular filtration rate was minimally increased at week 24 across all treatment groups, although these changes were not considered clinically meaningful: 0.8, 2.3, and 0.9 mL/min/1.73 m^2 for placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively.

Changes from baseline in other selected laboratory parameters are shown in Table IV. At week 24, dapagliflozin treatment was associated with small increases in mean hematocrit and mean blood urea nitrogen levels and a decrease in mean uric acid levels. Values for these parameters at 12 weeks versus those at 24 weeks showed no evidence of progressive change with dapagliflozin therapy. There were no clinically relevant mean changes from baseline in any liver function test results.

Change from baseline at week 24 in mean seated SBP was 0.8 mm Hg in the placebo group, −1.2 mm Hg in the dapagliflozin 5-mg group, and −2.3 mm Hg in the dapagliflozin 10-mg group (Table III). Change from baseline at week 24 in mean seated DBP was 0.4, −1.3, and −1.6 mm Hg in the placebo, dapagliflozin 5-mg, and dapagliflozin 10-mg groups. No clinically meaningful mean changes from baseline were observed in supine, standing, orthostatic, or seated heart rate. Proportions of patients with a vital sign examination indicating orthostatic hypotension were low at week 24 in the placebo group (1 of 107 [0.9%]) and the dapagliflozin 5-mg (5 of 103 [4.9%]) and 10-mg (2 of 107 [1.9%]) groups. No patient experienced an AE of volume depletion during the study.

Safety and laboratory outcomes were similar when the exclusively Chinese population was

Table III. Overall summary of patients with an adverse event (AE), AEs with frequency ≥2% in any group and higher in dapagliflozin versus placebo groups, AEs of special interest, and blood pressure measurements, including data after rescue therapy.

Preferred Term	Placebo (N = 132)	Dapagliflozin 5 mg (N = 128)	Dapagliflozin 10 mg (N = 133)
Overall summary of no. (%) of patients with an AE			
≥1 AE	84 (63.6)	79 (61.7)	81 (60.9)
AE leading to discontinuation	1 (0.8)	3 (2.3)	3 (2.3)
≥1 SAE	2 (1.5)	5 (3.9)	4 (3.0)
No. (%) of AEs with frequency ≥2% in any group (by MedDRA preferred term) and higher in dapagliflozin versus placebo groups			
Nasopharyngitis	5 (3.8)	7 (5.5)	4 (3.0)
Urinary tract infection	4 (3.0)	5 (3.9)	5 (3.8)
Toothache	2 (1.5)	4 (3.1)	3 (2.3)
Increased *N*-acetyl-β-D-glucosaminidase	2 (1.5)	3 (2.3)	3 (2.3)
Diarrhea	2 (1.5)	3 (2.3)	3 (2.3)
Thrombocytopenia	0	5 (3.9)	3 (2.3)
Diabetic nephropathy	2 (1.5)	2 (1.6)	3 (2.3)
Back pain	1 (0.8)	1 (0.8)	4 (3.0)
Constipation	1 (0.8)	2 (1.6)	3 (2.3)
Renal impairment	2 (1.5)	1 (0.8)	3 (2.3)
Cough	1 (0.8)	4 (3.1)	1 (0.8)
Increased blood creatine phosphokinase	0	3 (2.3)	2 (1.5)
Urgency of micturition	1 (0.8)	0	3 (2.3)
Gastritis	0	3 (2.3)	1 (0.8)
No. (%) of patients with an AE of special interest			
≥1 hypoglycemic event*	2 (1.5)	1 (0.8)	1 (0.8)
AEs of genital infection†	1 (0.8)	4 (3.1)	6 (4.5)
Balanoposthitis	0	1 (0.8)	2 (1.5)
Genital infection	0	2 (1.6)	1 (0.8)
Posthitis	0	0	1 (0.8)
Vaginal infection	0	0	1 (0.8)
Vulvovaginal mycotic infection	0	0	1 (0.8)
Fungal genital infection	1 (0.8)	1 (0.8)	0
AEs of urinary tract infection†	4 (3.0)	5 (3.9)	7 (5.3)
Urinary tract infection	4 (3.0)	5 (3.9)	5 (3.8)
Urethritis	0	0	2 (1.5)
Renal impairment†,‡	2 (1.5)	1 (0.8)	3 (2.3)
Blood pressure, mm Hg			
Baseline mean (SD) seated systolic blood pressure	n = 132 123.5 (14.7)	n = 128 124.1 (13.6)	n = 133 123.5 (14.7)
Adjusted mean (SE) absolute change at week 24	n = 113 0.8 (1.2)	n = 112 −1.2 (1.2)	n = 114 −2.3 (1.1)
Baseline mean (SD) seated diastolic blood pressure	n = 132 78.7 (8.2)	n = 128 76.8 (9.0)	n = 133 78.0 (8.5)
Adjusted mean (SE) absolute change at week 24	n = 113 0.4 (0.8)	n = 112 −1.3 (0.9)	n = 114 −1.6 (0.8)

N = number of treated patients; no. = number of patients evaluated at specified time point; SAE = serious AE.

*None led to study discontinuation.

†Based on definitive (prespecified) Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (version 15.0).

‡No events of renal failure were observed during the 24-week double-blind treatment period.

Table IV. Laboratory values of interest: change from baseline at weeks 12 and 24, including data after rescue therapy.

Variable	Placebo (N = 132)	Dapagliflozin 5 mg (N = 128)	Dapagliflozin 10 mg (N = 133)
Hematocrit, %			
Baseline	n = 132	n = 128	n = 133
Mean (SD)	43.67 (4.03)	43.73 (3.69)	43.93 (4.32)
Change at week 12	n = 121	n = 119	n = 119
Mean (SE)	−0.20 (0.20)	1.60 (0.22)	1.72 (0.20)
Change at week 24	n = 112	n = 112	n = 112
Mean (SE)	−0.50 (0.25)	0.79 (0.20)	1.05 (0.20)
Serum creatinine, mg/dL			
Baseline	n = 132	n = 128	n = 133
Mean (SD)	0.82 (0.16)	0.83 (0.16)	0.84 (0.20)
Change at week 12	n = 123	n = 119	n = 121
Mean (SE)	0.021 (0.016)	−0.003 (0.007)	0.004 (0.008)
Change at week 24	n = 113	n = 112	n = 113
Mean (SE)	−0.008 (0.008)	−0.014 (0.008)	−0.009 (0.009)
Estimated GFR, mL/min/1.73 m^2			
Baseline	n = 132	n = 128	n = 133
Mean (SD)	94.1 (17.7)	91.6 (17.1)	91.7 (20.2)
Change at week 12	n = 123	n = 119	n = 121
Mean (SE)	−1.0 (1.27)	0.5 (0.97)	−0.8 (1.07)
Change at week 24	n = 113	n = 112	n = 113
Mean (SE)	0.8 (1.06)	2.3 (1.06)	0.9 (0.98)
Blood urea nitrogen, mg/dL			
Baseline	n = 132	n = 128	n = 133
Mean (SD)	14.3 (3.4)	15.1 (3.9)	15.5 (4.0)
Change at week 12	n = 123	n = 119	n = 121
Mean (SE)	0.18 (0.29)	1.64 (0.36)	1.15 (0.33)
Change at week 24	n = 113	n = 112	n = 113
Mean (SE)	0.46 (0.33)	1.99 (0.41)	1.80 (0.39)
Uric acid, mg/dL			
Baseline	n = 132	n = 128	n = 133
Mean (SD)	5.4 (1.6)	5.2 (1.2)	5.0 (1.3)
Change at week 12	n = 123	n = 119	n = 121
Mean (SE)	0.04 (0.10)	−0.53 (0.09)	−0.41 (0.08)
Change at week 24	n = 113	n = 112	n = 113
Mean (SE)	−0.04 (0.11)	−0.71 (0.09)	−0.42 (0.10)

N = number of treated patients; n = number of patients evaluated at specified time point; GFR = glomerular filtration rate.

considered (**Supplemental Tables IV** and **V** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002).

DISCUSSION

The efficacy and safety findings observed in this study are similar to those in other studies of SGLT2

inhibitor treatment as monotherapy in non-Asian populations. In a Phase III study of dapagliflozin as monotherapy in treatment-naive patients enrolled from the United States, Canada, Mexico, and Russia, mean HbA_{1c} reductions from baseline at week 24 were −0.23% with placebo, −0.77% with dapagliflozin 5 mg, and −0.89% with dapagliflozin 10 mg, with no major hypoglycemic episodes observed.[10] In the current study of drug-naive Asian patients with T2DM and inadequate glycemic control with diet and exercise, dapagliflozin achieved the primary end point of statistically significant mean reductions in HbA_{1c} at week 24 versus placebo; reductions with dapagliflozin 5 and 10 mg were −1.04% and −1.11%, respectively, versus −0.29% with placebo.

In both studies, HbA_{1c} lowering was seen as early as week 4, the first time point examined.[10] The difference in HbA_{1c} reduction at week 24 between the 2 studies may be accounted for, at least in part, by a greater mean HbA_{1c} level at baseline in the current study (8.26%) versus the previous Western population study (7.92%). This suggestion is supported by the sensitivity analysis presented here, which demonstrates that although HbA_{1c} reductions occurred across all baseline HbA_{1c} subgroups with dapagliflozin, greater reductions were observed in the higher baseline HbA_{1c} subgroups. The proportion of patients achieving HbA_{1c} levels <7.0% (53 mmol/mol) was significantly greater in the dapagliflozin 5- and 10-mg groups versus the placebo group in this study (43% and 50% vs 21%, respectively), consistent with the findings in the Western population study (44% and 51% vs 32%).

Dose-dependent mean reductions in the secondary end points of FPG and 2-hour PPG (after a liquid meal challenge) were significantly greater for dapagliflozin compared with placebo in these analyses. Adjusted mean change from baseline in FPG after 24 weeks of therapy in the previous study of dapagliflozin in a Western population (−4.1, −24.1, and −28.8 mg/dL for placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively)[10] are comparable with findings reported in the current study (2.5, −25.1, and −31.6 mg/dL). It has previously been demonstrated that PPG regulation may vary according to ethnicity of the patient population.[27–29] In this study of Asian patients, dapagliflozin decreased 2-hour PPG levels after a liquid meal challenge, as reported previously with dapagliflozin treatment in non-Asian patient populations.[14,32,33]

The mean weight reductions of −1.64 and −2.25 kg observed for dapagliflozin 5 mg and 10 mg in the current study (and −0.27 kg for placebo) are lower than the mean weight loss observed in the study of dapagliflozin in the Western population: −2.83 and −3.16 kg, respectively, and −2.20 kg for placebo. However, the baseline patient characteristics in the current study are typical of an Asian population,[24–26] with mean weight and BMI lower than observations from comparable, non-Asian patients with T2DM.[10,34] Despite this lower mean baseline weight, use of dapagliflozin resulted in significant reductions in glycemia and mean weight versus placebo throughout the study, suggesting that it is an effective therapy in Asian populations with lower mean BMI, similar to previous findings in Western populations with higher BMIs.[9,10,13–15,17] Importantly, no safety or tolerability issues were identified with dapagliflozin-induced weight loss in this Asian population with lower mean BMI and T2DM; the safety profile in general was consistent with the overall dapagliflozin clinical program, which comprised both Western and Asian patients. A previous study of dapagliflozin in healthy Chinese subjects has also demonstrated similar pharmacodynamics and pharmacokinetics compared with non-Chinese subjects.[20] Taken together, these observations suggest that the overall effect of dapagliflozin is comparable in Asian and non-Asian populations.

Dapagliflozin induces weight loss via caloric loss from glycosuria. A study by Bolinder et al[22] found that the decrease in total weight observed with dapagliflozin was predominantly through reduced total body fat mass, both visceral adipose tissue and subcutaneous adipose tissue. The improved β-cell function and increases in mean insulin sensitivity observed in our study are also consistent with weight loss and relief of glucotoxicity, and in line with findings from clamp studies.[35]

AEs were balanced across groups in this Phase III study, with few patients experiencing AEs or SAEs leading to discontinuation, and no deaths observed. Because SGLT2 inhibition is independent of insulin secretion or action, dapagliflozin has a low intrinsic propensity to cause hypoglycemia.[36] In the current study, hypoglycemia was uncommon across treatment groups; there were no episodes of major hypoglycemia, and no events led to discontinuation. Proportions of patients experiencing genital infections and UTIs were low overall, although more common with dapagliflozin

versus placebo; none of the events was considered severe, only 1 dapagliflozin patient (10-mg group) discontinued treatment, and there were no reports of pyelonephritis. The relative risk of genital infections and UTIs is increased in patients with diabetes in general, potentially due to inadequate glycemic control, changes in immune function, or occurrence of glycosuria.[37–41] The balance of evidence from clinical studies to date suggests that SGLT2 inhibitors increase the incidence of genital infections[42,43]; the relationship to UTI incidence is less certain, with additional long-term studies required to address this issue. No AEs of renal failure were reported in this study, and there was no evidence of an adverse impact on renal function. Reductions from baseline in mean seated SBP and DBP were observed with dapagliflozin, without an increase in the proportion of patients with orthostatic hypotension, dehydration, or hypovolemia.

The majority of patients analyzed were resident in China; when the Chinese subpopulation was analyzed exclusively, efficacy and safety findings similar to the overall study population were observed. This high proportion of Chinese patients, and hence the generalizability of these findings to other Asian populations, may be considered a limitation of this study. However, similar efficacy and safety observations have recently been reported for dapagliflozin as monotherapy in a Phase II trial of 279 Japanese patients,[21] supporting the robustness of the findings in the current study.

CONCLUSIONS

In this study of drug-naive Asian patients, dapagliflozin as monotherapy was safe and effective in improving glycemic parameters, with low rates of hypoglycemia and the additional benefit of weight loss. These findings are consistent with previous studies of dapagliflozin in predominantly Western populations.

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CONFLICTS OF INTEREST

Dr. Ji has participated in advisory panels and has acted as a consultant for Sanofi, Novo Nordisk, and Merck Sharp & Dohme Ltd, and has received research support from Sanofi, Merck Sharp & Dohme Ltd, and Bristol-Myers Squibb. Drs. Li, Mansfield, Iqbal, Ptaszynska, and List are employees of Bristol-Myers Squibb and stockholders/shareholders. Ms. T'joen is an employee of Bristol-Myers Squibb. Dr. Ma has nothing to disclose. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

Supplemental materials accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.11.002.

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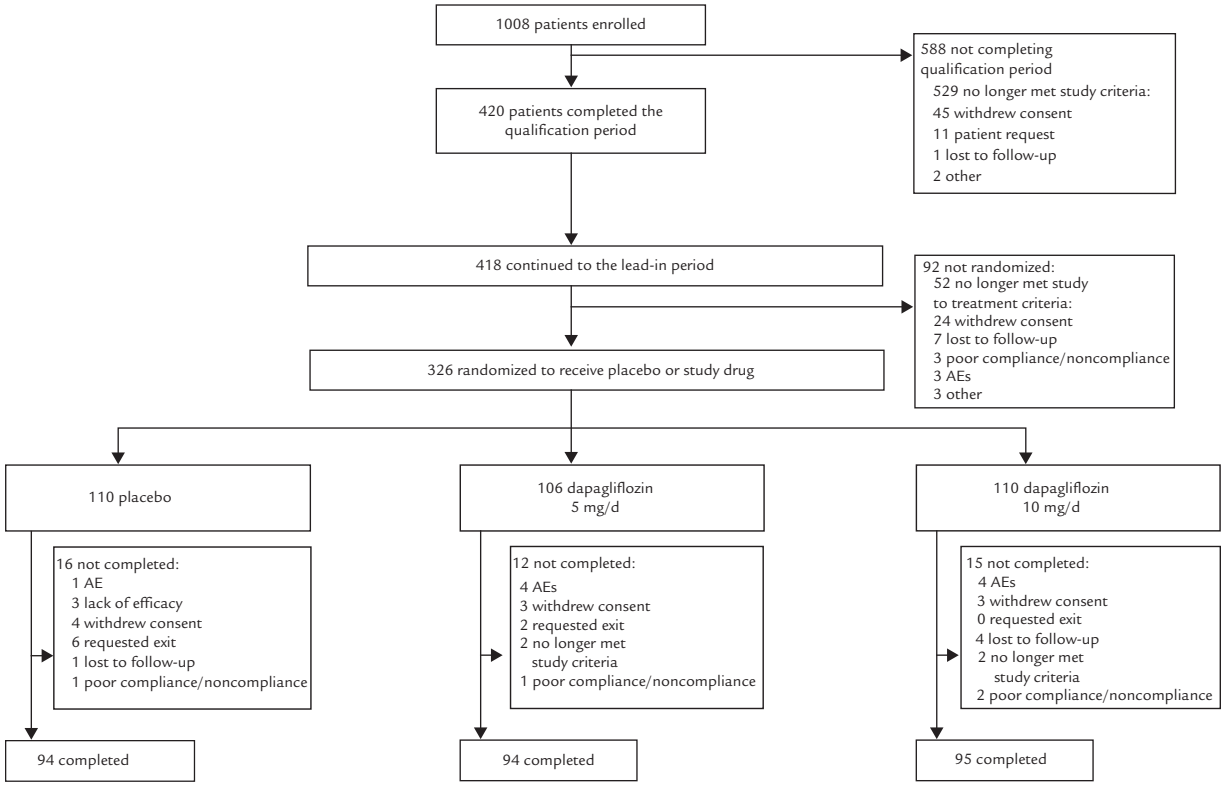
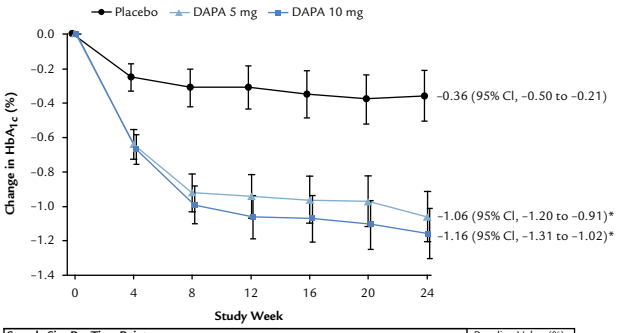


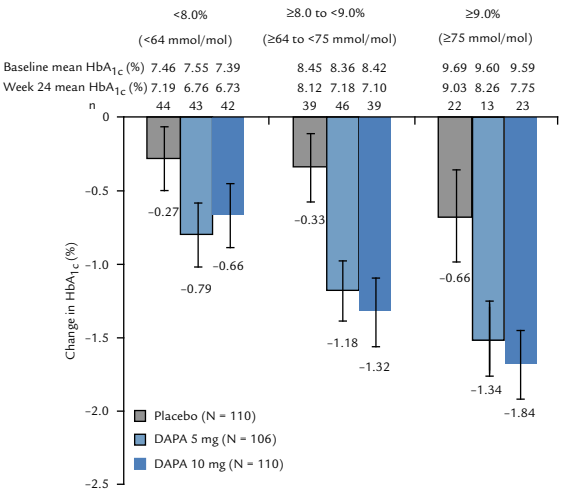
Supplemental Figure 1. Trial profile of the exclusively Chinese population.

A



Sample Size Per Time Point								Baseline Value (%)
Placebo	110	103	105	105	105	105	105	8.29
DAPA 5 mg	106	99	102	102	102	102	102	8.18
DAPA 10 mg	110	99	104	104	104	104	104	8.26

B



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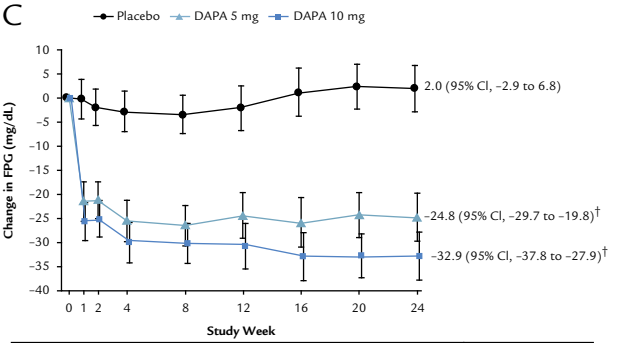
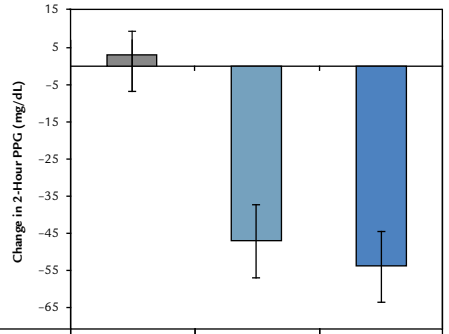


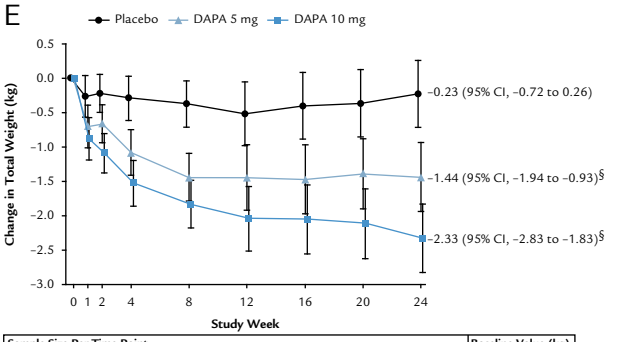
Sample Size Per Time Point										Baseline Value (mg/dL)
Placebo	110	95	108	109	109	109	109	109	109	166.5
DAPA 5 mg	106	91	103	105	105	105	105	105	105	156.1
DAPA 10 mg	110	95	104	105	105	105	105	105	105	161.9

D



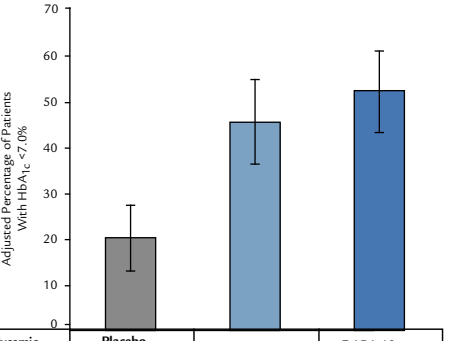
Week 24 PPG	Placebo (n = 88)	DAPA 5 mg (n = 85)	DAPA 10 mg (n = 88)
Baseline 2-hour PPG (mg/dL)	253.0	230.3	229.8
Change from baseline* (95% CI)	3.0 (−6.74 to 12.75)	−47.2 (−56.99 to −37.32)	−54.1 (−63.73 to −44.39)
Difference versus placebo (95% CI of difference)		−50.2 (−64.08 to −36.24)	−57.1 (−70.86 to −43.25)

E



Sample Size Per Time Point										Baseline Value (kg)
Placebo	110	97	109	110	110	110	110	110	110	72.38
DAPA 5 mg	106	91	104	106	106	106	106	106	106	68.18
DAPA 10 mg	110	95	104	105	105	105	105	105	105	70.39

F



Week 24 therapeutic glycemic response	Placebo (x/n = 21/105)	DAPA 5 mg (x/n = 48/102)	DAPA 10 mg (x/n = 54/104)
Percent with HbA1c<7% (95% CI)	20.3 (13.2 to 27.5)	45.7 (36.4 to 54.9)	52.5 (43.6 to 61.3)
Difference versus placebo (95% CI of difference)		25.3 14.0 to 36.7	32.1 21.1 to 43.2

Supplemental Figure 2. Primary and secondary end points in the exclusively Chinese population. (A) Primary end point: change in glycosylated hemoglobin (HbA_{1c}). *Difference versus placebo (95% CI) of −0.70% (−0.90 to −0.49) and −0.80% (−1.01 to −0.60) for dapagliflozin (DAPA) 5 mg and 10 mg, respectively. (B) Sensitivity analysis: change in HbA_{1c} according to baseline HbA_{1c} subgroups. In HbA_{1c} <8.0% (<64 mmol/mol) baseline subgroup: difference versus placebo (95% CI) of −0.52% (−0.83 to −0.21) and −0.39% (−0.70 to −0.08) for DAPA 5 mg and 10 mg, respectively. In HbA_{1c} ≥8.0 to <9.0% (≥64 to <75 mmol/mol): difference of −0.85% (−1.17 to −0.54) and −0.99% (−1.32 to −0.66), respectively. In HbA_{1c} ≥9.0% (≥75 mmol/mol) subgroup: difference of −0.68% (−1.19 to −0.17) and −1.18% (−1.61 to −0.75), respectively. (C) Change in fasting plasma glucose (FPG). †Difference versus placebo (95% CI) of −26.7 mg/dL (−33.7 to −19.8) [−1.48 mmol/L (−1.87 to −1.10)] and −34.8 mg/dL (−41.8 to −27.9) [−1.93 mmol/L (−2.32 to −1.55)] for DAPA 5 mg and 10 mg, respectively. (D) Change in 2-hour postprandial glucose (PPG) after a liquid meal challenge. (E) Change in total weight. §Difference versus placebo (95% CI) of −1.21 kg (−1.92 to −0.50) and −2.10 kg (−2.80 to −1.39) for DAPA 5 mg and 10 mg, respectively. (F) Adjusted proportion of patients with a therapeutic glycemic response, defined as an HbA_{1c} level <7.0% (53 mmol/mol). Analyses exclude data after rescue therapy. N is the number of randomized patients from China who received ≥1 dose of double-blind study medication; n is the number of randomized patients from China who received ≥1 dose of double-blind study medication with nonmissing baseline and week 24 (last-observation-carried-forward) values. For A, C, and D, data are adjusted mean change from baseline ± 95% CIs derived from ANCOVA, with treatment group as effect and baseline value as a covariate. For B, data are adjusted mean change from baseline ± 95% CIs derived from ANCOVA with terms for treatment group, baseline HbA_{1c} category, and interaction between treatment and baseline HbA_{1c} category. For F, data are adjusted percent with 95% CIs derived from logistic regression analysis based on the methods of Zhang et al,[30] with adjustment for baseline for baseline HbA_{1c}; x is the number of patients showing a response.

Supplemental Table I. Full exclusion criteria and definition of serious adverse events.

Exclusion criteria

- History of diabetes insipidus
- Symptoms of poorly controlled diabetes that would preclude participation in this trial, including but not limited to, marked polyuria and polydipsia with >10% weight loss during the 3 months before enrollment
- History of diabetic ketoacidosis or hyperosmolar nonketotic coma
- History of bone fracture secondary to diagnosed severe osteoporosis
- Severe uncontrolled hypertension defined as SBP ≥180 mm Hg and/or DBP ≥110 mm Hg
- Any of the following cardiovascular/vascular diseases within 6 months of the enrollment visit:
  - Myocardial infarction
  - Cardiac surgery or revascularization (coronary artery bypass graft/percutaneous transluminal coronary angioplasty)
  - Unstable angina
  - Unstable congestive heart failure
  - Congestive heart failure New York Heart Association class III or IV
  - Transient ischemic attack or significant cerebrovascular disease
  - Unstable or previously undiagnosed arrhythmia
- History of unstable or rapidly progressing renal disease
- Conditions of congenital renal glycosuria
- Significant hepatic disease, including but not limited to, chronic active hepatitis and/or severe hepatic insufficiency
- Documented history of hepatotoxicity with any medication
- Documented history of severe hepatobiliary disease
- History of hemoglobinopathy, with the exception of sickle cell trait or thalassemia minor, or chronic or recurrent hemolysis
- Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of >400 mL of blood during the 6 weeks before the enrollment visit
- Malignancy within 5 years of the enrollment visit (with the exception of treated basal cell or treated squamous cell carcinoma)
- Known immunocompromised status, including but not limited to, individuals who had undergone organ transplantation or who were positive for HIV
- Allergies or contraindication to the contents of dapagliflozin tablets or metformin
- Administration of any antidiabetic therapy, including Chinese traditional medicine, for >14 days (consecutive or not) during the 12 weeks before enrollment
  - In addition, administration of any antidiabetic therapy, including Chinese traditional medicine, other than any previously specified, at any dose, at any time during the 4 weeks before the enrollment visit, was an exclusion criterion
- Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for >4 weeks within 3 months before enrollment visit
- History of bariatric surgery or lap-band procedure
- Administration of sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylpropion, methamphetamine, and/or phendimetrazine within 30 days of enrollment visit
- Administration of (Chinese) traditional therapies after enrollment in the study that have renal toxic effects (aristolochic acid), including but not limited to:
  - Manchurian Dutchman's pipe stem/*guan-mu-tong* (*Caulis aristolochiae manshuriensis*)
  - Slender Dutchman's pipe root/Radix Aristolochiae/Qing mu xiang
  - Fangchi root/Radix Aristolochiae/Ma dou ling
  - Wooly Dutchman's pipe herb/Herba Aristolochiae Mollissimae/Xun gu feng
  - Dutchman's pipe vine/Caulis Aristolochiae/Tian xian teng
- Any subject who, in the judgment of the investigator, was at risk for dehydration or volume depletion that might affect the interpretation of efficacy or safety data
- Any subject who was currently abusing alcohol or other drugs or had done so within the last 6 months
- Previous participation in a clinical trial with dapagliflozin and/or any other SGLT2 inhibitors
- Administration of any other investigational drug within 30 days of planned enrollment to this study

Serious adverse event

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

SBP = systolic blood pressure; DBP = diastolic blood pressure; SGLT2 = renal sodium-glucose cotransporter 2.

Supplemental Table II. Demographic and baseline characteristics of the exclusively Chinese population.

Characteristic	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg
No. of patients	110	106	110
Age, mean (SD), y	49.9 (11.04)	53.4 (11.24)	51.5 (10.10)
Sex, no. (%)			
Male	75 (68.2)	67 (63.2)	73 (66.4)
Female	35 (31.8)	39 (36.8)	37 (33.6)
Race, no. (%)			
Chinese	110 (100)	106 (100)	109 (99.1)
Japanese	0	0	1 (0.9)*
Weight, mean (SD), kg	72.38 (13.42)	68.18 (10.22)	70.60 (11.46)
Waist circumference, mean (SD), cm	91.04 (9.53)	88.64 (8.15)	89.09 (8.71)
BMI, mean (SD), kg/m^2	25.71 (3.64)	24.90 (2.96)	25.48 (3.08)
History of dyslipidemia, no. (%)	43 (39.1)	37 (34.9)	46 (41.8)
History of hypertension, no. (%)	46 (41.8)	40 (37.7)	39 (35.5)
Duration of T2DM, y			
Mean (SD)	1.36 (2.1)	1.17 (2.4)	1.65 (2.8)
Median (range)	0.20 (0–9.9)	0.15 (0–14.7)	0.30 (0–13.0)
HbA_{1c}, mean (SD), %	8.32 (0.95)	8.17 (0.73)	8.26 (0.97)
FPG, mean (SD), mg/dL (mmol/L)	167.09 (43.25) (9.27 [2.40])	156.24 (31.84) (8.67 [1.77])	162.50 (44.97) (9.02 [2.50])
Fasting C-peptide, mean (SD), ng/mL (nmol/L)	2.67 (1.20) (0.88 [0.40])	2.36 (1.44) (0.78 [0.48])	2.37 (0.93) (0.78 [0.31])
Seated systolic blood pressure, mean (SD), mm Hg	123.9 (15.38)	123.8 (13.78)	123.1 (15.17)
Seated diastolic blood pressure, mean (SD), mm Hg	78.9 (8.53)	75.8 (8.72)	77.2 (7.92)

BMI = body mass index; T2DM = type 2 diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; FPG = fasting plasma glucose.

*After a database lock, it was determined that this patient was incorrectly entered into the study database as Japanese; the patient is actually Chinese.

Supplemental Table III. Exploratory end points at week 24. Data are last-observation-carried-forward (LOCF), excluding data after rescue therapy, in the exclusively Chinese population.

Characteristic	Placebo (N = 110)	Dapagliflozin 5 mg (N = 106)	Dapagliflozin 10 mg (N = 110)
Total cholesterol			
n	101	99	100
Baseline mean (SD), mg/dL	191.2 (43.8)	193.3 (64.3)	189.1 (33.4)
Adjusted mean percent change at week 24, % (95% CI)*	−1.96 (−4.99 to 1.16)	−3.29 (−6.31 to −0.18)	2.12 (−1.05 to 5.40)
Difference versus placebo		−1.35	4.17
95% CI of difference		−5.66 to 3.15	−0.37 to 8.91
LDL-C			
n	100	99	100
Baseline mean (SD), mg/dL	107.4 (34.9)	110.2 (39.0)	103.5 (30.2)
Adjusted mean percent change at week 24, % (95% CI)*	−1.69 (−6.78 to 3.67)	−3.01 (−8.06 to 2.31)	7.44 (1.88 to 13.31)
Difference versus placebo		−1.34	9.29
95% CI of difference		−8.50 to 6.38	1.38 to 17.83
HDL-C			
n	101	99	100
Baseline mean (SD), mg/dL	43.7 (9.9)	47.1 (10.3)	45.8 (12.0)
Adjusted mean percent change at week 24, % (95% CI)*	3.71 (0.66 to 6.85)	8.92 (5.68 to 12.25)	12.15 (8.86 to 15.55)
Difference versus placebo		5.02	8.14
95% CI of difference		0.64 to 9.59	3.67 to 12.80
Triglycerides			
n	101	100	103
Baseline mean (SD), mg/dL	232.8 (281.6)	189.6 (380.8)	210.0 (157.6)
Adjusted mean percent change at week 24, % (95% CI)*	−5.94 (−13.30 to 2.04)	−17.77 (−24.28 to −10.70)	−17.03 (−23.47 to −10.06)
Difference versus placebo		−12.57	−11.79
95% CI of difference		−22.18 to −1.78	−21.33 to −1.09
Urinary glucose:creatinine ratio, g/g			
n	97	93	94
Baseline mean (SD)	3.20 (8.89)	3.93 (10.29)	2.58 (6.55)
Adjusted mean absolute change at week 24 (95% CI)†	1.24 (−2.88 to 5.35)	28.21 (24.01 to 32.42)	36.64 (32.46 to 40.83)
Difference versus placebo		26.98	35.41
95% CI of difference		21.09 to 32.86	29.54 to 41.27
Fasting C-peptide (ng/mL)			
n	96	91	94
Baseline mean (SD)	2.64 (1.23)	2.31 (1.46)	2.40 (0.95)
Adjusted mean absolute change at week 24 (95% CI)†	0 (−0.15 to 0.15)	−0.41 (−0.56 to −0.26)	−0.40 (−0.55 to −0.25)
Difference versus placebo		−0.41	−0.40
95% CI of difference		−0.62 to −0.20	−0.61 to −0.19
Waist circumference, cm			
n	99	95	97
Baseline mean (SD)	90.9 (9.5)	88.2 (8.1)	89.0 (8.3)

(continued)

Supplemental Table III (continued).

Characteristic	Placebo (N = 110)	Dapagliflozin 5 mg (N = 106)	Dapagliflozin 10 mg (N = 110)
Adjusted mean absolute change at week 24 (95% CI)[†]	−0.62 (−1.50 to 0.25)	−2.67 (−3.56 to −1.77)	−2.31 (−3.20 to −1.43)
Difference versus placebo		−2.05	−1.69
95% CI of difference		−3.30 to −0.79	−2.94 to −0.44
HOMA-2 β-cell function, %			
n	96	91	94
Baseline mean (SD)	57.8 (30.6)	51.6 (23.2)	55.5 (22.6)
Adjusted mean absolute change at week 24 (95% CI)[†]	0.77 (−3.23 to 4.76)	8.88 (4.78 to 12.99)	12.62 (8.59 to 16.65)
Difference versus placebo		8.12	11.85
95% CI of difference		2.37 to 13.86	6.18 to 17.52
HOMA-2 insulin sensitivity, %			
n	96	91	94
Baseline mean (SD)	52.4 (23.7)	59.9 (22.3)	54.6 (20.4)
Adjusted mean absolute change at week 24, % (95% CI)[†]	0.42 (−3.92 to 4.75)	11.20 (6.74 to 15.66)	16.63 (12.27 to 20.99)
Difference versus placebo		10.78	16.21
95% CI of difference		4.54 to 17.03	10.07 to 22.36
Proportion of patients with ≥3% reduction in total weight, %			
n	110	106	105
Baseline mean weight, kg	72.4	68.2	70.4
Proportion (adjusted for baseline weight) at week 24, % (95% CI)[‡]	16.2 (9.3 to 23.1)	41.4 (32.0 to 50.7)	47.6 (38.1 to 57.1)
Difference versus placebo		25.2	31.4
95% CI of difference		13.5 to 36.8	19.6 to 43.2
Proportion of patients with ≥5% reduction in total weight, %			
n	110	106	105
Baseline mean weight, kg	72.4	68.2	70.4
Proportion (adjusted for baseline weight) at week 24, % (95% CI)[‡]	6.8 (2.3 to 11.3)	17.7 (10.4 to 25.0)	30.5 (21.7 to 39.3)
Difference versus placebo		10.9	23.7
95% CI of difference		2.3 to 19.4	13.8 to 33.6

N = number of randomized patients from China who received ≥1 dose of double-blind study medication; n = number of randomized patients from China who received ≥1 dose of double-blind study medication with nonmissing baseline and week 24 LOCF values; HOMA-2 = homeostasis model assessment version 2.

*Derived from ANCOVA model for (log [week 24 value] − log [baseline value]) for each end point with treatment group as an effect and log [baseline value] as a covariate.

†Derived from ANCOVA model with treatment group as an effect and baseline value as a covariate.

‡Proportion analyzed by using the methods of Zhang et al,[30] with adjustment for baseline total weight. Measures for urinary glucose:creatinine ratio were derived from a urinary spot-check performed in the morning fasting state.

Supplemental Table IV. Overall summary of patients with an adverse event (AE), AEs with frequency ≥2% in any group and higher in dapagliflozin versus placebo groups, AEs of special interest, and blood pressure measurements, including data after rescue therapy, in the exclusively Chinese population.

Preferred Term	Placebo (N = 110)	Dapagliflozin 5 mg (N = 106)	Dapagliflozin 10 mg (N = 110)
Overall summary of no. (%) of patients with an AE			
≥1 AE	68 (61.8)	63 (59.4)	64 (58.2)
AE leading to discontinuation	1 (0.9)	3 (2.8)	3 (2.7)
≥1 SAE	2 (1.8)	5 (4.7)	4 (3.6)
No. (%) of AEs with frequency ≥2% in any group (by MedDRA preferred term) and higher in dapagliflozin versus placebo groups			
Urinary tract infection	4 (3.6)	5 (4.7)	4 (3.6)
Nasopharyngitis	2 (1.8)	4 (3.8)	3 (2.7)
Toothache	2 (1.8)	4 (3.8)	3 (2.7)
Increased *N*-acetyl-β-D-glucosaminidase	2 (1.8)	3 (2.8)	3 (2.7)
Diarrhea	2 (1.8)	3 (2.8)	3 (2.7)
Diabetic nephropathy	2 (1.8)	1 (0.9)	3 (2.7)
Renal impairment	2 (1.8)	1 (0.9)	3 (2.7)
Thrombocytopenia	0	3 (2.8)	3 (2.7)
Dizziness	2 (1.8)	3 (2.8)	1 (0.9)
Back pain	1 (0.9)	1 (0.9)	3 (2.7)
Cough	0	3 (2.8)	1 (0.9)
Urgency of micturition	0	0	3 (2.7)
No. (%) of patients with an AE of special interest			
≥1 hypoglycemic event[*]	2 (1.5)	1 (0.8)	0
AEs of genital infection[†]	0	3 (2.8)	4 (3.6)
Genital infection	0	2 (1.9)	1 (0.9)
Posthitis	0	0	1 (0.9)
Vaginal infection	0	0	1 (0.9)
Vulvovaginal mycotic infection	0	0	1 (0.9)
Fungal genital infection	0	1 (0.9)	0
AEs of urinary tract infection[†]	4 (3.6)	5 (4.7)	6 (5.5)
Urinary tract infection	4 (3.6)	5 (4.7)	4 (3.6)
Urethritis	0	0	2 (1.8)
Renal impairment[†,‡]	2 (1.8)	1 (0.9)	3 (2.7)
Blood pressure, mm Hg			
Baseline mean (SD) seated systolic blood pressure	n = 110 123.9 (15.4)	n = 106 123.8 (13.8)	n = 110 123.1 (15.2)
Adjusted mean (SE) absolute change at week 24	n = 95 0.6 (1.4)	n = 93 −0.5 (1.2)	n = 94 −1.9 (1.3)
Baseline mean (SD) seated diastolic blood pressure	n = 110 78.9 (8.5)	n = 106 75.8 (8.7)	n = 110 77.2 (7.9)
Adjusted mean (SE) absolute change at week 24	n = 95 −0.2 (1.0)	n = 93 −0.8 (0.9)	n = 94 −1.1 (1.0)

N = number of treated patients from China; n = number of patients from China evaluated at specified time point; SAE = serious AE.

*None led to study discontinuation.

[†]Based on definitive (prespecified) Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (version 15.0).

[‡]No events of renal failure were observed during the 24-week double-blind treatment period.

Supplemental Table V. Laboratory values of interest: change from baseline at weeks 12 and 24, including data after rescue therapy, in the exclusively Chinese population.

Characteristic	Placebo (N = 110)	Dapagliflozin 5 mg (N = 106)	Dapagliflozin 10 mg (N = 110)
Hematocrit, %			
Baseline	n = 110	n = 106	n = 110
Mean (SD)	44.09 (3.97)	43.69 (3.57)	44.24 (4.39)
Change at week 12	n = 102	n = 99	n = 97
Mean (SE)	−0.20 (0.22)	1.55 (0.23)	1.78 (0.23)
Change at week 24	n = 94	n = 93	n = 92
Mean (SE)	−0.40 (0.27)	0.86 (0.22)	1.11 (0.22)
Serum creatinine, mg/dL			
Baseline	n = 110	n = 106	n = 110
Mean (SD)	0.83 (0.15)	0.82 (0.16)	0.85 (0.19)
Change at week 12	n = 102	n = 99	n = 99
Mean (SE)	0.008 (0.009)	−0.013 (0.007)	0 (0.009)
Change at week 24	n = 95	n = 93	n = 93
Mean (SE)	−0.012 (0.008)	−0.017 (0.008)	−0.009 (0.009)
Estimated GFR, mL/min/1.73 m^2			
Baseline	n = 110	n = 106	n = 110
Mean (SD)	92.6 (15.8)	91.5 (16.8)	91.0 (19.8)
Change at week 12	n = 102	n = 99	n = 99
Mean (SE)	−0.7 (1.22)	2.1 (0.98)	−0.4 (1.10)
Change at week 24	n = 95	n = 93	n = 93
Mean (SE)	1.5 (1.10)	2.8 (1.13)	1.0 (1.03)
Blood urea nitrogen, mg/dL			
Baseline	n = 110	n = 106	n = 110
Mean (SD)	14.5 (3.3)	15.6 (3.9)	15.7 (4.1)
Change at week 12	n = 102	n = 99	n = 99
Mean (SE)	0.28 (0.31)	1.54 (0.40)	1.06 (0.38)
Change at week 24	n = 95	n = 93	n = 93
Mean (SE)	0.51 (0.37)	1.95 (0.47)	1.64 (0.42)
Uric acid, mg/dL			
Baseline	n = 110	n = 106	n = 110
Mean (SD)	5.6 (1.6)	5.2 (1.3)	5.0 (1.3)
Change at week 12	n = 102	n = 99	n = 99
Mean (SE)	0.10 (0.12)	−0.52 (0.10)	−0.38 (0.09)
Change at week 24	n = 95	n = 93	n = 93
Mean (SE)	−0.06 (0.13)	−0.74 (0.10)	−0.34 (0.11)

N = number of treated patients from China; n = number of patients from China evaluated at specified time point; GFR = glomerular filtration rate.