AstraZeneca

24-week Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1690C00010
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A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin

Report for the 24-week short-term treatment period

Study dates:	First subject enrolled:	*10 October 2009*
	Last subject last visit for the 24-week period:	*10 March 2011*
Phase of development:	Therapeutic confirmatory (III)	

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study center(s)

Study D1690C00010 was conducted at 102 centers in 3 European countries (Germany, Poland, and the UK), the USA, Argentina, and Mexico. (Only active centers are mentioned.)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary and key secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	
To compare the change from baseline in hemoglobin A1c (HbA1c) at 24 weeks between dapagliflozin and placebo in subjects with type 2 diabetes mellitus (T2DM) who were inadequately controlled on sitagliptin alone or on sitagliptin plus metformin	Change in HbA1c from baseline to week 24
Key secondary	
To compare the change in total body weight achieved with dapagliflozin versus placebo from baseline to week 24	Change in body weight from baseline to week 24
To compare the change in HbA1c in subjects with baseline HbA1c ≥8% achieved with dapagliflozin versus placebo from baseline to week 24	Change in HbA1c from baseline to week 24 in subjects with baseline HbA1c ≥8%
To compare the change in fasting plasma glucose (FPG) achieved with dapagliflozin versus placebo from baseline to week 24	Change in FPG from baseline to week 24
To compare the change in seated systolic blood pressure (SBP) in subjects with baseline seated SBP ≥130 mmHg achieved with dapagliflozin versus placebo from baseline to week 8	Change in seated SBP from baseline to week 8 in subjects with baseline seated SBP ≥130 mmHg
To compare the change in 2-hour post liquid meal glucose achieved with dapagliflozin versus placebo from baseline to week 24	Change in 2-hour post liquid meal glucose from baseline to week 24
To compare the proportion of subjects achieving a therapeutic glycemic response, defined as a reduction in HbA1c of ≥0.7% compared to baseline, with dapagliflozin versus placebo at week 24	Proportion of subjects achieving a therapeutic glycemic response, defined as a reduction in HbA1c of ≥0.7% from baseline to week 24
Safety	
To evaluate the safety and tolerability of dapagliflozin by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure, hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR) and physical examination findings	AEs, laboratory values, ECG, pulse, blood pressure, hypoglycemic events, calculated creatinine clearance, eGFR and physical examination findings

The primary and all key secondary objectives/variables were efficacy objectives/variables. For a complete list of other secondary objectives/variables see the Clinical Study Report (CSR).

Study design

This was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase III study with a 24-week short-term treatment period followed by a 24-week extension period, to evaluate the effect of dapagliflozin 10 mg once daily (qd) in combination with sitagliptin or sitagliptin plus metformin on HbA1c in adult subjects with T2DM who have inadequate glycemic control.

Note that this synopsis includes only results from the 24-week short-term treatment period.

Target subject population and sample size

The study entry criteria specified enrollment of male or female subjects ≥18 years of age, diagnosed with T2DM who were drug naïve, or who were treated with sitagliptin 100 mg qd or vildagliptin 50 mg twice daily (bid) monotherapy, or a combination of sitagliptin 100 mg qd or vildagliptin 50 mg bid with metformin ≥1500 mg/day, or metformin ≥1500 mg/day monotherapy.

The subjects had to show inadequate glycemic control, defined as HbA1c ≥7.2% and ≤10.0% for subjects who received sitagliptin or vildagliptin monotherapy or sitagliptin or vildagliptin in combination with metformin, and ≥7.7% and ≤10.5% for subjects who received metformin monotherapy or who were drug naïve.

Subjects eligible for the study were stratified according to their use of metformin, and within each stratum they were randomized to dapagliflozin or placebo treatment.

To detect a difference of 0.5% between dapagliflozin and placebo for the change in HbA1c from baseline to week 24, assuming a standard deviation (SD) of 1.1%, 103 evaluable subjects (full analysis set) in each treatment group within each stratum provided >99% power for the analysis of the two strata combined at a significance level of 0.050 and 90% power for the analysis of each stratum separately at a significance level of 0.050. Assuming that 5% of the subjects were not evaluable in the full analysis set, 108 subjects per treatment group within each stratum (432 subjects in total) were planned for randomization.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Subjects in stratum 1 received dapagliflozin 10 mg qd or matching placebo, according to their assignment to treatment groups, as add-on therapy to open-label sitagliptin 100 mg qd during the 24-week short-term treatment period.

Subjects in stratum 2 received dapagliflozin 10 mg qd or matching placebo, according to their assignment to treatment groups, as add-on therapy to open-label sitagliptin 100 mg qd plus open-label metformin ≥1500 mg/day during the 24-week short-term treatment period. The subject's metformin dose was based on his/her metformin dose during the last 10 weeks prior to enrollment and was kept stable (see the CSR for details).

Dapagliflozin or matching placebo should be taken orally, once daily, with or without food, at approximately the same time of the day during the study period. Sitagliptin should be taken orally, once daily, and could be taken with or without food; metformin should be taken orally, twice daily, with or after a meal. Dapagliflozin and matching placebo were manufactured by Bristol-Myers Squibb. Batch numbers of dapagliflozin and matching placebo are listed in Appendix 12.1.7.2 to the CSR.

Duration of treatment

According to the protocol, subjects were to be treated with study medication for 48 weeks (24-week short-term treatment period plus 24-week extension period). Note that this synopsis includes only results from the 24-week short-term treatment period.

Statistical methods

A hierarchical closed testing procedure was used to control the type I error rate ≤0.050 (two-sided) across the primary and key secondary efficacy variables, based on data from the two strata combined. Analyses were also conducted within each stratum to separately evaluate the effect in the two background treatment regimens. For variables found to be significant with the combined strata analysis, corresponding within-stratum treatment comparisons were individually tested at a two-sided significance level of 0.050. For all other variables, nominal p-values were reported for both overall and within-strata comparisons, without significance testing. The primary efficacy variable and continuous key secondary efficacy variables were analyzed with an analysis of covariance (ANCOVA) model. When assessing the results overall, the model included terms for treatment group, strata, and baseline covariate. For analyses within each stratum, the ANCOVA model included terms for treatment group and baseline covariate. The ANCOVA model was used to derive a least squares estimate of the treatment difference in mean change with corresponding p-value and two-sided 95% confidence interval. Further, two-sided 95% confidence intervals for the mean change within each treatment group as well as treatment group and stratum were calculated. Comparisons between treatment groups in proportions were performed using the methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang, and Lu. The combined strata analysis was adjusted for baseline value and stratum. For analyses within each stratum, adjustment for baseline value was taken into account. Efficacy was evaluated using the full analysis set. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 833 subjects were enrolled out of whom 452 were randomized. The most common reasons for not being randomized were incorrect enrollment (i.e., the subject did not meet all inclusion and exclusion criteria) (333 subjects) and withdrawal of consent (21 subjects). Approximately 90% of the randomized subjects completed the 24-week short-term treatment period and continued into the 24-week extension period. Primary reason for not completing the 24-week short-term treatment period and not continuing into the 24-week extension period was withdrawal of consent (17 subjects), followed by AEs, and loss of subjects to follow-up. One subject in the placebo group died during the 24-week short-term treatment period. In

total, 451 randomized subjects were included in the safety analysis set. The full analysis set included 447 subjects.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 55 years of age with around 18% aged above 65 years. There were around 55% male and 45% female subjects in both treatment groups. Three quarters of the subjects were White. Around 55% of the subjects were of Hispanic/Latino ethnicity. Mean duration of T2DM was 5.7 years with around 14% of the subjects having T2DM for over 10 years. At baseline, mean HbA1c was around 7.9%, and around 12% of the subjects had a baseline HbA1c ≥9%. Mean total body weight at baseline amounted to 90.1 kg. The subjects had a mean body mass index (BMI) of 32.4 kg/m^2 with almost 90% of the subjects being overweight (BMI ≥25 kg/m^2), and approximately 62% of the subjects being obese (BMI ≥30 kg/m^2). Half of the subjects took metformin at enrollment and were included in stratum 2.

Demographic and baseline characteristics showed differences between strata: almost two thirds of the subjects in stratum 1 came from Argentina and Mexico, and almost two thirds of the subjects in stratum 2 came from Europe. Proportions of male subjects (stratum 1: 50.2%, stratum 2: 59.3%), Whites (stratum 1: 59.3%, stratum 2: 88.9%), and subjects of non hispanic/latino ethnicity (stratum 1: 15.8%, stratum 2: 73.9%) were larger in stratum 2 than in stratum 1. Subjects in stratum 2 were older (stratum 1: 53.0 years, stratum 2: 56.7 years), taller (stratum 1: 163.8 cm, stratum 2: 169.0 cm), and heavier (stratum 1: 86.10 kg, stratum 2: 94.06 kg) than subjects in stratum 1; their average duration of T2DM (stratum 1: 4.74 years, stratum 2: 6.58 years) was longer compared to subjects in stratum 1; their baseline mean HbA1c (stratum 1: 8.03%, stratum 2: 7.83%) was slightly lower compared to subjects in stratum 1.

Summary of efficacy results

Primary and key secondary efficacy endpoints are summarized in Table S2.

Table S2 Summary of primary and key secondary efficacy endpoints - full analysis set

	PLA + SIT N = 224	DAPA 10 MG + SIT N = 223
Primary endpoint		
HbA1c (%) at week 24 (LOCF)		
Adjusted mean change from baseline (SE)	0.04 (0.0509)	-0.45 (0.0509)
p-value vs. PLA + SIT		<0.0001 *
Key secondary endpoints		
Total body weight (kg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE)	-0.26 (0.1741)	-2.14 (0.1745)
p-value vs. PLA + SIT		<0.0001 *

	PLA + SIT N = 224	DAPA 10 MG + SIT N = 223
HbA1c (%) at week 24 (LOCF) in subjects with baseline HbA1c ≥8%		
Adjusted mean change from baseline (SE)	0.03 (0.0775)	-0.80 (0.0797)
p-value vs. PLA + SIT		<0.0001 *
FPG (mg/dL) at week 24 (LOCF)		
Adjusted mean change from baseline (SE)	3.81 (2.3474)	-24.11 (2.3474)
p-value vs. PLA + SIT		<0.0001 *
Seated SBP (mmHg) at week 8 (LOCF) in subjects with baseline seated SBP ≥130 mmHg		
Adjusted mean change from baseline (SE)	-5.12 (1.0211)	-5.98 (1.0638)
p-value vs. PLA + SIT		0.5583
2-hour post liquid meal glucose (mg/dL) at week 24 (LOCF)		
Adjusted mean change from baseline (SE)	-6.84 (2.5098)	-21.65 (2.4604)
p-value vs. PLA + SIT		<0.0001
Subjects with HbA1c decrease ≥0.7% at week 24 (LOCF)		
Percent adjusted (SE)	16.6% (2.491)	35.4% (3.083)
p-value vs. PLA + SIT		<0.0001

DAPA, dapagliflozin; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c; LOCF, last observation carried forward; N, number of subjects; PLA, placebo; SE, standard error; SIT, sitagliptin.
* Significant p-value: the primary endpoint was tested at $\alpha = 0.050$ (two-sided). If this p-value was significant, the results of the key secondary endpoints were tested following a hierarchical closed testing procedure.

Primary endpoint

Subjects in the dapagliflozin group showed a statistically significant mean reduction in HbA1c from baseline to week 24 (last observation carried forward [LOCF]) compared to placebo in the overall study population (-0.48%) and in both strata (stratum 1: -0.56%; stratum 2: -0.40%).

Key secondary endpoints

Subjects in the dapagliflozin group showed a statistically significant mean reduction in total body weight from baseline to week 24 (LOCF) compared to placebo in the overall study population (-1.89 kg) and in both strata (stratum 1: -1.85 kg, stratum 2: -1.87 kg).

Subjects in the dapagliflozin group with a baseline HbA1c ≥8% and a post-baseline measurement of HbA1c (94 subjects in the dapagliflozin and 99 subjects in the placebo group) showed a statistically significant mean reduction in HbA1c from baseline to week 24 (LOCF) compared to placebo in the overall study population (-0.83%) and in both strata (stratum 1: -0.87%, stratum 2: -0.80%).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in FPG from baseline to week 24 (LOCF) compared to placebo in the overall study population (-27.92 mg/dL) and in both strata (stratum 1: -26.58 mg/dL, stratum 2: -29.18 mg/dL).

Subjects in the dapagliflozin group with a baseline seated SBP ≥130 mmHg and a post-baseline measurement of seated SBP (101 subjects in the dapagliflozin and 111 subjects in the placebo group) showed a mean decrease in seated SBP from baseline to week 8 (LOCF), compared to placebo in the overall study population (-0.86 mmHg), that was not statistically significant. Evaluations by strata showed a placebo-corrected mean decrease in seated SBP of 2.38 mmHg in stratum 1 and no meaningful change in stratum 2 (0.23 mmHg). The results in either stratum were not subject to statistical testing because the result for the overall study population was not significant. Nominal p-values for the difference in change of seated SBP between treatment groups exceeded 0.05 in both strata.

Statistical testing stopped with the previous key secondary endpoint. p-values for comparisons between treatment groups regarding subsequent key secondary endpoints are interpreted in the exploratory sense in the overall study population and in both strata.

Subjects in the dapagliflozin group showed a mean reduction in the increase of plasma glucose levels 2 hours after intake of a liquid test meal from baseline to week 24 (LOCF) compared to placebo in the overall study population (-14.82 mg/dL) and in both strata (stratum 1: -16.67 mg/dL, stratum 2: -12.57 mg/dL). The nominal p-value for the difference in the reduction of the 2-hour post liquid meal glucose increase between treatment groups was <0.05 in the overall study population and in both strata.

A larger proportion of subjects in the dapagliflozin group compared to placebo achieved therapeutic glycemic response, defined as a reduction in HbA1c of ≥0.7% from baseline to week 24 (LOCF), in the overall study population (18.8%) and in both strata (stratum 1: 25.6%, stratum 2: 12.1%). The nominal p-value for the difference in the proportion of subjects achieving therapeutic glycemic response between treatment groups was <0.05 in the overall study population and in both strata.

Summary of safety results

Numbers (%) of subjects with AEs are summarized by categories of AEs in Table S3.

Table S3 Summary of subjects with AEs - safety analysis set

	PLA + SIT N = 226	DAPA 10 MG + SIT N = 225
At least one AE	109 (48.2)	119 (52.9)
At least one event of hypoglycemia	4 (1.8)	6 (2.7)
Death	1 (0.4)	0
At least one serious adverse event (SAE)	9 (4.0)	10 (4.4)
AE leading to discontinuation*	5 (2.2)	7 (3.1)
SAE leading to discontinuation*	2 (0.9)	1 (0.4)
Hypoglycemia leading to discontinuation*	0	0
At least one event suggestive of genital infection	1 (0.4)	19 (8.4)
At least one event suggestive of urinary tract infection	9 (4.0)	11 (4.9)

AE, adverse event; DAPA, dapagliflozin; N, number of subjects; PLA, placebo; SAE, serious adverse event; SIT, sitagliptin.
* of study medication.

Adverse events and events of hypoglycemia

Similar proportions of subjects in the dapagliflozin and placebo group experienced at least one AE (52.9% vs. 48.2%) or SAE (4.4% vs. 4.0%) or were discontinued from study medication due to an AE (3.1% vs. 2.2%). One subject in the placebo group died due to a metastatic squamous cell carcinoma. One further subject died due to a malignant lung neoplasm. Death of the latter subject occurred during the dose stabilization period prior to randomization and is not included in the analysis of the 24-week short-term treatment period.

Six subjects in the dapagliflozin and 4 subjects in the placebo group experienced at least one hypoglycemic event. One hypoglycemic event in 1 subject in the dapagliflozin group was classified as major. No subject was discontinued from the study or study medication due to a hypoglycemic event.

Events suggestive of genital infections or urinary tract infections (UTI) and events of genital infections or UTI were identified using pre-specified lists of preferred terms (PTs). These events were reported spontaneously, as well as in response to questions related to the signs and symptoms of these infections proactively posed to subjects during study visits.

Proportions of subjects with events suggestive of genital infections (8.4% vs. 0.4%), events of genital infections (8.4% vs. 0.4%), and events of UTI (4.4% vs. 1.8%) were larger in the dapagliflozin than in the placebo group. Similar proportions of subjects in the dapagliflozin and placebo group experienced events suggestive of UTI (4.9% vs. 4.0%). In the dapagliflozin group proportions of subjects with events in these categories were larger in women than in men. No kidney infections were reported.

Few subjects in the dapagliflozin and placebo groups experienced AEs in the categories renal impairment or failure (5 subjects vs. 3 subjects), hypotension, dehydration, or hypovolemia (3 subjects vs. 1 subject), or fracture (0 subjects vs. 1 subject) (categories defined according to pre-specified lists of PTs). No subject in either treatment group experienced an AE in the category urinary stones.

One subject in the dapagliflozin and 6 subjects in the placebo group experienced at least one AE of hepatic disorder. The subject with an AE of hepatic disorder in the dapagliflozin group experienced an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Laboratory evaluation

Nine subjects in the dapagliflozin and 1 subject in the placebo group showed at least one marked abnormality (MA) of hematocrit >55%. Six subjects in the dapagliflozin and no subject in the placebo group showed at least one MA of hemoglobin >18 g/dL. None of these subjects showed thromboembolic AEs. There was a small increase in mean hematocrit from baseline to week 12 in the dapagliflozin group. Thereafter, hematocrit remained almost stable. In the placebo group, mean hematocrit did not show a meaningful change during the 24-week short-term treatment period. The imbalances in MAs of hematocrit >55% and hemoglobin >18 g/dL are consistent with the observed small increase in mean hematocrit in the dapagliflozin group and are likely at least in part due to the mild osmotic diuresis associated with dapagliflozin therapy.

Few subjects in the dapagliflozin and placebo group showed at least one MA of AST or ALT >3 x upper limit of normal (ULN) (5 subjects vs. 4 subjects), total bilirubin (TB) >1.5 x ULN (0 subjects vs. 2 subjects), or alkaline phosphatase (ALP) >1.5 x ULN (7 subjects vs. 4 subjects). No subject in either treatment group showed a combined MA of ALT or AST and TB. Subjects in the dapagliflozin group showed a slight decrease in mean ALT and a slight increase in mean ALP from baseline to week 24. In the placebo group a slight decrease in mean ALP was observed.

Four subjects in the dapagliflozin and 2 subjects in the placebo group showed at least one MA of creatinine ≥1.5 x baseline concentration. Subjects in the dapagliflozin group showed a slight increase from baseline to week 24 in mean blood urea nitrogen (BUN) and cystatin-C compared to placebo and no meaningful change from baseline to week 24 in mean serum creatinine, calculated creatinine clearance, and eGFR compared to placebo.

Few subjects in the dapagliflozin and placebo groups showed at least one MA of calcium <7.5 mg/dL (2 subjects vs. 0 subjects), potassium ≥6.0 mEq/L (2 subjects vs. 3 subjects), sodium <130 mEq/L (1 subject vs. 0 subjects), sodium >150 mEq/L (1 subject vs. 0 subjects), or inorganic phosphorus (3 subjects vs. 0 subjects). Subjects in the dapagliflozin group showed an increase in mean magnesium, a slight increase in mean inorganic phosphorus, and a decrease in mean uric acid from baseline to week 24. In the placebo group a slight decrease in mean inorganic phosphorus was observed.

No subject in either treatment group showed an MA of creatine kinase (CK) >5 x ULN. Subjects in the dapagliflozin group showed a slight decrease and subjects in the placebo group showed a slight increase in mean CK from baseline to week 24.

Vital signs

Seated diastolic blood pressure (DBP) and SBP did not show a meaningful mean change in either treatment group from baseline to week 24 (LOCF). Seated heart rate did not show a meaningful mean change in either treatment group from baseline to week 24.

The proportion of subjects with orthostatic hypotension (decrease from supine to standing of >20 mmHg in SBP or >10 mmHg in DBP) during the 24-week short-term double-blind treatment period was slightly larger in the dapagliflozin (11.2%) than in the placebo group (8.1%).