AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | Dapagliflozin |
| Study Code | D1692C00006 |
| Edition Number | 1 |

Clin.Trials.gov Id. NCT01294423

# A 24-week randomised, double-blind, parallel-group, multi-centre, placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with Type 2 diabetes who have inadequate glycemic control with diet and exercise

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| **Study dates:** | First subject enrolled: 25 February 2011<br>Last subject last visit: 12 March 2012 |
| **Phase of development:** | Therapeutic confirmatory (III) |

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

### Study center(s)

Study D1692C00006 was conducted at 30 centers in Japan (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 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Efficacy | To compare the change from baseline in HbA1c achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment | Change in HbA1c from baseline to week 24 (LOCF) |
| Key secondary | Efficacy | To compare the change from baseline in FPG achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment | Change in FPG from baseline to week 24 (LOCF) |
| Key secondary | Efficacy | To compare the change from baseline in total body weight achieved with each dose of dapagliflozin versus placebo after 24 weeks double-blind treatment | Change in total body weight from baseline to week 24 (LOCF) |

HbA1c glycosilated hemoglobin, LOCF last observation carried forward, FPG fasting plasma glucose

### Study design

This was a 24-week randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multi-center, Phase III study to evaluate the efficacy and safety of dapagliflozin as monotherapy in Japanese subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control with diet and exercise.

### Target subject population and sample size

Subjects who had inadequate glycemic control (HbA1c $\geq$6.5% but $\leq$10%) on diet and exercise alone at Visit 5 (1 week before randomization) were eligible to be randomized at Visit 6. The subjects who received ongoing medical treatment for diabetes within 6 weeks of enrollment needed a 6-week Wash-out Period before a 4-week Placebo Lead-in Period.

In order to detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in HbA1c from baseline to week 24, assuming a standard deviation (SD) = 0.9%, and at a 2-sided significance level of 0.027, 80 evaluable subjects were needed in each treatment group to provide 90% power. The assumed SD = 0.9% was considered to be appropriate based on the Japanese Phase IIb study and global monotherapy Phase III study results where SD was approximately 0.52% and 0.91%, respectively. Assuming that approximately 5% of the subjects did not have a post-baseline efficacy measurement, 85 subjects per treatment group (255 subjects total) were planned for randomization.

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

Eligible subjects received dapagliflozin 5 mg, 10 mg, or placebo according to their randomization at Visit 6 during the 24-week Treatment Period.

**Duration of treatment**

According to the protocol, subjects were to be treated with study medication for 24 weeks.

**Statistical methods**

The primary outcome variable, change from baseline to week 24 in HbA1c, was analyzed by an analysis of covariance (ANCOVA) model, which included treatment group and gender as fixed effects and baseline HbA1c as covariate. The ANCOVA model was used to derive a least squares estimate of the treatment difference with 95% confidence interval and corresponding 2-sided p-value.

For the primary variable, the change from baseline in HbA1c to week 24 (last observation carried forward [LOCF]), each pair-wise treatment group comparison was tested at a significance level of approximately 0.027, according to Dunnett's method, in order to maintain an overall type I error rate <0.050 for the primary objective.

A hierarchical closed testing procedure was used to control the type I error rate across the primary and key secondary objectives within each dapagliflozin treatment group. Key secondary objectives were to compare the effects of each dose of dapagliflozin with placebo after a 24-week double-blind Treatment Period by evaluation of:

(1) The change from baseline in fasting plasma glucose (FPG) at week 24 (LOCF)

(2) The change from baseline in total body weight at week 24 (LOCF)

The statistical testing of the primary and key secondary efficacy endpoints proceeded in a sequential manner, to control the type I error rate within each dapagliflozin group at the 0.05 level. Specifically, the significance or non-significance of the treatment comparisons for the primary efficacy endpoint determined which, if any, statistical inferences were made for the key secondary efficacy endpoints. Only those dapagliflozin groups significantly superior to placebo for the primary efficacy endpoint had statistical inference compared with placebo for the first key secondary endpoint, (1). Then, the testing for the other key secondary

efficacy endpoints proceeded so that the significance or non-significance of the treatment comparisons for (1) determined which, if any, statistical inferences were made in treatment comparisons for (2). If a result for one of the dapagliflozin treatment groups was not significant, statistical inference ended at that endpoint, and no statistical inference was applied to the subsequent key secondary endpoints for that treatment group.

If at least one of the primary comparisons between a dapagliflozin treatment group and the placebo treatment group was significant at the 0.027 level for the primary endpoint, all statistical tests for the 2 key secondary efficacy endpoints were performed and nominal p-values were reported. However, in order to protect the global type I error rate of the hierarchical testing procedure, the interpretation of the statistical significance of treatment comparisons for each key secondary efficacy endpoint was done using the step-wise procedure at the 0.05 level described above.

Other secondary outcome variables and exploratory outcome variables had to provide supportive efficacy and safety information regarding the differences between the treatment groups. For other secondary efficacy variables, supportive statistical analyses were performed with nominal p-values reported. 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 gender and 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, 354 subjects were enrolled, 286 subjects entered the Lead-in Period, thereafter 251 subjects skipped the Wash-out Period and 35 subjects underwent the Wash-out Period. In total, 261 subjects were randomized. The most common reasons for not being randomized were incorrect enrollment (ie, the subject did not meet all inclusion and exclusion criteria) (68 subjects) and withdrawal of consent (16 subjects). In total 5 subjects in 1 study center were not randomized due to safety concerns of the investigator.

In general, all treatment groups showed similar baseline characteristics and were representative for the intended Japanese study population. The average age was 59 years. The proportion of male and female subjects was similar in all treatment groups: around 59% male and 41% female subjects. Mean duration of T2DM was relatively short (around 5 years). The mean baseline HbA1c of 7.5% indicated a relatively good control of diabetes. Mean FPG was 138.6 mg/dL at baseline. Mean weight was around 67 kg, and approximately 15% of subjects were obese (BMI $\geq$30 kg/m$^2$).

**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 N = 87 | DAPA 5MG N = 86 | DAPA 10MG N = 88 |
|---|---|---|---|
| **Primary endpoint** | | | |
| HbA1c (%) at week 24 (LOCF) | | | |
| Adjusted mean change from baseline (SE) | -0.06 (0.0607) | -0.41 (0.0606) | -0.45 (0.0605) |
| p-value vs. PLA | | <.0001 * | <.0001 * |
| **Key secondary endpoints** | | | |
| Fasting plasma glucose (mg/dL) at week 24 (LOCF) | | | |
| Adjusted mean change from baseline (SE) | 5.8 (2.167) | -8.6 (2.191) | -13.7 (2.154) |
| p-value vs. PLA | | <.0001 * | <.0001 * |
| Total body weight (kg) ) at week 24 (LOCF) | | | |
| Adjusted mean change from baseline (SE) | -0.84 (0.2636) | -2.13 (0.2655) | -2.22 (0.2598) |
| p-value vs. PLA | | 0.0003 * | 0.0001 * |

DAPA: dapagliflozin; HbA1c: glycosilated hemoglobin, LOCF: last observation carried forward; PLA: placebo; SE: standard error

- Significant p-value: primary endpoint was tested at $\alpha = 0.027$, and secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$.

Primary endpoint

Subjects in both dapagliflozin groups showed a statistically significant mean reduction in HbA1c from baseline to week 24 (LOCF) compared to placebo.

Key secondary endpoints

Since the test of the primary endpoints yielded a significant result, the secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$ (2-sided).

Subjects in both dapagliflozin groups showed a statistically significant mean reduction in FPG from baseline to week 24 (LOCF) compared to placebo.

Subjects in both dapagliflozin groups showed a statistically significant mean reduction in total body weight from baseline to week 24 (LOCF) compared to placebo.

**Summary of safety results**

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

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

| | PLA N = 87 | DAPA 5MG N = 86 | DAPA 10MG N = 88 |
|---|---|---|---|
| At least one AE | 45 (51.7) | 41 (47.7) | 57 (64.8) |
| At least one event of hypoglycemia | 0 | 0 | 2 (2.3) |
| Death | 0 | 0 | 0 |
| At least one SAE | 1 (1.1) | 0 | 1 (1.1) |
| AE leading to discontinuation[a] | 5 (5.7) | 3 (3.5) | 7 (8.0) |
| SAE leading to discontinuation[a] | 1 (1.1) | 0 | 0 |
| Hypoglyc. leading to discontinuation[a] | 0 | 0 | 0 |
| At least one AE of genital infection | 0 | 1 (1.2) | 1 (1.1) |
| At least one AE of urinary tract infection | 2 (2.3) | 0 | 2 (2.3) |

AE: adverse event; DAPA: dapagliflozin; PLA: placebo; SAE: serious adverse event
[a] of study medication

Adverse events and events of hypoglycemia

The proportion of subjects with overall AEs was higher in the dapagliflozin 10 mg group (64.8%) compared to the dapagliflozin 5 mg group (47.7%) and the placebo group (51.7%). A major contribution to this difference were preferred terms (PTs) more common in the dapagliflozin 10 mg group than in the other groups that were not related to dapagliflozin treatment and included mainly nasopharyngitis (15 subjects) and dental caries (4 subjects), whereas common PTs that were assessed as related in the dapagliflozin 10 mg group and less frequent in the other treatment groups included noticeably smaller numbers (pollakiuria: 4 subjects; thirst: 2 subjects; polyuria: 1 subject; and renal failure: 1 subject).

There were no events of major or minor hypoglycemia in this study. There were 2 events of other hypoglycemia in dapagliflozin 10 mg treatment group. No event of hypoglycemia led to discontinuation.

There were no deaths.

There was 1 serious adverse event (SAE) in the dapagliflozin 10 mg group and 1 SAE in the placebo group.

Slightly more subjects in the dapagliflozin 10 mg (8.0%) compared to the dapagliflozin 5 mg group (3.5%) and placebo group (5.7%) experienced an AE leading to discontinuation from study medication.

The incidence rate amounted to 184.1, 248.1 and 214.1 events count*100/person years of exposure in the dapagliflozin 5 mg, 10 mg, and placebo group.

Genital and urinary tract infections were rare and evenly distributed across all treatment groups, including placebo. No kidney infections were reported.

Proportions of subjects reporting AEs of renal impairment or failure were rare but slightly more common in the dapagliflozin 10 mg group compared to the dapagliflozin 5 mg and placebo groups. In all subjects discontinued due to an AE of renal impairment or failure, the AE was assessed as resolved.

There was 1 AE of fracture each in the placebo and dapagliflozin 5 mg groups and 2 AEs of fracture in the dapagliflozin 10 mg group.

Laboratory evaluation

One subject in the dapagliflozin 5 mg group showed marked abnormalities (MAs) of increased hematocrit/hemoglobin, and no associated thromboembolic AE was reported. Furthermore, subjects in the dapagliflozin groups showed slight mean increases in hemoglobin and hematocrit until week 24, which were reversible at follow-up. In the placebo group, no MAs of hematocrit and hemoglobin were observed, and the 2 hematology parameters did not show any meaningful mean changes during the 24-week double-blind treatment period.

Analysis of liver MAs, AEs, and mean changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL) did not suggest any signs of hepatic impairment in any treatment group. AEs of hepatic disorder were reported in 1 subject each in the dapagliflozin 5 mg and 10 mg groups. One subject in the dapagliflozin 5 mg group and 2 subjects each in the dapagliflozin 10 mg and placebo groups showed at least 1 MA of ALT, AST, ALP, or TBL. One subject each in the dapagliflozin 10 mg and placebo groups showed a single value of TBL >1.5 x ULN. In no subject did ALT/AST values >3 x ULN in combination with TBL values >1.5 x ULN occur.

No subject showed an MA of BUN or serum creatinine. Subjects in the dapagliflozin groups showed a slight mean increase in BUN from baseline to week 24 that was reversible at follow-up. In the placebo group, BUN did not show a meaningful mean change during the 24-week double-blind treatment period. Subjects in any treatment group did not show a meaningful change in mean estimated glomerular filtration rate (eGFR) from baseline to week 24. Overall, there were no clinically meaningful signs of worsening of renal function.

Few subjects showed at least 1 MA of serum electrolytes including inorganic phosphorus. One subject each in the dapagliflozin 10 mg group showed at least 1 measurement of serum potassium ≥6.0 meq/L and of serum sodium <130 meq/L. Both MAs of electrolytes did not have any associated AEs. Subjects in both dapagliflozin groups showed a slight increase in mean magnesium from baseline to week 24 that was reversible at follow-up. In the placebo group no meaningful change in any serum electrolyte was observed from baseline to week 24.

Vital signs

Subjects in both dapagliflozin groups showed a slight mean decrease in seated systolic blood pressure (SBP) and no meaningful mean change in seated diastolic blood pressure (DBP) from baseline to week 24 compared to placebo. The change in SBP was reversible at follow-up. In the placebo group, a small mean decrease was observed in seated SBP and seated DBP. Seated heart rate did not show a meaningful mean change from baseline to week 24 in any treatment group.

Overall, the proportion of subjects with measurements of orthostatic hypotension during the 24-week double-blind treatment period was slightly larger in the dapagliflozin 5 mg (20.9%) and 10 mg groups (17.0%) than in the placebo group (14.0%).