AstraZeneca

24-week Clinical Study Report Synopsis

Drug Substance Dapagliflozin

Study Code D1693C00005

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A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on a background combination of Metformin and Sulfonylurea

Report for the 24-week short-term treatment period

Study dates: First subject enrolled: 24 October 2011
Last subject completing 24-week double-blind treatment period: 07 January 2013

Phase of development: Therapeutic confirmatory (III)

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

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study center(s)

Study D1693C00005 was conducted at 46 centers in North America (Canada) and Europe (Czech Republic, Germany, Poland, Slovak Republic, and Spain) that enrolled subjects, and 45 centers randomized subjects. (Only active centers are mentioned.)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and outcome variables of the 24-week double-blind treatment period are presented in Table S1.

Table S1 Objectives and outcome variables of the short-term period

Objectives	Outcome variables
Primary	
The primary objective of this study was to compare the change from baseline in HbA1c to week 24 between dapagliflozin 10 mg in combination with metformin and sulfonylurea and placebo in combination with metformin and sulfonylurea.	Change in HbA1c from baseline to week 24 (LOCF)
Key secondary	
To compare the change from baseline in FPG to week 24 between dapagliflozin and placebo	Change in FPG from baseline to week 24 (LOCF)
To compare the change from baseline in total body weight to week 24 between dapagliflozin and placebo	Change in total body weight from baseline to week 24 (LOCF)
To compare the proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0%, at week 24 between dapagliflozin and placebo	Proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0%, at week 24 (LOCF)
To compare the change from baseline in seated SBP to week 8 between dapagliflozin and placebo	Change in seated SBP from baseline to week 8 (LOCF)
To evaluate the safety and tolerability of dapagliflozin by assessment of AEs, including CV events, laboratory values, electrocardiogram, pulse, blood pressure, hypoglycemic events, and physical examination findings	AEs, safety laboratory values, ECG, pulse, BP, hypoglycemic events, and physical examination findings

Only outcome variables are mentioned that correspond to the primary or key secondary outcome variables of the ST period referring to the parameter investigated. For other outcome variables, see the Clinical Study Report (CSR). Results of other outcome variables are not included in this Synopsis but can be found in the CSR.

AE, adverse event; BP, blood pressure; CV, cardiovascular; ECG, electrocardiogram; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LOCF, last observation carried forward; SBP, systolic blood pressure; ST, short-term.

Study design

This was a 24-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase IIIb study with a 28-week site- and subject blinded extension period

to evaluate the efficacy and safety of dapagliflozin 10 mg once daily (QD) in subjects with type 2 diabetes. Dapagliflozin or placebo was added to the therapy of subjects who had inadequate glycemic control on combination of metformin and sulfonylurea (SU).

Target subject population

Subjects who had inadequate glycemic control at Visit 3 (hemoglobin A1c [HbA1c] ≥7.0% and ≤10.5%) on a stable dose combination therapy of metformin ≥1500 mg/day and maximum tolerated dose that had to be at least half the maximum dose of SU for at least 8 weeks prior to enrolment were eligible to be randomized at Visit 4 (week 0, baseline) in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo in addition to the combination therapy of metformin and SU.

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

Dapagliflozin 10 mg QD or matching placebo was administered orally QD according to their assignment to treatment groups as add-on therapy to the combination of metformin and SU during the 24-week double-blind treatment period and the 28-week site-and subject-blinded extension period. 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 of the Clinical Study Report.

Duration of treatment

According to the Clinical Study Protocol, subjects were to be treated with study medication for 52 weeks (24-week double-blind treatment period and the 28-week site- and subject-blinded extension period).

Statistical methods

Statistical analyses were performed for the 24-week double-blind treatment period. The primary analysis was to compare dapagliflozin versus placebo in terms of the primary efficacy variable, change in HbA1c from baseline to week 24.

Four key secondary variables had been identified: (1) change in fasting plasma glucose (FPG) from baseline to week 24 (last observation carried forward [LOCF]), (2) change in total body weight from baseline to week 24 (LOCF), (3) proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0% at week 24 (LOCF), and (4) change in seated systolic blood pressure (SBP) from baseline to week 8 (LOCF).

A hierarchical closed testing procedure was used to control the type I error rate across the primary and key secondary objectives. If the primary endpoint was statistically significant, key secondary variables were tested in the order presented. Treatment comparisons were individually tested at a 2-sided significance level of 0.050. For all other variables, nominal p-values were reported without significance testing.

The primary efficacy variable, change in HbA1c from baseline to week 24, was analyzed by a longitudinal repeated measures analysis using 'direct likelihood,' with fixed categorical effects of treatment, week, treatment-by-week interaction, as well as the continuous fixed covariates of baseline and baseline-by-week interaction. Data for scheduled timepoints up to week 24 prior to rescue were included in the longitudinal repeated measures analysis. The model provided least-squares mean estimates, standard errors, and 2-sided 95% confidence intervals for mean change at week 24 within and between treatments. The treatment group comparison between dapagliflozin 10 mg and placebo at week 24 was performed at the 2-sided 0.05 confidence level. Other continuous variables were analyzed using an analysis of covariance model including terms for treatment group and baseline covariate, using LOCF to impute missing week 24 values.

The proportion of subjects achieving a therapeutic glycemic response, defined as HbA1c <7.0%, at week 24, was analyzed using the methodology of Zhang, Tsiatis, and Davidian and Tsiatis, Davidian, Zhang, and Lu when there are at least 5 responders on average by treatment group. For proportion of responders, estimates, confidence intervals, and tests were obtained using this methodology with adjustment for baseline HbA1c. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 311 subjects were enrolled, with 268 subjects entered the lead-in period. In total, 219 subjects 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) (77 subjects) and withdrawal of consent (12 subjects). One subject died prior to randomization.

Approximately 93% of the subjects completed the 24-week short-term (ST) period. The most common reasons for not completing the 24-week ST period were incorrect enrollment (5 subjects), occurrence of an adverse event (AE) (4 subjects), and other (5 subjects).

In total, 199 of 202 subjects completing the24-week treatment period also entered the extension period.

Summary of efficacy results

The primary and key secondary outcome variables of the ST period are summarized in Table S2.

Table S2 Summary of the primary and key secondary outcome variables of the ST period - full analysis set

		PLA + MET + SU N = 108	DAPA 10 MG + MET + SU N = 108
HbA1c (%)			
Week 24	Adjusted mean change from baseline (SE)	-0.17 (0.0730)	-0.86 (0.0714)
	Difference vs. placebo (SE)		-0.69 (0.1022)
	p-value for difference vs. placebo		<0.0001[a]
FPG			
Week 24 (LOCF)	Adjusted mean change from baseline (SE)	-0.78 (3.4424)	-34.23 (3.4262)
	Difference vs. placebo (SE)		-33.45 (4.8846)
	p-value for difference vs. placebo		<0.0001[a]
Total body weight (kg)			
Week 24 (LOCF)	Adjusted mean change from baseline (SE)	-0.58 (0.2580)	-2.65 (0.2580)
	Difference vs. placebo (SE)		-2.07 (0.3651)
	p-value for difference vs. placebo		<0.0001[a]
Subjects with HbA1c <7%			
Week 24 (LOCF)	Percent adjusted (95% CI)	11.1% (5.4, 16.8)	31.8% (23.3, 40.2)
	Difference vs. placebo (95% CI)		20.7% (10.7, 30.6)
	p-value for difference vs. placebo		<0.0001[a]
Seated SBP (mmHg)			
Week 8 (LOCF)	Adjusted mean change from baseline (SE)	-0.27 (1.1782)	-4.04 (1.1782)
	Difference vs. placebo (SE)		-3.76 (1.6677)
	p-value for difference vs. placebo		0.0250[a]

CI, confidence interval; DAPA, dapagliflozin; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LOCF, last observation carried forward; MET, metformin; N, number of subjects in the full analysis set; PLA, placebo; SBP, systolic blood pressure; SE, standard error; SU, sulfonylurea.

[a] Significant p-value.

Efficacy based on the primary and key secondary outcome variables of the ST period

The primary objective was to compare the change from baseline in HbA1c after 24 weeks of double blind therapy, achieved with dapagliflozin 10 mg versus placebo.

The mean reduction in HbA1c from baseline to week 24 was statistically significantly greater in the dapagliflozin group (-0.86%) than in the placebo group (-0.17%). The placebo-adjusted HbA1c reduction of -0.69% in the dapagliflozin group was clinically relevant. Subgroup analyses suggested a potential treatment-by-baseline interaction for subgroups based on baseline HbA1c ($p = 0.0038$), with a larger HbA1c reduction in subjects with higher baseline HbA1c that was expected due to the mechanism of action of dapagliflozin. Furthermore, treatment-by-baseline interaction was also suggested for age subgroups ($p = 0.0154$) and subgroups based on region ($p = 0.0422$). In these subgroups, reduction in HbA1c appeared larger in younger subjects compared with older subjects and in subjects from North America compared to Europe.

In addition to the primary endpoint, all 4 key secondary endpoints were met in a clinically meaningful way.

The dapagliflozin group showed a statistically significant reduction in FPG change from baseline to week 24 (LOCF) vs. placebo of -33.45 mg/dL, a statistically significant reduction in body weight from baseline to week 24 (LOCF) vs. placebo of -2.07 kg, a statistically significant difference in the proportion of subjects with HbA1c <7% at week 24 (LOCF) vs. placebo of 20.7%, and the dapagliflozin group showed a statistically significant reduction in SBP from baseline vs. placebo at week 8 (LOCF) of -3.76 mmHg.

Summary of safety results

Numbers (%) of subjects with AEs and events of hypoglycemia during the ST period are summarized in Table S3.

Table S3 Summary of subjects with AEs and events of hypoglycemia during the ST period - including data after rescue - safety analysis set

	Number (%) of subjects	
	PLA + MET + SU N = 109	**DAPA 10 MG + MET + SU N = 109**
At least one AE	56 (51.4)	53 (48.6)
At least one event of hypoglycemia	4 (3.7)	14 (12.8)
Death	0	0
At least one SAE	6 (5.5)	1 (0.9)
AE leading to discontinuation[a]	3 (2.8)	2 (1.8)
SAE leading to discontinuation[a]	1 (0.9)	1 (0.9)
Hypoglycemia leading to discontinuation[a]	0	0
At least one event of genital infection	0	6 (5.5)
At least one event of urinary tract infection	7 (6.4)	7 (6.4)

AE, adverse event; DAPA, dapagliflozin; MET, metformin; N, number of subjects; PLA, placebo; SAE, serious adverse event; SU, sulfonylurea.
[a] Discontinuation of study medication.

Adverse events and events of hypoglycemia

The overall proportions of subjects with AEs, related AEs, and discontinuation of investigational product due to an AE were similar in both treatment groups. The proportion of subjects with serious AEs was higher in the placebo group. There was no death during the 24-week ST treatment period.

Hypoglycemic events were more common in the dapagliflozin group than in the placebo group. No major episodes and no discontinuations due to hypoglycemic events were reported.

In this study, the proportion of subjects who reported events of/events of urinary tract infection (UTI) in the dapagliflozin group was overall low and comparable to placebo. A comparison by gender showed that events of UTI were mainly reported by women. Events of genital infection were more common in the dapagliflozin group than in the placebo group. Events of genital infection were almost exclusively reported by women. All events of UTI and genital infection were of mild or moderate intensity.

One subject each in the dapagliflozin group (bladder neoplasm) and placebo group (renal cell carcinoma) experienced an AE of malignant and unspecified neoplasms.

AEs of renal impairment or failure, diagnosed based on laboratory results and not on clinical findings, were rare but slightly more common in the dapagliflozin group compared to the placebo group (2 vs. 0 subjects, respectively). No subjects were discontinued due to an AE of renal impairment or failure. For other AEs of special interest (such as events of volume depletion, AEs of fractures, or hepatic disorders), there was no increased risk associated with dapagliflozin therapy, compared to therapy with placebo.

Laboratory evaluation

No subject showed marked abnormalities (MAs) of increased hematocrit/hemoglobin. However, subjects in the dapagliflozin group showed slight mean increases in hemoglobin and hematocrit until week 24. In the placebo group, the 2 hematology parameters did not show any meaningful mean changes during the 24-week double-blind treatment period.

AEs of hepatic disorder were reported in 1 subject in the dapagliflozin group. One subject in the dapagliflozin group showed at least 1 MA of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin (TBL), namely a single value of TBL >2 × upper limit of normal (ULN). According to the Investigator, the increase occurred in connection to an event of heavy alcohol consumption reported by the subject. In no subject did ALT/AST values >3 × ULN in combination with TBL values >1.5 × ULN occur. Analysis of liver MAs, AEs, and mean changes from baseline in ALT, AST, ALP, and TBL did not suggest any signs of hepatic impairment in any treatment group.

No subject showed an MA of blood urea nitrogen (BUN). MAs of high serum creatinine were rare but more common in the dapagliflozin group than in the placebo group (4 vs. 2 subjects, respectively). Subjects in the dapagliflozin group showed a slight mean increase in BUN from baseline to week 24. In the placebo group, BUN did not show a meaningful mean change during the 24-week double-blind treatment period. Subjects in both treatment groups did not show a meaningful change in mean estimated glomerular filtration rate from baseline to week 24.

Few and similar proportions of MAs were reported for calcium, potassium, phosphorous, and magnesium. Subjects in the dapagliflozin group showed a slight increase in mean magnesium and a decrease in mean uric acid from baseline to week 24 during the ST period. No meaningful change was observed in the placebo group or for other electrolytes.

Vital signs

Subjects in the dapagliflozin group showed a small mean decrease in seated SBP and no relevant change in seated diastolic blood pressure (DBP) from baseline to week 24 compared to placebo. In the placebo group, no consistent mean change in either seated SBP or seated DBP was observed. Seated heart rate did not show a consistent mean change in either treatment group from baseline to week 24.

The proportion of subjects with measured orthostatic hypotension was balanced during the 24-week double-blind treatment period (11 vs. 14 subjects in the dapagliflozin and placebo group, respectively).