AstraZeneca

24-week Clinical Study Report Synopsis	
Drug Substance	Dapagliflozin
Study Code	D1690C00019
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A 24-week, multicentre, randomised, double-blind, age-stratified, placebo controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycaemic control on usual care

Report for the 24-week short-term treatment period

Study dates: First subject enrolled: *15 March 2010*
Last subject last visit for the 24-week period: *30 May 2011*

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study center(s)

Study D1690C00019 was conducted at 173 centers in Europe, North America, South America, and Australia. (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	
There were 2 parallel primary objectives of equal weight in this study:	
• To assess the glycemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes mellitus (T2DM) subjects with cardiovascular disease (CVD), measured as the mean change in glycosylated hemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).	Mean change in HbA1c from baseline to week 24
• To assess the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with CVD at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as: - an absolute drop of 0.5% or more from baseline HbA1c, and - a relative drop of 3% or more from baseline for total body weight, and - an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure (SBP), in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).	Proportion of subjects achieving: - an absolute reduction in HbA1c of ≥0.5% from baseline to week 24, and - a relative reduction in total body weight of ≥3% from baseline to week 24, and - an absolute reduction in seated SBP of ≥3 mmHg from baseline to week 24
Key secondary	
• To compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Mean percent change in body weight from baseline to week 24

Objectives	Outcome variables
• To compare the proportion of subjects with baseline body mass index (BMI) ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24 in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Proportion of subjects with baseline BMI ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight from baseline to week 24
• To compare the mean change in seated SBP from baseline to week 8 between dapagliflozin 10 mg versus placebo in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Mean change in seated SBP from baseline to week 8
• To compare the mean change in seated SBP from baseline to week 24 between dapagliflozin 10 mg versus placebo in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Mean change in seated SBP from baseline to week 24
• To compare the mean change in seated SBP in subjects with baseline seated SBP ≥130 mmHg achieved with dapagliflozin versus placebo from baseline to week 8 in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Mean change in seated SBP from baseline to week 8 SBP in subjects with baseline seated SBP ≥130 mmHg
Safety	
To evaluate the safety and tolerability of dapagliflozin by assessment of adverse events (AEs), including cardiovascular (CV) events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), and physical examination findings, and in a subset of the study population, evaluate the occurrence of asymptomatic bacteriuria and the potential risk of subsequent urinary tract infections (UTI)	AEs, including CV events, 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 a multicenter, randomized, double-blind, age-stratified, placebo-controlled Phase III study with a 24-week short-term treatment period followed by a 28-week extension period to evaluate the effect of dapagliflozin 10 mg once daily (qd) in combination with pre-existing anti-hyperglycemic treatment on HbA1c and on the proportion of subjects who achieved a clinical benefit in adult subjects with T2DM and CVD 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 subjects ≥45 years of age and female subjects ≥50 years of age diagnosed with T2DM and CVD who received monotherapy or dual combination therapy with oral anti-diabetic drugs (OADs), insulin therapy in combination

with OADs, or insulin monotherapy on a daily basis for 8 weeks and stable for at least 4 weeks before enrollment and who showed inadequate glycemic control (7.2% ≤HbA1c ≤10.5%). Subjects on anti-hypertensive treatment should have used this treatment uninterruptedly on a daily basis in the last 4 weeks before enrollment.

Subjects eligible for the study were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying CV event (>1 year or ≤1 year [i.e., within 12 months] before enrollment). A total of 8 strata were formed for the purposes of randomization by each combination of the three factors, and within each stratum subjects were randomized to dapagliflozin or placebo at a ratio of 1:1.

A total of 362 subjects (181 per group) provided 90% power to detect a difference in proportions of subjects who achieved a clinical benefit of 25% versus 10% (Δ=15%) within a given age stratum at a significance level of 0.0125 using a chi-square test. Assuming that 3.7% of the randomized subjects were not evaluable in the full analysis set, a total of 376 randomized subjects at minimum were required for each age stratum. The smaller age stratum could contain as few as 40% of the total randomized subjects. Therefore, 940 subjects had to be randomized in total, and the larger age stratum contained 564 randomized subjects (60% of total) at most.

A total of 181 evaluable subjects (full analysis set) for each treatment group within a given age stratum provided >99% power to detect a difference of 0.5% between dapagliflozin and placebo for mean change in HbA1c from baseline to week 24 at a significance level of 0.0125, assuming a standard deviation (SD) of 0.9%, using a two-sample t-test.

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

Subjects were administered dapagliflozin 10 mg qd or matching placebo according to their assignment to treatment groups as add-on therapy to pre-existing anti-hyperglycemic treatment during the 24-week short-term treatment period. Dapagliflozin or matching placebo was taken orally once daily within 30 minutes before breakfast and at approximately the same time of the day. 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.

Pre-existing anti-hyperglycemic treatment comprised of monotherapy or dual combination therapy with OADs, insulin therapy in combination with OADs, or insulin monotherapy. In subjects treated with insulin, the average daily insulin dose was reduced by 25% on the day of randomization, Visit 4. Apart from that, the dose of anti-hyperglycemic medications should not have been changed during the 24-week short-term treatment period unless rescue criteria or a definition of hypoglycemia were met.

Subjects received pre-existing anti-hypertensive, anti-platelet, and lipid lowering treatment. No changes in anti-hypertensive medications were allowed during the 24-week short-term treatment period, except when rescue criteria for SBP or diastolic BP (DBP) were exceeded,

or the subject experienced symptomatic or orthostatic hypotension. Subjects were instructed to keep anti-platelet and lipid lowering treatment constant throughout the 24-week short-term treatment period. Anti-hypertensive, anti-platelet, and lipid lowering treatment could be changed if in the subject's best interest according to the investigator's judgment.

Duration of treatment

According to the protocol, subjects were to be treated with study medication for 52 weeks (24-week short-term treatment period plus 28-week extension period). Note that this synopsis includes only results from the 24-week short-term treatment period.

Statistical methods

A hierarchical testing procedure was used to control the type I error rate across the two primary and five key secondary endpoints, both in the overall population as well as within individual age strata. Initially, a Bonferroni multiplicity correction was applied to the two tests associated with the primary efficacy variables in the overall study population so that each variable was tested at a significance level of 0.025 (2-sided). Only if the given primary efficacy variable proved significant for the overall population, an additional Bonferroni correction was applied so that each test within age strata was performed at a significance level of 0.0125 (2-sided).

Testing for the key secondary variables was performed in a fixed order sequence and applied separately for the overall population and for each of the two age strata. If both primary variables were statistically significant, the alpha level 0.05 (2-sided) was used; if only one of the primary variables was statistically significant, testing was done at a significance level of 0.025 (2-sided). If none of the primary variables was statistically significant, no testing was done.

The primary efficacy variables and key secondary efficacy variables were analyzed overall and in each age stratum. For the overall evaluation of the first primary efficacy variable and the continuous secondary efficacy variables, analysis of covariance (ANCOVA) model with treatment group and age-by-insulin use-by-time from most recent qualifying CV event group (8 levels) as fixed effects and baseline value as a covariate was used. For the analysis within each age stratum, the ANCOVA model included terms (fixed effects) for treatment group, insulin use-by-time from most recent qualifying CV event group (4 levels), and baseline covariate. The model was used to derive a least squares estimate of the treatment difference with corresponding p-value and two-sided confidence interval. The level applied to the respective test was determined by the Bonferroni correction. Further, two-sided 95% confidence intervals for the mean change within each treatment group were calculated. For variables analyzed as percent change from baseline, the ANCOVA model was applied to logarithm-transformed data and resulting least-squares means ,and confidence intervals were back-transformed to provide estimates in the original scale. The second primary efficacy variable was analyzed by the Cochran-Mantel-Haenszel (CMH) method. For the overall analysis, the CMH model included age-by-insulin use-by-time from most recent qualifying CV event group as a strata variable. For the analysis within each age stratum, the CMH model included insulin use-by-time from most recent qualifying CV event as a strata variable. The

difference in the response rates between treatment groups was displayed along with a confidence interval derived from asymptotic theory. The level applied to the respective test is determined by the Bonferroni correction. P-values were calculated from a chi-square test using the appropriate CMH model.

Comparisons between treatment groups in proportions were performed using the methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang, and Lu with adjustment for baseline value. Efficacy was evaluated using the full analysis set. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 1489 subjects were enrolled out of which 964 were randomized. The most common reason for not being randomized was incorrect enrolment (i.e., not meeting inclusion/exclusion criteria) (460 subjects). Around 90% of the randomized subjects completed the 24-week short-term treatment period and continued into the 28-week extension period. Primary reason for not completing the 24-week short-term double-blind treatment period was occurrence of a discontinuation criterion (28 subjects). Two subjects in the dapagliflozin group and 1 subject in the placebo group died during the 24-week short-term treatment period. All treated subjects were included in the safety analysis set. The full analysis set included 962 subjects, 511 subjects in age stratum <65 years and 451 in age stratum ≥65 years.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 64 years of age with around 47% aged ≥65 years. There were about 67% male and 33% female subjects in both treatment groups. Around 95% of the subjects were at least overweight (BMI ≥25 kg/m^2), and more than two thirds were obese (BMI ≥30 kg/m^2).

Mean duration of T2DM was 13.2 years with around 58% of the subjects have had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%. Around 60% of the subjects reported the use of insulin. Subjects had been on insulin treatment for about 3 years, and the average calculated mean daily insulin dose was 55 IU. Around 80% of the subjects were on OAD treatment with or without concomitant insulin use.

As qualifying CV event, most subjects reported coronary heart disease (76.5%) or stroke/transitory ischemic attack (TIA) (19.6%). The median time from diagnosis or occurrence of the most recent qualifying CV event was 4.5 years, and 85.3% of the subjects had their most recent qualifying CV event diagnosed more than 1 year ago.

Almost 93% of subjects had hypertension. The duration of hypertension was ≥3 years in almost 87% of the subjects and ≥10 years in 55.1% of the subjects. Hypertension was well controlled as indicated by a mean seated SBP and DBP of 134.7 mmHg and 77.8 mmHg, respectively. Almost 16% of the subjects had cardiac heart failure (CHF).

Summary of efficacy results

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

Note: The change in HbA1c and the HbA1c item of the 3-item endpoint of clinical benefit was analyzed excluding data after glycemic rescue and including data after anti-hypertensive rescue. The change in total body weight and the total body weight item of the 3-item endpoint of clinical benefit was analyzed including data after glycemic rescue and including data after anti-hypertensive rescue. The change in seated SBP and the seated SBP item of the 3-item endpoint of clinical benefit was analyzed including data after glycemic rescue and excluding data after anti-hypertensive rescue.

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

	PLA N=482	DAPA 10 MG N=480
Primary endpoints		
HbA1c (%) at week 24 last observation carried forward (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.07 (0.0435), 471	-0.33 (0.0434), 474 <0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent p-value vs. PLA	1.9%, 469	10.0%, 468 <0.0001 *
Key secondary endpoints		
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N# p-value vs. PLA	-0.61 (0.1770), 481	-2.53 (0.1736), 480 <0.0001 *
Subjects with body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI ≥27 kg/m^2		
Percent adjusted (SE), N# p-value vs. PLA	4.8% (1.051), 415	18.4% (1.876), 428 <0.0001 *
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.86 (0.7105), 479	-1.85 (0.7135), 473 0.0007 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N# p-value vs. PLA	0.32 (0.7109), 479	-2.70 (0.7140), 473 0.0002 *

	PLA N=482	DAPA 10 MG N=480
Seated SBP (mmHg) at week 8 (LOCF) in subjects with baseline SBP≥130 mmHg		
Adjusted mean change from baseline (SE), N#	-1.89 (0.8612), 309	-5.33 (0.8612), 300
p-value vs. PLA		0.0004 *

* Significant p-value: the primary endpoints were tested at α=0.025 (two-sided); the secondary endpoints were tested following a sequential testing procedure at α=0.05 (two-sided).

Primary endpoints

Subjects in the dapagliflozin group showed a statistically significant mean reduction in HbA1c from baseline to week 24 (LOCF) compared to the placebo group in all subjects of the full analysis set (0.40%) and in both age strata (<65 years: -0.46%; ≥65 years: -0.34%).

The proportion of subjects with a clinical benefit based on response for a 3-item endpoint of clinical benefit at week 24 (LOCF) was significantly larger in the dapagliflozin group compared to the placebo group in all subjects of the full analysis set (7.0%) and in both age strata (<65 years: 7.8%; ≥65 years: 6.2%).

Key secondary endpoints

Since the tests of both primary endpoints yielded a significant result, the secondary endpoints were tested following a sequential testing procedure at α=0.05 (two-sided).

Subjects in the dapagliflozin group showed a statistically significant mean percent reduction in total body weight from baseline to week 24 (LOCF) compared to the placebo group in all subjects of the full analysis set (-1.93%) and in both age strata (<65 years: -1.94 %; ≥65 years: -1.91%).

The proportion of subjects with a baseline BMI ≥27 kg/m^2 and with a total body weight reduction of at least 5% from baseline to week 24 (LOCF) was significantly larger in the dapagliflozin group compared to the placebo group in all subjects of the full analysis set (13.6%) and in both age strata (<65 years: 14.4%; ≥65 years: 12.7%).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in seated SBP from baseline to week 8 (LOCF) compared to the placebo group in all subjects of the full analysis set (-2.71 mmHg) and in both age strata (<65 years: -3.03 mmHg; ≥65 years: -2.36 mmHg).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in seated SBP from baseline to week 24 (LOCF) compared to the placebo group in all subjects of the full analysis set (-3.02 mmHg) and in the age stratum <65 years (-4.34 mmHg). The placebo-corrected mean change in seated SBP from baseline to week 24 (LOCF) in the age stratum ≥65 years (-1.53 mmHg, confidence interval [-3.86, 0.80]) was not statistically significant.

Subjects in the dapagliflozin group showed a statistically significant mean reduction in seated SBP from baseline to week 8 (LOCF) in subjects with baseline SBP ≥130 mmHg compared to the placebo group in all subjects of the full analysis set (-3.44 mmHg) and in the age stratum <65 years (-3.46 mmHg). In age stratum ≥65 years, statistical inference stopped with the fourth key secondary endpoint.

Summary of safety results

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

Table S3 Summary of subjects with adverse events - safety analysis set

Subjects (%)	PLA N=483	DAPA 10 MG N=482
At least one AE	263 (54.5)	275 (57.1)
At least one event of hypoglycemia	84 (17.4)	101 (21.0)
Death	1 (0.2)	2 (0.4)
At least one SAE	46 (9.5)	41 (8.5)
AE leading to discontinuation*	23 (4.8)	21 (4.4)
SAE leading to discontinuation*	10 (2.1)	1 (0.2)
Hypoglycemia leading to discontinuation*	0	0
At least one event suggestive of genital infection	2 (0.4)	33 (6.8)
At least one event suggestive of urinary tract infection	24 (5.0)	41 (8.5)

* of study medication.

Adverse events and events of hypoglycemia

Similar proportions of subjects in the dapagliflozin group and placebo group experienced at least one AE (57.1% vs. 54.5%) or serious adverse event (SAE) (8.5% vs. 9.5%). The proportion of subjects discontinued from study medication due to an AE (4.4% vs. 4.8%) was similar in the dapagliflozin group and placebo group.

There were 3 deaths during the 24-week short-term treatment period: one subject in the dapagliflozin group died due to heart failure, another subject in the dapagliflozin group died from myocardial infarction, and 1 subject in the placebo group died from myocardial infarction.

Proportions of subjects who experienced at least one hypoglycemic event in the dapagliflozin group (21.0%) were slightly higher than in the placebo group (17.4%). No hypoglycemic event was classified as major. No subject was discontinued from double-blind 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 AEs suggestive of genital infections (6.8% vs. 0.4%) and AEs of genital infections (6.0% vs. 0.2%) were larger in the dapagliflozin group than in the placebo group. Higher proportions of subjects in the dapagliflozin group than in the placebo group experienced AEs suggestive of UTI (8.5% vs. 5.0%) and AEs of UTI (7.3% vs. 4.6%). About two thirds of the subjects with events of these categories were female.

Proportions of subjects with AEs of the categories renal impairment or failure (predominantly laboratory abnormalities) (4.4% vs. 2.3%) were low but larger in the dapagliflozin group than in the placebo group. In age stratum ≥65 years, the proportion of subjects with renal impairment or failure was higher in both groups and the difference in subjects with renal impairment or failure between treatment groups was more pronounced (7.0% vs. 4.4%).

Few subjects in the dapagliflozin group and placebo group experienced AEs of the categories hypotension, dehydration, or hypovolemia (5 subjects vs. 9 subjects), fracture (2 subjects vs. 5 subjects), urinary stones (2 subjects vs. 3 subjects), hepatic disorder (1 subject vs. 9 subjects), and malignant and unspecified neoplasms (3 subjects vs. 2 subjects).

Laboratory evaluation

Three subjects in the dapagliflozin group and 2 subjects in the placebo group showed at least one marked abnormality (MA) of hematocrit >55%. Three subjects in the dapagliflozin group and 4 subjects placebo group showed at least one MA of hemoglobin >18 g/dL. None of the subjects with an MA of hematocrit or hemoglobin showed thromboembolic AEs. There was a small increase in mean hematocrit, hemoglobin, and red blood cell count (RBC) from baseline to week 16 in the dapagliflozin group. Thereafter, the 3 hematology parameters remained almost stable. In the placebo group, mean hematocrit, hemoglobin, and RBC did not show a meaningful change during the 24-week short-term treatment period.

Few subjects in the dapagliflozin group and placebo group showed at least one MA of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) (1 subject vs. 4 subjects), total bilirubin (TB) >1.5 x ULN (2 subjects vs. 2 subjects), and alkaline phosphatase (ALP) >1.5 x ULN (3 subjects vs. 2 subjects). No subject in either treatment group showed a combined MA of ALT or AST and TB. Subjects in the dapagliflozin group showed a decrease in ALT and no meaningful change in mean AST, ALP, and TB from baseline to week 24. In the placebo group, no meaningful change in mean AST, ALT, ALP, and TB was observed from baseline to week 24.

Few subjects in the dapagliflozin group and placebo group showed at least one MA of creatinine ≥1.5 x baseline concentration (10 subjects vs. 9 subjects). Subjects in the dapagliflozin group showed an increase in mean blood urea nitrogen (BUN), cystatin-C, and mean serum creatinine from baseline to week 24. Mean calculated creatinine clearance and eGFR did not show a meaningful change from baseline to week 24 in the dapagliflozin group.

In the placebo group, no meaningful change in any of these renal laboratory parameters was observed from baseline to week 24.

Few subjects in the dapagliflozin group and placebo group showed at least one MA of calcium <7.5 mg/dL (6 subjects vs. 0 subject), calcium ≥1 mg/dL from ULN and ≥0.5 mg/dL from pre-randomization value (1 subject vs. 2 subjects), potassium ≥6.0 mEq/L (15 subjects vs. 20 subjects), magnesium <1 mEq/L (1 subject vs. 1 subject), sodium <130 mEq/L (0 subject vs. 6 subjects), sodium >150 mEq/L (5 subjects vs. 2 subjects), and inorganic phosphorus (5 subjects vs. 7 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. The other electrolytes did not show a meaningful change from baseline to week 24 in the dapagliflozin group. In the placebo group, no meaningful change in any serum electrolyte was observed from baseline to week 24.

One subject each in the dapagliflozin group and placebo group showed at least one MA of creatine kinase (CK) >10 x ULN. Subjects in the dapagliflozin group showed a slight decrease in mean CK from baseline to week 24. In the placebo group, no meaningful change in mean CK was observed from baseline to week 24.

Vital signs

Subjects in the dapagliflozin group showed a slight mean decrease in seated SBP and no meaningful mean decrease in seated DBP from baseline to week 24 (LOCF). In the placebo group, no meaningful mean change in both seated SBP and seated DBP was observed. Seated heart rate did not show a meaningful mean change in either treatment group from baseline to week 24.

Overall, the proportion of subjects with measured orthostatic hypotension during the 24-week short-term double-blind treatment period was larger in the dapagliflozin group (17.2%) than in the placebo group (14.4%).

Conclusion(s)