AstraZeneca

**50-week Clinical Study Report Synopsis**

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| Drug Substance | Dapagliflozin |
| Study Code | D1690C00012 |
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# A 24-week, Multi-centre, International, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study with a 78-week Extension Period to Evaluate the Effect of Dapagliflozin in Combination with Metformin on Body Weight in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Metformin Alone

## Report for the first 50 weeks of treatment

***This synopsis is revised based on the CSR Errata list dated 7 August 2012. The revision was done due to minor corrections in Summary of efficacy results.***

**Study dates:**

First subject enrolled: *13 February 2009*
Last subject last visit for the 50-week period: *02 December 2010*

**Phase of development:**

Therapeutic exploratory (III)

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

## Study center(s)

Study D1690C00012 was conducted at 40 centers in 5 countries. (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 combined 50-week treatment period (24-week short-term treatment period + the first 26 weeks of treatment in the 78-week extension period) are presented in Table S1. In the following, the 24-week short-term treatment period will be referred to as the short-term (ST) period, the first 26 weeks of the 78-week extension period will be referred to as long-term 1 (LT1) period, and the combined periods will be referred to as ST + LT1 period.

**Table S1 Objectives and outcome variables**

| Objectives | Outcome variables* |
|---|---|
| **Objectives as defined in the original Clinical Study Protocol (CSP)** | |
| **Safety** | |
| To assess the effect of dapagliflozin 10 mg daily in combination with metformin compared to placebo in combination with metformin after 50 weeks of double-blind treatment on: | |
| • Bone mineral density (BMD) at lumbar spine (L1-4), femoral neck and total hip as measured by dual energy x-ray absorptiometry (DXA), | Percent change in bone mineral density at lumbar spine (L1-4) from baseline to week 50.<br>Percent change in bone mineral density at femoral neck from baseline to week 50.<br>Percent change in bone mineral density at total hip from baseline to week 50. |
| • Biochemical markers of bone formation and bone resorption. | Change in biochemical markers of bone formation and resorption from baseline to week 50. |
| **Objectives introduced with Amendment 2 to the CSP** | |
| **Safety** | |
| To evaluate the safety and tolerability by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure, hypoglycemic events, calculated creatinine clearance and physical examination findings (eg, edema) after 50 weeks of double-blind treatment. | Aes, laboratory values, ECG, pulse, blood pressure, hypoglycemic events, calculated creatinine clearance, and physical examination findings from baseline to week 50. |

| Objectives | Outcome variables* |
|---|---|
| **Efficacy** | |
| To assess the same objectives as for the 24-week short-term treatment period after 50 weeks of double-blind treatment (if 50-week data are available). | Change in body weight from baseline to week 50.<br>Change in waist circumference from baseline to week 50.<br>Proportion of subjects with body weight decrease ≥5% from baseline to week 50. |

* Referring to efficacy, only outcome variables are mentioned that correspond to the primary or key secondary outcome variables of the ST period. 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.

## Study design

This was an international, multi-center, randomized, double-blind, placebo-controlled, parallel-group, Phase III study with a 24-week short-term treatment period followed by a 78-week extension period to evaluate the effect of dapagliflozin 10 mg in combination with metformin on body weight in adult subjects with Type 2 diabetes mellitus (T2DM) who have inadequate glycemic control (HbA1c ≥6.5% and ≤8.5%) on metformin therapy alone. In a sub-population, the effect of dapagliflozin in combination with metformin on visceral adipose tissue volume and percent hepatic lipid content was evaluated using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy. Note that this synopsis includes only results from the ST + LT1 period.

### Target subject population and sample size

The study entry criteria specified enrollment of male subjects ≥30 and ≤75 years of age and female subjects ≥55 and ≤75 years of age, diagnosed with T2DM and treated with metformin monotherapy on a stable dose of ≥1500 mg/day for at least 12 weeks prior to enrollment. The subjects had to show inadequate glycemic control, defined as HbA1c ≥6.5% and ≤8.5%, a body mass index (BMI) ≥25 kg/m$^2$, and a body weight ≤120 kg. Female subjects had to be post menopausal (or have had hysterectomy) for a period of at least 5 years at the time of consenting. At the start of the placebo lead-in period and at randomization, male and female subjects had to show a fasting plasma glucose (FPG) level ≤13.2 mmol/L (≤240 mg/dL) to be eligible for the study.

Neither gender should exceed 60% of the total number of randomized subjects. Therefore, randomization was stratified by gender.

A difference of 2% for percent change in BMD at week 50 was selected as a clinically relevant difference for this endpoint. Assuming a standard deviation of 3.2% (AstraZeneca clinical study report: 08-CR-3039), 55 evaluable subjects per treatment group were required to detect a 2% difference between treatment groups with 90% power for a two-sided test with a 0.050 significance level. An exclusion rate of 20% was estimated for BMD endpoints, due to potential difficulties in collecting and reading DXA scans. Given the planned sample size for this study based on considerations for the primary efficacy endpoint (see the CSP), the anticipated number of evaluable subjects for this endpoint was 73 subjects per group. This

number would provide 96% power to detect a 2% difference in BMD, and would provide a 95% CI for the difference with a width of approximately ±1.0% from the point estimate.

Separate sample size calculations were performed for the primary efficacy endpoint (change in body weight from baseline to week 24) and the MR sub-study (see the CSP).

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

Subjects administered dapagliflozin 10 mg or matching placebo according to their assignment to treatment groups as add-on therapy to metformin during the ST + LT1 period. Dapagliflozin or matching placebo was to be taken orally once daily in the morning, as instructed by the investigator, immediately before or together with a meal. Dapagliflozin or matching placebo was to be taken at approximately the same time of the day during the study 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 to the CSR.

Subjects in both treatment groups received open-label metformin at a dose of 1500, 2000 or 2500 mg/day during the ST + LT1 period, based on his/her metformin dose during the last 12 weeks prior to enrollment. Metformin was to be taken orally just before or together with a meal according to the investigator's instruction. For metformin a commercially available product was used manufactured by MerckSantee.

**Duration of treatment**

According to the original CSP, subjects were to be treated with study medication for 102 weeks (24-week short-term treatment period + 78-week long-term extension period). Note that this synopsis includes only results from the 24-week short-term treatment period + the first 26 weeks of treatment in the 78-week extension period referred to as ST + LT1 period.

**Statistical methods**

Statistical analyses were performed for the ST + LT1 period. The safety analyses were focused on BMD and biochemical markers of bone formation and resorption and primarily performed on the safety set using non-missing measurements at week 50 only. As a sensitivity analysis, the analysis was repeated using a last observation carried forward (LOCF) approach where the last measurement available between week 12 and week 50 was used for analysis, if no data was available at 50 weeks. BMD and bone markers were analyzed using an analysis of covariance model (ANCOVA) with treatment group and gender as fixed effects and baseline value as a covariate. The model was used to derive a least squares estimate of the treatment difference in mean (percent) change with corresponding p-value and two-sided 95% confidence interval (CI). Further, two-sided 95% Cis for the mean (percent) change within each treatment group were calculated. The safety analysis set was also used in all summaries of safety data.

All long-term efficacy analyses were considered exploratory. In general, the LOCF 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 and gender as well as the continuous fixed covariates of baseline value and baseline value-by-week interaction. Rescue was added as an additional effect in the model for analyses including rescued subjects. The model provided least squares estimates, standard errors and two-sided 95% Cis for mean change from baseline to all post-baseline time points within treatment groups and for differences between the dapagliflozin treatment group vs. 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 and gender was used to analyze proportions. Efficacy was evaluated using the full analysis set. Change in HbA1c from week 24 over time to week 50 and proportion of subjects achieving a therapeutic glycemic response defined as HbA1c <7% at week 50 were analyzed for the short-term completers analysis set.

**Subject population**

In total, 314 subjects were enrolled out of which 182 were randomized. All randomized subjects received at least one dose of study medication and were included in the safety analysis set. The full analysis set included 180 subjects. Based on the safety analysis set, 92.9% of the subjects completed the ST period and continued into the LT1 period, and 90.7% of the subjects completed the LT1 period and continued into the LT2 period. The most common reason for not completing the ST and the LT1 period was withdrawal of consent (n = 5 and n = 2, respectively). During the ST period, 2 subjects were withdrawn from the study due to adverse events and one subject died. One subject was withdrawn from the study due to an adverse event during the LT1 period.

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 70% aged below 65 years. There were around 55% male and 45% female subjects in both treatment groups. All subjects were White and of non-Hispanic/Latino ethnicity. Mean duration of T2DM was 5.77 years with 16.7% of the subjects suffering from T2DM over 10 years. At baseline, mean HbA1c was around 7.2%, and around 7% of the subjects had a baseline HbA1c ≥8%. Mean total body weight at baseline amounted to around 91.5 kg. The subjects had a mean BMI of around 32 $kg/m^2$ with almost all subjects being overweight (BMI ≥25 $kg/m^2$), and two-thirds of the subjects being obese (BMI ≥30 $kg/m^2$).

**Summary of efficacy results**

Efficacy endpoint of the ST + LT1 period are summarized in Table S2.

**Table S2 Summary of efficacy endpoints, including data after rescue (full analysis set)**

| | PLA + MET N = 91 | DAPA 10MG + MET N = 89 |
|---|---|---|
| Total body weight (kg) at week 50 | | |
| Adjusted mean change from baseline (SE) | -2.03 (0.4461) | -4.39 (0.4663) |
| Waist circumference (cm) at week 50 | | |
| Adjusted mean change from baseline (SE) | -3.0 (0.773) | -5.0 (0.815) |
| Subjects with body weight decrease of at least 5% at week 50 | | |
| Percent adjusted (SE) | 14.0% **(3.633)** | **38.7% (5.116)** |

Only efficacy endpoints are mentioned that correspond to the primary or key secondary efficacy endpoints of the short-term period referring to the parameter investigated. For other efficacy endpoints see the CSR. Results of other efficacy endpoints are not included in this Synopsis, but can be found in the CSR.

Subjects in both treatment groups showed a further mean decrease in total body weight and waist circumference from week 24 to week 50. The mean decrease in total body weight and waist circumference from week 24 to week 50 was slightly larger in the dapagliflozin than in the placebo group.

The proportion of subjects with a decrease in total body weight of at least 5% increased in both treatment groups from week 24 to week 50. At week 50, **38.7%** of the subjects in the dapagliflozin group and 14.0% in the placebo group had lost at least 5% of their initial body weight.

Body fat mass was not determined at week 50.

**Summary of safety results**

Bone mineral density

There was no change in BMD at lumbar spine (L1-4), femoral neck, and total hip in both treatment groups at week 50 (adjusted mean percent change from baseline in all anatomical regions: <0.5%).

Seven subjects in the dapagliflozin and 4 subjects in the placebo group showed a decrease in BMD ≥5% from baseline to week 50.

Biochemical markers of bone formation and bone resorption

Subjects in the dapagliflozin group did not show a meaningful change in bone formation markers at week 50 (adjusted mean change from baseline in osteocalcin: -0.61 ng/mL, bone-specific alkaline phosphatase: -0.78 U/L, and procollagen type-1 N-terminal propeptide: -1.11 µg/L), while in the placebo group a decrease of all bone formation markers was observed. The difference in the mean change of osteocalcin between dapagliflozin and placebo was statistically relevant (nominal $p<0.05$).

Subjects in the dapagliflozin group showed an increase in C-terminal cross-linking telopeptides of type I collagen in serum (adjusted mean change from baseline: 0.04 ng/mL) and a decrease in N-terminal cross-linking telopeptides of type I collagen in urine (adjusted mean change from baseline: -41.7 nmol BCE) at week 50. Subjects in the placebo group showed changes in the same direction but of smaller magnitude compared to subjects in the dapagliflozin group. The changes in the dapagliflozin group were not statistically relevant compared to the changes in the placebo group.

Fractures

No AEs of bone fractures were noted in either treatment group.

Adverse events and events of hypoglycemia

Numbers (%) of subjects with AEs and events of hypoglycemia during the ST + LT1 period are summarized by categories of AEs in Table S3.

**Table S3 Summary of subjects with adverse events, including data after rescue (safety analysis set)**

| | **PLA + MET N = 91** | **DAPA 10MG + MET N = 91** |
|---|---|---|
| At least one AE | 51 (56.0) | 53 (58.2) |
| At least one event of hypoglycemia | 3 (3.3) | 4 (4.4) |
| Death | 0 | 1 (1.1)** |
| At least one SAE | 8 (8.8) | 11 (12.1) |
| AE leading to discontinuation* | 2 (2.2) | 6 (6.6) |
| SAE leading to discontinuation* | 0 | 2 (2.2) |
| Hypoglyc. leading to discontinuation* | 0 | 0 |
| At least one event suggestive of genital infection | 1 (1.1) | 3 (3.3) |
| At least one event suggestive of urinary tract infection | 4 (4.4) | 6 (6.6) |

* of study medication; ** the subject died during hospitalization for pneumonia due to a sudden, massive oral gastrointestinal bleeding.

Proportions of subjects with at least one AE were similar in the dapagliflozin (58.2%) and placebo group (56.0%). A higher proportion of subjects in the dapagliflozin group compared to placebo experienced at least one SAE (12.1% vs. 8.8%) or was discontinued from study medication due to an AE (6.6% vs. 2.2%), however, the total number of subjects with an SAE or discontinued from study medication due to an AE was small. One subject in the dapagliflozin group died during hospitalization for pneumonia due to a sudden, massive gastrointestinal bleeding on Study Day 68.

Four subjects in the dapagliflozin and 3 subjects in the placebo group experienced at least one hypoglycemic event. No hypoglycemic event was classified as major, and no subject was discontinued from the study or study medication due to a hypoglycemic event.

Events suggestive of genital infections or urinary tract infections (UTI) were identified using pre-specified lists of preferred terms (PTs). Events suggestive of genital infections and UTIs were reported spontaneously as well as in response to questions related to the signs and symptoms of these infections proactively posed to subjects during study visits.

Three subjects in the dapagliflozin and one subject in the placebo group experienced at least one event suggestive of genital infection. The numbers of subjects with at least one event suggestive of UTI were similar in the dapagliflozin (6 subjects) and in the placebo group (4 subjects). In the dapagliflozin group, the proportion of subjects with events suggestive of UTI was higher in females (11.9%) than in males (2.0%). No kidney infections were reported.

Three subjects in the dapagliflozin group reported AEs of hepatic disorders: one subject experienced a massive oral gastrointestinal bleeding during hospitalization for pneumonia and died. An autopsy was performed which reported dilated vessels in the esophagus, erosive gastritis and based on macroscopic examination liver fibrosis was mentioned. No histological sample was taken. There was no documented past history of liver disease, and there were no signs or symptoms suggestive of liver disorder including abnormal liver function tests during the study prior to the fatal upper gastrointestinal bleeding. Another subject was treated with itraconazole and experienced marked abnormalities (MAs) of ALT and total bilirubin (TB) (see below). The MAs were reported as an AE of ‘hepatic enzyme increased’. The third subject showed a 1.5 cm diffuse lesion in the right liver lobe as an incidental finding during MRI after 24 weeks. A follow-up ultrasound was negative and led to no specific action regarding this finding. In the placebo group, a single ALT value of 104 U/L was reported as an AE of ALT increased.

No AEs of the categories renal impairment or failure, fracture, or urinary stones were reported (categories defined according to pre-specified lists of PTs).

Laboratory evaluation

Two subjects in the dapagliflozin and no subject in the placebo group showed MAs of hematocrit >55% and/or hemoglobin concentration >18 g/dL. The MAs of hematocrit and/or hemoglobin were not associated with any thromboembolic events. There was a small increase in mean hematocrit until week 16 (2.44%) in the dapagliflozin group which plateaued out at week 50 (2.82%). In the placebo group, mean hematocrit did not show a meaningful change during the ST + LT1 period (mean change from baseline to week 50: -0.06%).

Four subjects in the dapagliflozin group showed MAs of hepatic enzymes: one subject treated with itraconazole had ALT values >3 x ULN in combination with TB values >1.5 x ULN. The other 3 subjects had (1) single MAs of ALT >3 x ULN and alkaline phosphatase >1.5 x ULN, (2) a single MA of TB >1.5 x ULN, and (3) two MAs of TB >1.5 x ULN, respectively. In the placebo group, one subject showed a single alkaline phosphatase value

>1.5 x ULN and no MA of any other hepatic enzyme. Subjects both in the dapagliflozin and in the placebo group showed a decrease in mean ALT (-4.8 U/L vs. -6.6 U/L) and AST (-2.5 U/L vs. -5.2 U/L) from baseline to week 50.

No subject in the dapagliflozin and one subject in the placebo group showed an MA of blood urea nitrogen (BUN) or serum creatinine. In the dapagliflozin group, an increase in mean BUN (1.1 mg/dL) and a decrease in mean calculated creatinine clearance (-5.5 mL/min) was observed from baseline to week 50. No such changes were observed in the placebo group (BUN: 0.2 mg/dL, calculated creatinine clearance: -1.7 mL/min). Subjects in both treatment groups did not show a consistent change in mean eGFR during the ST + LT1 period. Mean serum cystatin-C showed a slight increase from baseline to week 50 in the dapagliflozin group (0.047 mg/L), while no meaningful change was observed in the placebo group (0.014 mg/L).

One subject in the dapagliflozin and 6 subjects in the placebo group showed an MA of serum electrolytes. Except for a slight increase in mean magnesium (0.05 mEq/L) and mean inorganic phosphorus (0.20 mg/dL) in the dapagliflozin group and a slight decrease in mean magnesium (-0.07 mEq/L) in the placebo group, serum electrolytes did not show any meaningful changes from baseline to week 50 in both treatment groups. Furthermore, subjects in the dapagliflozin group showed a decrease in mean serum uric acid (-0.97 mg/dL). No such change was observed in the placebo group (-0.13 mg/dL).

No subject in either treatment group showed an MA of creatine kinase (CK) elevation. Subjects in the dapagliflozin group did not show a meaningful change in mean CK from baseline to week 50 (0.0 U/L), while in the placebo group, a slight decrease in mean CK was observed at week 50 (-7.7 U/L).

Vital signs

Subjects in both the dapagliflozin and the placebo group did not show a meaningful change in mean seated systolic blood pressure (SBP) (-0.860 mmHg vs. 0.016 mmHg), diastolic blood pressure (DBP) (-1.518 mmHg vs. -0.199 mmHg), and heart rate (0.3 bpm vs. 0.0 bpm) from baseline to week 50.