AstraZeneca

Final 48-week Clinical Study Report Synopsis	
Drug Substance	Dapagliflozin
Study Code	D1690C00005
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A 24-Week, International, Randomized, Double-blind, Parallel-group, Multi-center, Placebo-controlled Phase III Study with a 24-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination with Glimepiride (a Sulphonylurea) in Subjects with Type 2 Diabetes who Have Inadequate Glycemic Control on Glimepiride Therapy Alone

Report for the 24-week short-term treatment period plus the 24-week long-term extension period.

Study dates: First subject enrolled: 30-Apr-2008
Last subject completed: 20-May-2010

Phase of development: Therapeutic exploratory (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 D1690C00005 was conducted at 84 centers in 7 countries. (Only active centers are mentioned.)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Main objectives and outcome variables are presented in Table S1.

Table S1 Main objectives and outcome variables

Objectives	Outcome variables
To assess the safety and tolerability parameters over 48 weeks of treatment.	Adverse events (AEs), laboratory values, electro-cardiogram, pulse, blood pressure, hypoglycemic events, calculated creatinine clearance, and physical examination findings
To assess the maintenance of efficacy of each dose of dapagliflozin plus glimepiride versus glimepiride alone over 48 weeks of treatment.	The change in glycosylated hemoglobin A1c (HbA1c) from baseline to Week 48
	The change in body weight from baseline to Week 48
	The change in 2-h post-challenge plasma glucose rise in response to an oral glucose tolerance test (OGTT) from baseline to Week 48
	The proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7% at Week 48
	The change in body weight from baseline to Week 48 in subjects with baseline body mass index (BMI) ≥27 kg/m^2
	The change in fasting plasma glucose (FPG) from baseline to Week 48

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Only outcome variables are mentioned that correspond to the primary or key secondary outcome variables of the short-term period referring to the parameter investigated. For other outcome variables see the full Clinical Study Report (CSR).

Study design

This was a 24-week, international, randomized, double-blind, parallel-group, multi-center, placebo-controlled phase III trial with a 24-week extension period to evaluate the efficacy, safety and tolerability of dapagliflozin in combination with glimepiride (a sulphonylurea) in subjects with type 2 diabetes with HbA1c value of ≥7% and ≤10% on glimepiride (4 mg/day) therapy alone. Subjects were randomized to one of the dapagliflozin groups or placebo at a

1:1:1:1 ratio. In case of lack of glycemic control at predefined levels of FPG or HbA1c, subjects could receive rescue medication with either metformin, pioglitazone or rosiglitazone. Note that this report includes results from the 24-week short-term treatment period combined with the 24-week long-term extension period. Safety and efficacy results from the 24-week short-term treatment period were already reported separately.

Target subject population and sample size

The study entry criteria specified enrollment of male or female subjects ≥18 years of age, with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10%) on current sulphonylurea monotherapy of at least half maximal recommended dose for at least 8 weeks prior to enrollment were eligible to enter the study.

According to the original protocol, 544 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 standard deviation of 1.1% and assuming that 5% of the subjects would not have a post-baseline efficacy measurement and were not evaluable in the full analysis set. Actually, 597 subjects were randomized and 592 subjects were included in the full analysis set (154, 142, 151, and 145 subjects in the dapagliflozin 2.5 mg, 5 mg, 10 mg, and placebo groups).

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 glimepiride.

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 + 24-week long-term treatment period.

Dapagliflozin and matching placebo were manufactured by Bristol-Myers Squibb. Batch numbers of study medication are listed in Listing 12.1.7.2 of 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).

Statistical methods

Statistical analyses were performed for the 24-week short-term treatment period combined with the 24-week long-term extension period. All long-term efficacy analyses were considered exploratory. In general, last observation carried forward method was not used. Continuous efficacy variables were analyzed using a longitudinal repeated measures analysis with the fixed categorical effects of treatment, week and treatment-by-week interaction as well as the continuous fixed covariates of baseline value and baseline value-by-week interaction. The model provided least squares estimates, standard errors (SEs) and two-sided 95% confidence intervals for mean change from baseline to all post-baseline time points within treatment groups and for differences between each dapagliflozin treatment group versus placebo. No p-values for treatment group comparisons were calculated. The methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang, and Lu with adjustment for baseline value was used to analyze proportions. Efficacy was evaluated using the full analysis set. Change in HbA1c from Week 24 over time to Week 48 and proportion of subjects achieving therapeutic glycemic response defined as HbA1c <7% at Week 48 were analyzed for the short-term completers analysis set. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 859 subjects were enrolled out of which 597 were randomized. The most common reason for not being randomized was not fulfilling all the inclusion criteria or fulfilling at least one exclusion criterion (229 subjects).

In total, 546 (91.6%) of the subjects in the safety analysis set completed the short-term treatment period and 519 (87.1%) of the subjects in the safety analysis set completed the long-term extension period. The most common reasons for not completing the periods were withdrawal of consent, occurrence of an AE, and violations of the study criteria. The numbers of subjects continuing in the study in the dapagliflozin groups and in the placebo group were similar.

After end of treatment, 510 (85.6%) of the subjects in the safety analysis set completed the follow-up period until End of Study. The most common reason for not completing the study was withdrawal of consent. The numbers of subjects completing the study in the dapagliflozin groups and in the placebo group were similar.

The full analysis set included 592/597 randomized subjects. The safety analysis set included 596/597 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 around 33% ≥65 years and around 5% ≥75 years. The proportions of male and female subjects were similar. About 70% of subjects were White and about 30% Asian and no subjects were of Hispanic/Latino ethnicity. Mean duration of type 2 diabetes was 7.4 years with one quarter of the subjects suffering from type 2 diabetes over 10 years. At baseline, mean HbA1c was 8.11% and approximately 15% of subjects had a baseline HbA1c ≥9.0%.

Summary of efficacy results

Main efficacy endpoints are summarized in Table S2.

Table S2 Summary of main efficacy endpoints - full analysis set

	PLA + GLI N=145	DAPA 2.5 MG + GLI N=154	DAPA 5 MG + GLI N=142	DAPA 10 MG + GLI N=151
Main endpoints*				
HbA1c (%) at Week 48				
Adjusted mean change from baseline (SE)	-0.04 (0.0873)	-0.41 (0.0764)	-0.56 (0.0764)	-0.73 (0.0721)
Body weight (kg) at Week 48				
Adjusted mean change from baseline (SE)	-0.77 (0.3315)	-1.36 (0.2926)	-1.54 (0.2926)	-2.41 (0.2766)
2-h post-challenge plasma glucose rise at Week 48				
Adjusted mean change from baseline (SE)	-7.7 (7.862)	-23.6 (6.561)	-32.5 (6.397)	-29.4 (5.776)
The proportion of subjects achieving glycemic response (defined as HbA1c <7% at 48 weeks**)				
Percent adjusted (SE)	10.6% (2.509)	15.7% (2.870)	28.2% (3.597)	29.6% (3.605)
Body weight (kg) at Week 48 in subjects with baseline BMI ≥27 kg/m^2 ***				
Adjusted mean change from baseline (SE)	-0.60 (0.3537)	-1.71 (0.3542)	-1.83 (0.3598)	-2.83 (0.3621)
FPG (mg/dL) at Week 48				
Adjusted mean change from baseline (SE)	2.6 (3.645)	-16.7 (3.055)	-16.5 (2.991)	-28.8 (2.778)

* Data are presented for the full analysis set, excluding data after rescue due to lack of glycemic control.
** Subjects rescued or discontinued were considered as not achieving glycemic response.
*** Data are presented for the full analysis set, including data after rescue due to lack of glycemic control.

Over time, a mean reduction in HbA1c compared to baseline was observed in all treatment groups using longitudinal repeated measure analyses. Most of the reduction occurred during the first 12 weeks and the effect was stable until Week 48. The reductions were clinically meaningful (differences compared to placebo >0.5%) for most observations after Week 12 (including Week 48) in the dapagliflozin 5 mg group and for all observations after Week 8 in the dapagliflozin 10 mg group (analyses excluding data after rescue). The greatest HbA1c reduction was observed in the dapagliflozin 10 mg group. Analyses including data after rescue were comparable to analyses excluding data after rescue. The HbA1c reduction observed at Week 24 was maintained until Week 48. For HbA1c, this was observed also in analyses including only subjects who completed short-term treatment period.

At Week 48, a modest weight loss compared to baseline was observed in the dapagliflozin groups. The effect was most pronounced in the dapagliflozin 10 mg group (analyses

excluding data after rescue). Analyses including data after rescue showed similar results. The weight reduction achieved at Week 24 using repeated measures analyses was maintained until Week 48.

The 2-h post-challenge plasma glucose rise (OGTT) showed a reduction from baseline to Week 48 in all dapagliflozin groups (analyses excluding data after rescue). The OGTT reduction observed at Week 24 was maintained until Week 48.

At Week 48, the proportion of subjects achieving glycemic response defined as HbA1c <7% was higher in the dapagliflozin groups than in the placebo group (subjects rescued, discontinued or with missing measurements at Week 24 or Week 48 were considered as not achieving glycemic response). Similar proportions were observed when including only subjects who completed the short-term treatment period. The proportion of subjects with HbA1c <7% at Week 24 was maintained until Week 48, except for the dapagliflozin 2.5 mg group that showed a small reduction in subjects with goal.

The subgroup of subjects with BMI ≥27 kg/m^2 at baseline consisted of 68.1% of the total study population. The mean weight reduction in subjects with BMI ≥27 kg/m^2 (analyses including data after rescue) was slightly larger compared to the effect in the overall population (analyses excluding data after rescue).

FPG showed an immediate reduction from baseline to Week 4 in all dapagliflozin groups. This reduction was maintained until Week 48 (analyses excluding data after rescue). Analyses including data after rescue were comparable. The FPG reduction observed at Week 24 appeared to be maintained until Week 48 in the dapagliflozin groups with the best effect in the dapagliflozin 10 mg group.

The proportion of subjects who discontinued or received rescue medication due to lack of glycemic control prior to or at Week 48 was higher in the placebo group than in the dapagliflozin groups.

Summary of safety results

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

Table S3 Summary of subjects with AEs and events of hypoglycemia - safety analysis set

	PLA + GLI N = 146	DAPA 2.5 MG + GLI N = 154	DAPA 5 MG + GLI N = 145	DAPA 10 MG + GLI N = 151
At least one AE	81 (55.5%)	90 (58.4%)	88 (60.7%)	89 (58.9%)
At least one event of hypoglycemia	10 (6.8%)	15 (9.7%)	15 (10.3%)	17 (11.3%)
At least one related AE	8 (5.5%)	12 (7.8%)	12 (8.3%)	16 (10.6%)
Deaths	0	2 (1.3%)	0	1 (0.7%)
At least one serious adverse event (SAE)	13 (8.9%)	16 (10.4%)	16 (11.0%)	13 (8.6%)
At least one related SAE	0	0	0	0
AE leading to discontinuation*	5 (3.4%)	5 (3.2%)	5 (3.4%)	4 (2.6%)
SAE leading to discontinuation*	3 (2.1%)	3 (1.9%)	1 (0.7%)	1 (0.7%)
Hypoglycemia leading to discontinuation*	0	0	0	0
At least one event suggestive of genital infection	2 (1.4%)	8 (5.2%)	9 (6.2%)	13 (8.6%)
At least one event suggestive of urinary tract infection	11 (7.5%)	7 (4.5%)	11 (7.6%)	12 (7.9%)

* of study medication.

Around 58% of the subjects in all treatment groups experienced at least one AE. 226 subjects in the dapagliflozin and 69 subjects in the placebo groups reported at least one AE during the short-term period (total of 49.5%).

The overall proportions of subjects experiencing any AE, SAE or AE leading to discontinuation of study medication were similar across treatment groups. Higher proportions of subjects in the dapagliflozin groups than in the placebo group had AEs reported as related to the study medication.

There were three deaths reported, one subject with aortic valve replacement due to pulmonary embolism after ischemic stroke in the dapagliflozin 10 mg group (short-term period) and two subjects in the dapagliflozin 2.5 mg group, one due to cardiopulmonary arrest (short-term period) and one due to sudden cardiac death (long-term period).

Hypoglycemic events were reported by 9.7 to 11.3% of subjects in the dapagliflozin treatment groups and by 6.8% in the placebo group. From a total of 57 subjects, for 40 subjects, the first event was reported during the 24-week short-term period. There was one major episode of hypoglycemia reported in the dapagliflozin 2.5 mg group which was associated with watery diarrhea and decreased oral intake. No subject discontinued study treatment due to a hypoglycemic event.

Both in males and in females, higher proportions of subjects in the dapagliflozin treatments groups, compared with placebo, reported signs, symptoms, and other reports suggestive of genital infections. No subjects reported events suggestive of genital infection assessed as severe or very severe in intensity, serious or leading to discontinuation from study medication. Similar proportions of subjects reported signs, symptoms, and other reports suggestive of urinary tract infection (UTIs) in the dapagliflozin and placebo groups. No kidney infections were reported. The majority of subjects with events suggestive of genital infection or UTI had their first event during the 24-week short treatment period.

Less than 1% of subjects in each treatment group experienced an AE of hypotension, dehydration or hypovolemia. The proportion of subjects with an AE of hypotension, dehydration or hypovolemia did not show any differences between the placebo group and the dapagliflozin groups nor a dose-dependent increase in the dapagliflozin groups.

There was a small mean increase in hematocrit in the dapagliflozin groups, most of the increase occurred over the first 12 weeks. After Week 12, no meaningful further mean change in hematocrit compared to placebo was observed.

Overall, hepatic parameters did not show any signs of hepatic impairment associated with dapagliflozin treatment. During the 24-week short-term treatment + 24-week long-term extension period, 5.8, 3.5, and 5.3% of subjects in the dapagliflozin 2.5, 5, and 10 mg groups and 4.9% of subjects in the placebo group showed marked abnormalities (MAs) of elevated liver function tests.

Blood urea nitrogen and serum creatinine did not show any meaningful mean changes, indicating no apparent worsening of renal function in the dapagliflozin groups.

There were small mean decreases in systolic blood pressure (SBP) in all dapagliflozin groups compared to placebo. Subjects with SBP >140 mmHg at baseline showed a more pronounced decrease in SBP including the placebo group. Diastolic blood pressure (DBP) and heart rate did not show any meaningful change.