AstraZeneca

24-week Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1690C00006
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A 24-week international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24*-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycemic control on insulin.

Report for the first 24-week treatment period.

* A second 56-week extension period was introduced with Amendment 2.

Study dates: First subject enrolled: *30 April 2008*
Last subject completed: *19 May 2009*

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

Study D1690C00006 was conducted at 122 centers in 13 countries. (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 key secondary objectives and outcome variables

Objectives	Outcome variables
Primary	
The primary objective of this study was to assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycemic control in subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control on ≥30 IU injectable insulin daily for at least 8 weeks prior to enrollment, as determined by the change in HbA1c levels from baseline to week 24.	Change in HbA1c from baseline to week 24
Key secondary	
To examine whether treatment with dapagliflozin in combination with insulin was superior in reducing body weight or causing less weight gain as compared to placebo added to insulin treatment after 24 weeks of treatment.	Change in body weight from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin led to a lower absolute calculated mean daily insulin dose as compared to placebo added to insulin treatment alone, from baseline to week 24.	Absolute change in calculated mean daily insulin dose from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin led to higher percentage of subjects with calculated mean daily insulin dose reduction from baseline to week 24 as compared to placebo added to insulin treatment.	Proportion of subjects with calculated mean daily insulin dose reduction from baseline to week 24
To examine whether treatment with dapagliflozin in combination with insulin was superior in reducing Fasting Plasma Glucose (FPG) as compared to placebo added to insulin treatment after 24 weeks of treatment.	Change in FPG from baseline to week 24
Safety	
To evaluate the safety and tolerability by assessment of adverse events (AE), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), total protein/creatinine ratio (mg/g) and physical examination findings	AEs, laboratory values, ECG, pulse, BP, hypoglycemic events, calculated creatinine clearance, eGFR, total protein/creatinine ratio (mg/g) and physical examination findings

The primary and all key secondary objectives/variables were efficacy objectives/variables. For other secondary objectives/variables see the Clinical Study Report (CSR). Results of other secondary objectives/variables are not included in this Synopsis, but can be found in the CSR.

Study design

This was an international, randomized, parallel-group, double-blind, placebo-controlled Phase III study with a 24-week short-term treatment period, followed by 2 extension periods (24 weeks and 56 weeks, respectively) to evaluate the efficacy and safety of dapagliflozin 2.5 mg, 5 mg and 10 mg as add-on therapy to insulin in adult subjects with T2DM with inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%). Subjects were randomized to one of the dapagliflozin groups or placebo at a 1:1:1:1 ratio. 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 and ≤80 years of age, with inadequate glycemic control, defined as HbA1c ≥7.5% and ≤10.5%, who were on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrollment. Subjects could also be treated with maximally two oral anti-diabetic drugs (OADs). OAD treatment should be at a stable dose for a period of at least 8 weeks as well. Subjects were stratified according to whether their treatment regimen included OADs or not. No more than 60% of enrolled subjects were allowed to take insulin plus OADs.

According to the original protocol, 644 subjects were planned for randomization in order to detect a difference of 0.5% between each dapagliflozin group versus placebo for changes from baseline to week 24 in HbA1c at a two-sided significance level of 0.019 and with 90% power, assuming a SD of 1.2% and assuming that 5% of the subjects were not evaluable in the full analysis set. The number of subjects planned for randomization was increased according to the request of the EU regulatory agency (CHMP) to include a sufficient number of subjects on insulin only. Actually, 808 subjects were randomized and 800 subjects were included in the full analysis set (202, 211, 194, and 193 in the dapagliflozin 2.5 mg, 5 mg, 10 mg, and placebo group).

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

Subjects administered dapagliflozin 2.5 mg, 5 mg, 10 mg or placebo according to their assignment to a treatment group as add-on therapy to insulin with or without additional use of 1 or 2 OADs.

Since dapagliflozin 2.5 mg and 5 mg tablets were different in size compared to dapagliflozin 10 mg tablets, subjects in the dapagliflozin 2.5 mg and 5 mg groups had to take one tablet dapagliflozin 2.5 mg or 5 mg **plus** one tablet matching placebo for dapagliflozin 10 mg per day, subjects in the dapagliflozin 10 mg group had to take one tablet dapagliflozin 10 mg **plus** one tablet matching placebo for dapagliflozin 2.5 mg and 5 mg per day, and subjects in the placebo group had to take one tablet matching placebo for dapagliflozin 2.5 mg and 5 mg **plus** one tablet matching placebo for dapagliflozin 10 mg per day. Thus, every subject had to administer two tablets orally once daily during the 24-week short-term treatment period.

Dapagliflozin and matching placebo was manufactured by Bristol-Myers Squibb. Batch numbers of study medication are listed in Appendix 12.1.7.2 to the CSR.

Duration of treatment

According to the original protocol, subjects were treated with study medication for 48 weeks (24-week short-term treatment period **plus** 24-week long-term extension period I). A second long-term extension period of 56 weeks immediately following long-term extension period I was introduced to the study with Amendment 2. 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 across the primary and key secondary efficacy variables. The primary efficacy variable was statistically analyzed using Dunnett's method at an overall type I error rate ≤0.05. The significance level for each pair-wise group comparison of dapagliflozin versus placebo was approximately 0.019 for the primary efficacy variable. The statistical testing of the primary and key secondary efficacy variables proceeded in a sequential manner, to control the type I error rate within each dapagliflozin group at the 0.05 level. The primary efficacy variable and continuous key secondary efficacy variables were analyzed using an analysis of covariance model (ANCOVA) with factors for treatment group and use of other OADs as fixed effects, and covariate for baseline value. The model was used to derive least squares estimates of the treatment differences (each dapagliflozin group versus placebo) 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 were calculated. Comparisons of the dapagliflozin treatment groups versus placebo in proportions were performed using the methodology of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu with adjustment for baseline value and use of other OADs. Efficacy was primarily evaluated using the full analysis set. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 1240 subjects were enrolled out of which 808 were randomized. The most common reason for **not** being randomized was not fulfilling all the inclusion criteria and fulfilling at least one exclusion criterion (396 subjects). More than 85% of the subjects completed the 24-week short-term treatment period and continued into the 24-week extension period I. The most common reason for **not** completing the short-term treatment period and **not** continuing into the extension period I was withdrawal of the consent. The full analysis set included 800/808 randomized subjects. The safety analysis set included 807/808 randomized subjects.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 60 years of age with 75% aged below 65 years and less than 3% aged over 75 years. The proportions of male and female subjects were almost equal. 95% of the subjects were white and almost 99% were of non-Hispanic/ Latino ethnicity. Mean duration of T2DM was 13.6 years with two thirds of the subjects

suffering from T2DM over 10 years. On average, subjects had been on insulin treatment for about 6 years. At baseline, mean HbA1c was around 8.5% and approx. 30% of the subjects had a baseline HbA1c ≥9%. The median calculated mean daily insulin dose was 65 IU/day with 20% of the subjects on a dose >100 IU/day. 50% of the subjects used 1 or 2 OADs in addition to insulin treatment.

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 + INS N = 193	DAPA 2.5 MG + INS N = 202	DAPA 5 MG + INS N = 211	DAPA 10 MG + INS N = 194
Primary endpoint				
HbA1c (%) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	-0.30 (0.0521)	-0.75 (0.0507)	-0.82 (0.0493)	-0.90 (0.0515)
p-value vs. PLA + INS		<0.0001 *	<0.0001 *	<0.0001 *
Key secondary endpoints				
Body weight (kg) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	0.02 (0.1833)	-0.98 (0.1786)	-0.98 (0.1734)	-1.67 (0.1814)
p-value vs. PLA + INS		0.0001 *	<0.0001 *	<0.0001 *
Calculated mean daily insulin dose (IU/day) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	5.08 (0.9432)	-1.80 (0.9217)	-0.61 (0.9012)	-1.16 (0.9354)
p-value vs. PLA + INS		<0.0001 *	<0.0001 *	<0.0001 *
Subjects with calculated mean daily insulin dose reduction ≥10% at week 24 (LOCF)				
Percent adjusted	11.0%	18.2%	16.7%	19.6%
p-value vs. PLA + INS		0.0411 *	0.0923	0.0168 *
Fasting plasma glucose (mg/dL) at week 24 (LOCF)				
Adjusted mean change from baseline (SE)	3.3 (3.370)	-12.5 (3.247)	-18.8 (3.140)	-21.7 (3.309)
p-value vs. PLA + INS		0.0008 *	<0.0001	<0.0001 *

* Significant p-value: primary endpoint was tested at $\alpha = 0.019$ applying the Dunnett adjustment, and secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$.

HbA1c showed a mean decrease from baseline to week 24 (LOCF) in all treatment groups. The mean decrease in HbA1c was significantly larger in all dapagliflozin groups compared to placebo. The effect of dapagliflozin on HbA1c appears to be dose-dependent and the effect was clinically relevant for the treatment of T2DM (>0.5% placebo corrected) in the 5 mg and 10 mg dapagliflozin groups.

Body weight showed a mean decrease from baseline to week 24 (LOCF) in the dapagliflozin groups and almost no change in the placebo group. The mean decrease in body weight was

statistically significant in all dapagliflozin groups compared to placebo. The effect of dapagliflozin on body weight was larger in the dapagliflozin 10 mg than in the dapagliflozin 2.5 mg and 5 mg groups.

Calculated mean daily insulin dose showed a slight mean decrease from baseline to week 24 (LOCF) in the dapagliflozin groups and a mean increase of around 5 UI in the placebo group. The mean change in calculated mean daily insulin dose was statistically significant in all dapagliflozin groups compared to placebo.

More than 10% of the subjects in all treatment groups showed a calculated mean daily insulin dose reduction ≥10% from baseline to week 24 (LOCF). The proportion of subjects with a calculated mean daily insulin dose reduction ≥10% was significantly higher in the dapagliflozin 2.5 mg and 10 mg groups compared to placebo.

FPG showed a mean decrease from baseline to week 24 (LOCF) in the dapagliflozin groups and almost no change in the placebo group. The mean decrease in FPG was statistically significant in the dapagliflozin 2.5 mg and 10 mg groups compared to placebo. The p-value for the 5 mg group was <0.05 but cannot be interpreted as statistically significant under the hierarchical closed testing procedure.

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

	PLA + INS N = 197	DAPA 2.5 MG + INS N = 202	DAPA 5 MG + INS N = 212	DAPA 10 MG + INS N = 196
At least one AE	127 (64.5)	130 (64.4)	139 (65.6)	132 (67.3)
At least one event of hypoglycemia	83 (42.1)	111 (55.0)	101 (47.6)	88 (44.9)
Death	0	0	1 (0.5)**	0
At least one SAE	14 (7.1)	15 (7.4)	10 (4.7)	14 (7.1)
AE leading to discontinuation*	8 (4.1)	5 (2.5)	12 (5.7)	8 (4.1)
SAE leading to discontinuation*	3 (1.5)	1 (0.5)	3 (1.4)	4 (2.0)
Hypoglyc. leading to discontinuation*	0	0	0	0
At least one AE of genital infection	4 (2.0)	10 (5.0)	16 (7.5)	18 (9.2)
At least one AE of urinary tract infection	8 (4.1)	15 (7.4)	19 (9.0)	17 (8.7)

* of study medication; ** subject died due to cardiogenic shock caused by post-operative complications.

Proportions of subjects experiencing at least one adverse event (AE) or serious adverse event (SAE) and proportions of subjects discontinued from study medication due to an AE or SAE were similar across treatment groups. Hypoglycemic events were reported by approximately half of the subjects. They were evenly distributed across all treatment groups, including placebo. No hypoglycemic event led to discontinuation of study medication.

One subject each in the placebo group and in the dapagliflozin 5 mg and 10 mg groups and 2 subjects in the dapagliflozin 2.5 mg group experienced a major hypoglycemic episode (symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration).

There was one death (due to cardiogenic shock caused by post-operative complications) in the dapagliflozin 5 mg group. One further subject in the dapagliflozin 10 mg group died from hepatocellular carcinoma more than 30 days after the last dose of double-blind study medication, and one further subject in the dapagliflozin 10 mg group died from pancreatic carcinoma after the follow-up visit was performed. Death of these subjects is not included in the analysis of the 24-week short-term treatment period (for details see the CSR).

A higher proportion of subjects in the dapagliflozin groups, compared to placebo, reported an AE of genital infection. The proportion of subjects with an AE of genital infection increased with increasing doses of dapagliflozin. The majority of subjects reporting genital infections experienced AEs reported as mycotic genital infection.

A higher proportion of subjects in the dapagliflozin groups, compared to placebo, reported an AE of urinary tract infection (UTI). There was no clear dose dependency for AEs of UTI. One subject each in the dapagliflozin 2.5 mg and 5 mg groups experienced a pyelonephritis and one subject in the dapagliflozin 2.5 mg group experienced a kidney infection.

There was a small, dose-dependent, mean increase in hematocrit over the first 12 weeks in the dapagliflozin groups, compared to placebo. After week 12, no further mean change in hematocrit compared to placebo was observed. Laboratory values did not show any signs of hepatic impairment or decreasing renal function associated with dapagliflozin treatment.

Dapagliflozin led to a mean decrease in systolic and a slight mean decrease in diastolic blood pressure compared to placebo. Decreases in systolic blood pressure appeared to be dose-related. Decreases in blood pressure were not associated with an increased occurrence of orthostatic hypotension.