AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1692C00005
Edition Number	1
Date	20 October 2010

A multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 2 trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus who have inadequate glycemic control

Study dates: First subject enrolled: 17 August 2009
Last subject last visit: 8 May 2010

Phase of development: Therapeutic exploratory (II)

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

Study center(s)

During the study, 26 centers enrolled subjects and 26 centers randomised subjects in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	**Efficacy**
To compare the mean changes from baseline in glycosylated hemoglobin (HbA1c) achieved with each dose of dapagliflozin vs placebo after 12 weeks of double-blind therapy.	The primary efficacy endpoint was the change in HbA1c from baseline to Week 12 or the last post-baseline measurement prior to Week 12, if no Week 12 assessment was available. The term "change" here and hereafter refers to absolute change.	
Secondary	**Secondary**	**Efficacy**
To compare the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters: (a) Fasting plasma glucose (FPG) (b) Proportion of subjects achieving therapeutic glycemic response defined as HbA1c < 7%	(a) Change from baseline in FPG at Week 12. (b) Proportion of subjects achieving therapeutic glycemic response (HbA1c < 7.0%) at Week 12.	
Tertiary	**Tertiary**	**Efficacy**
1. To assess the differences of the change from baseline for each dose of dapagliflozin vs placebo after 12 weeks of oral administration of double-blind treatment for the following parameters: (a) Area under the curve (AUC) from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an oral glucose tolerance test (OGTT) (b) Fasting plasma insulin (c) Fasting plasma C-peptide (d) Beta-cell function (as measured by Homeostasis Model Assessment version 2 (HOMA2)) (e) Insulin resistance index (as measured by HOMA2)	1. (a) Change from baseline in AUC from 0 to 180 minutes for postprandial glucose, insulin, and C-peptide response to an OGTT at Week 12. (b) Change from baseline in fasting plasma insulin at Week 12. (c) Change from baseline in fasting plasma C-peptide at Week 12. (d) Change from baseline in beta-cell function (as measured by HOMA2) at Week 12. (e) Change from baseline in insulin resistance (as measured by HOMA2) at Week 12.	

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
2. To assess each dose of dapagliflozin and placebo after 12 weeks of oral administration of double-blind treatment for the following: (a) Changes from baseline in glucose, C-peptide, and insulin concentrations at 0, 30, 60, 120 and 180 minutes during an OGTT (b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide, and insulin concentrations (defined as the difference between 0 and 30, 60, 120 and 180 minute postprandial values) during an OGTT (c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide, and glucose during the OGTT (d) Change from baseline in body mass index (BMI), waist circumference, and total body weight (e) Percent change from baseline in fasting lipids (total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, (HDL-C), triglycerides (TG), and free fatty acids (FFA)) (f) Change from base line in 24-hour urinary glucose/creatinine ratio.	2. (a) Change from baseline in glucose, C-peptide and insulin concentrations at 0, 30, 60, 120, and 180 minutes postprandial values during an OGTT at Week 12. (b) Change from baseline in the respective excretion profiles for plasma glucose, C-peptide and insulin concentrations (defined as the difference between 0 and the 30, 60, 120, and 180 minutes postprandial values) during an OGTT at Week 12. (c) Change from baseline in the insulin sensitivity and beta-cell function derived from measurements of insulin, C-peptide and glucose during the OGTT at Week 12. (d) Change from baseline in BMI, waist circumference, and total body weight at Week 12. (e) Percent change from baseline in fasting lipids (Total-C, LDL-C, HDL-C, TG, and FFA) at Week 12. (f) Change from base line in 24-hour urinary glucose/creatinine ratio at Week 12.	
Safety To assess the safety and tolerability of each dose of dapagliflozin in reference to that of placebo.	**Safety** Adverse event (AE), Laboratory variables, Physical examination, ECG, Vital signs, Urinary and Genital infections, Hypoglycemic events, Hyperglycemic events	**Safety**
Exploratory To explore relationships between dapagliflozin plasma exposure measures and efficacy variables such as reduction in HbA1c from baseline. Pharmacokinetic (PK) results were documented in a separate population PK report.	**Exploratory**	**PK**

Study design

This was a Phase 2b, multicenter, randomized, 5-arm, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of dapagliflozin in Japanese subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control.

Target subject population and sample size

Japanese male and female subjects with T2DM aged 18 to ≤ 79 years, with inadequate glycemic control defined as HbA1c ≥ 7.0% and ≤ 10% on diet and exercise alone.

According to the original protocol, 55 subjects each in 5 groups (1, 2.5, 5, 10 mg or placebo group), i.e., in total 275 subjects were planned for randomisation.

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

Each dose was composed of 3 tablets. Investigational drug was taken once daily in the morning.

Treatment Phase (Period C)

1 mg dose: 1 mg 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

2.5 mg dose: 1 mg placebo 1 tablet + 2.5 mg 1 tablet + 10 mg placebo 1 tablet

5 mg dose: 1 mg placebo 1 tablet + 5 mg 1 tablet + 10 mg placebo 1 tablet

10 mg dose: 1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg 1 tablet

Comparator, dosage and mode of administration

Comparator dose was composed of 3 tablets. Investigational drug was taken once daily in the morning.

Placebo Lead-in Phase (Period B) and Treatment Phase (Period C)

Placebo dose: 1 mg placebo 1 tablet + 2.5 mg/5 mg placebo 1 tablet + 10 mg placebo 1 tablet

Duration of treatment

This study consisted of an enrolment visit, a 6-week wash-out phase (Period A), a 4-week single-blind, placebo lead-in phase (Period B), a 12-week double-blind, placebo-controlled treatment phase (Period C), and a 4-week follow-up phase (Period D).

Statistical methods

The primary efficacy analysis was based on the full analysis set, and the change from baseline in HbA1c at Week 12 was analysed based on an analysis of covariance (ANCOVA) model including treatment group as a fixed effect and baseline as a covariate. Based on the ANCOVA model, the point estimates and 2-sided 95% confidence intervals for the mean changes within each treatment group as well as for the differences in mean changes between each of dapagliflozin treatment group and the placebo treatment group were calculated. Pair-wise comparisons of dapagliflozin treatment groups vs. placebo group were made with multiplicity of tests adjusted by Dunnett's method at overall 2-sided significance level 0.05.

The change from baseline at Week 12 in FPG, 180 minutes AUC on postprandial glucose, insulin and C-peptide response to OGTT, fasting plasma insulin, fasting plasma C-peptide, beta-cell function (using HOMA2), and insulin resistance index (using HOMA2) were also analysed based on the similar ANCOVA model as in the primary efficacy analysis for HbA1c.

All efficacy and safety variables were summarised descriptively by treatment group.

Subject population

A total of 417 Japanese subjects with T2DM were enrolled into the enrolment period with 90 subjects (21.58%) out of them not completing the enrolment period (including the washout period) and 138 subjects (33.09%) discontinued prior to randomisation. The most common reason for discontinuation during the enrolment and the lead-in periods was the incorrect enrolment (119 subjects). Out of the 279 subjects who were randomised, 7.5% were prematurely discontinued. The most common reason for not completing the double-blind period was subject no longer meets study criteria (3.2%); the second most common reason was subject withdrew consent (1.8%). There was one death reported due to multi-organ failure after sepsis in the dapagliflozin 1 mg group during the follow-up period.

All randomised subjects were included in the full analysis set (FAS) and safety analysis set. Only one subject in the dapagliflozin 1 mg group was excluded from the per protocol analysis set because of a relevant protocol deviation.

All subjects were Japanese and the mean age was 57.3 years and most subjects (74.6%) were less than 65 years of age. A total of 215 subjects (77.1%) were male and there were differences in gender across the treatment groups: the proportion of female subjects was highest in the dapagliflozin 2.5 mg group (30.4%) and lowest in the dapagliflozin 5 mg group (19.0%). Around half of the subjects had a BMI <25. The mean duration of T2DM at baseline was 4.83 years: the proportion of subjects suffering from T2DM for <3 years was 39.8% and that for 3 to 10 years was 48.0%. The mean baseline HbA1c was 8.07%: the proportion of subjects who had a baseline HbA1c values <8% was 49.1% and that of subjects who had a baseline HbA1c values in 8 to 9% was 39.1%. Baseline mean FPG was comparable across the treatment groups (range: 158.94 to 164.49 mg/dL).

The overall demographic and baseline characteristics of the subjects in this study were representative of Japanese T2DM populations of interest except for the higher proportion of male compared with that in Japanese T2DM population. Subject disposition, protocol deviations, demographic and baseline characteristics as well as the use of concomitant medication and treatment compliance showed that the treatment groups were generally well balanced.

Summary of efficacy results

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

Table S2 Primary and Key Secondary Efficacy Endpoints (LOCF) (FAS)

	PLA N=54	DAPA 1 MG N=59	DAPA 2.5 MG N=56	DAPA 5 MG N=58	DAPA 10 MG N=52
Primary efficacy endpoint					
HbA1c (%) at Week 12 (LOCF)					
Adjusted mean change from baseline (SE)	0.35 (0.0719)	-0.12 (0.0675)	-0.10 (0.0708)	-0.37 (0.0681)	-0.44 (0.0721)
P-value vs. PLA (*)		<.0001 *	<.0001 *	<.0001 *	<.0001 *
Key secondary efficacy endpoints					
FPG (mg/dL) at Week 12 (LOCF)					
Adjusted mean change from baseline (SE)	9.45 (3.3656)	-16.63 (3.3631)	-19.97 (3.2992)	-23.49 (3.3325)	-31.92 (3.4694)
P-value vs. PLA (*)		<.0001 *	<.0001 *	<.0001 *	<.0001 *
The proportion of subjects achieving glycemic response (defined as HbA1c <7% at 12 weeks, LOCF)					
Percent	1.9%	1.7%	9.3%	5.2%	9.6%
P-value vs. PLA (*)		1.0000	0.2057	0.6203	0.2050

(*) Significant p-value: Primary endpoint is tested at alpha=0.015 applying Dunnett adjustment

Statistically significant greater mean reductions in HbA1c from baseline to Week 12 (LOCF) were achieved in all dapagliflozin groups compared with the placebo group ($p < 0.0001$ for each dapagliflozin group versus the placebo group). Clinically relevant effect on HbA1c (>0.5% placebo corrected reduction) was seen in the dapagliflozin 5 and 10 mg groups.

Statistically significant greater mean reductions in FPG from baseline to Week 12 (LOCF) were achieved in all dapagliflozin groups compared with the placebo group ($p < 0.0001$ for each dapagliflozin group versus the placebo group). An apparent dose dependent mean decrease in FPG from baseline to Week 12 (LOCF) was observed.

No statistically significant difference in the proportion of subjects achieving therapeutic glycemic response (defined as HbA1c<7% at Week 12 regardless of baseline HbA1c value) was observed between the placebo and dapagliflozin groups.

A mean reduction in postprandial glucose AUC from baseline to Week 12 was observed in all dapagliflozin groups compared with the placebo group. A mean reductions in body weight from baseline to Week 12 was observed in all dapagliflozin groups compared with the placebo group. An increase in 24-hour urinary glucose-creatinine ratio from baseline to Week 12 was observed in all dapagliflozin groups compared with the placebo group. The mean change in this parameter was generally dose dependent.

Summary of safety results

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

Table S3 Overall Adverse Events Summary - Double-blind Treatment Period (Safety Analysis Set)

	PLA N = 54	DAPA 1 MG N = 59	DAPA 2.5 MG N = 56	DAPA 5 MG N = 58	DAPA 10 MG N = 52
At least one AE	21 (38.9)	24 (40.7)	26 (46.4)	24 (41.4)	28 (53.8)
At least one hypoglycemia	1 (1.9)	0	1 (1.8)	0	1 (1.9)
At least one AE or hypoglycemia	22 (40.7)	24 (40.7)	26 (46.4)	24 (41.4)	28 (53.8)
At least one related AE	1 (1.9)	2 (3.4)	1 (1.8)	0	3 (5.8)
Deaths	0	1 (1.7)	0	0	0
At least one SAE	0	2 (3.4)	1 (1.8)	2 (3.4)	1 (1.9)
At least one related SAE	0	0	0	0	0
SAE leading to discontinuation *	0	0	1 (1.8)	1 (1.7)	0
AE leading to discontinuation *	0	1 (1.7)	1 (1.8)	1 (1.7)	0
Hypoglycemia leading to discontinuation *	0	0	0	0	0

* of study treatment

The proportion of subjects experiencing any AE was higher in the dapagliflozin 10 mg group but similar across the other treatment groups. There were few SAEs and DAEs in the dapagliflozin groups, none in the placebo group. Higher proportions of subjects in the dapagliflozin groups than in the placebo group had reported AEs considered related to study drug by the investigator. The majority of AEs were mild or moderate in intensity.

There was one death reported due to multi-organ failure after sepsis in the dapagliflozin 1 mg group during the follow-up period.

Only 3 hypoglycemic events were reported (1 subject in the placebo, dapagliflozin 2.5 mg and 10 mg group each). There was no major episode of hypoglycemia reported in this study. No subject discontinued study drug due to a hypoglycemic event.

Only 2 and 5 subjects reported signs, symptoms and other reports suggestive of genital infection or urinary tract infection (UTI), respectively in the dapagliflozin and placebo groups. No kidney infections were reported. Two subjects (1 subject in the dapagliflozin 1 mg and 5 mg group each) reported fracture. Both events were traumatic and not related to dapagliflozin as judged by the investigator. No AEs of hypotension, dehydration, hypovolemia, renal impairment, failure or urinary stones were reported.

Five subjects in the dapagliflozin and no subject in the placebo group showed a marked

abnormality of hematocrit >55%. The marked abnormalities of hematocrit were not associated with any thromboembolic events. There was a small mean increase in hematocrit over the 12-week double-blind treatment period in the dapagliflozin groups. The mean change in hematocrit from baseline at the end of follow-up period was minimal in all treatment groups. In the placebo group, no meaningful mean changes were observed in hematocrit during the 12-week double-blind period.

Eight subjects in the dapagliflozin and 1 subject in the placebo group showed a marked abnormality of hemoglobin >18 g/dL. The marked abnormalities of hemoglobin were not associated with any thromboembolic events. There was a small mean increase in hemoglobin over the 12-week double-blind period in the dapagliflozin groups. The mean change in hemoglobin from baseline at the end of follow-up period was minimal in all treatment groups. In the placebo group, no meaningful mean changes were observed in hemoglobin during the double-blind period.

Overall, in hepatic parameters there were no signs of hepatic impairment associated with dapagliflozin treatment. No subject had a marked abnormality for ALT or AST that was >3 x upper limit of normal (ULN). One subject in the dapagliflozin 1 mg and 2.5 mg group each experienced a marked abnormality of total bilirubin.

There were no clinically relevant mean changes in serum creatinine levels in the dapagliflozin groups when compared to the placebo group. Mean changes and shifts of the urine albumin to creatinine ratios did not indicate any meaningful effect of dapagliflozin on progression of diabetic nephropathy.

No clinically significant mean changes were observed in serum electrolytes in the dapagliflozin groups, compared to placebo. Greater mean increases from baseline were observed in magnesium and inorganic phosphorus in the dapagliflozin groups compared with the placebo group, but the mean changes were small and not clinically significant. Greater mean decrease from baseline were observed in serum uric acid in the dapagliflozin groups compared with the placebo group. The mean changes in magnesium, inorganic phosphorus and serum uric acid from baseline at the end of follow-up period were minimal in all treatment groups. No subjects in any of the treatment groups showed a marked abnormality regarding serum electrolytes except for potassium and inorganic phosphorus during the 12-week double-blind treatment period.

Two subjects in the placebo group and 1 subject in the dapagliflozin 10 mg group had a marked abnormality of creatine kinase (CK) >5 x ULN without any associated AE. There were no clinically meaningful median changes in CK during the 12 week double-blind treatment period in any of the treatment groups

Small mean decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in all dapagliflozin groups compared to placebo. These mean decreases were more pronounced for SBP than for DBP. The mean changes in SBP and DBP from baseline at the end of follow-up period were minimal in all treatment groups. No increases in ratio of orthostatic blood pressure were observed during treatment with dapagliflozin.