**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | Dapagliflozin |
| Study Code | D1692C00012 |
| Edition Number | 1 |
| Date | |

# A long term open label study to evaluate the safety and efficacy of dapagliflozin as monotherapy or combination therapies with anti-diabetic drugs in Japanese subjects with type 2 diabetes who have inadequate glycemic control

**Study dates:** First subject enrolled: 28 February 2011
Last subject last visit: 15 September 2012

**Phase of development:** Therapeutic confirmatory (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)

During the study, 56 centers in Japan enrolled subjects.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

Primary and main secondary objectives and outcome variables are presented in Table S1.

**Table S1 Objectives and main outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Safety | To evaluate the safety and tolerability of long-term treatment up to 52 weeks with the dosing regimen of dapagliflozin, when it started with 5 mg and titrated up to 10 mg depending on subjects' condition of glycemic control for total subjects and for each subgroup of monotherapy or combination therapies with any anti-diabetic drugs, including SU, rapid-acting insulin secretagogue (glinides), MET, AGI, TZD, DPP-4, and GLP-1 agonists | AEs and SAEs<br>Hypoglycemic events<br>Safety Laboratory parameters (including eGFR)<br>ECG<br>Vital signs (pulse and BP)<br>Physical examination findings |
| Secondary | Efficacy | To evaluate the efficacy of the dosing regimen of dapagliflozin for up to 52 weeks for each subgroup of monotherapy or combination therapy with SU, glinides, MET, AGI, TZD, DPP-4 inhibitors, or GLP-1 agonists with regard to glycemic, weight, and BP parameters. | Change in HbA1c, FPG, total body weight, BMI, waist circumference, seated SBP and DBP, blood lipids, in from baseline over time (observed and/or LOCF) during treatment period until week 52<br>Proportion of subjects discontinued or rescued for failing to achieve pre-specified glycemic targets during treatment period until week 52<br>Change in HbA1c and FPG from last pre-titration until week 8, week 16, and week 24 after up-titration (LOCF) |

AE: adverse event, AGI: α-glucosidase inhibitors, BMI: body mass index, BP: blood pressure, DPP-4: dipeptidyl peptidase -4 inhibitors, ECG: electrocardiogram, eGFR: estimated glomerular filtration rate, FPG: fasting plasma glucose, GLP-1: glucagon-like peptide-1, HbA1c: glycosylated hemoglobin, LOCF: last observation carried forward, MET: metformin, SAE: serious adverse event, SU: sulfonylurea, TZD: thiazolidinediones.

## Study design

This was a long-term, single-arm, open-label study to evaluate the safety and efficacy of dapagliflozin as monotherapy or in combination therapy. The study consisted of a single active treatment arm without any comparator. However, the active treatment arm consisted of 8 subgroups, including monotherapy and combination therapies with sulfonylurea (SU), rapid-acting insulin secretagogue (glinides), metformin (MET), α-glucosidase inhibitors (AGI), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4), and glucagon-like peptide-1 (GLP-1) agonists.

## Target subject population and sample size

Japanese subjects with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control on diet and exercise or on concomitant anti-diabetic treatment (glycosylated hemoglobin A1c [HbA1c] ≥6.5% and ≤10% for all subjects at Visit 5).

Either gender needed to be 40% or higher of total number of treated subjects for each subgroup. Only in the monotherapy group, the proportion of subjects with HbA1c ≥6.5% but ≤7% at Visit 5 needed to be at most approximately 25%.

A total of 700 Japanese subjects with T2DM who had inadequate glycemic control on diet and exercise or on concomitant antidiabetic agents were planned with number of subjects in each subgroup as follows:

- Monotherapy: 240 subjects.
- Combination therapies with SU: 120 subjects.
- Combination therapies with DPP-4, AGI, MET, or TZD: 60 subjects for each.
- Combination therapy with glinides or GLP-1: 50 subjects for each.

The number of subjects were determined in consideration of Japanese Guideline on Clinical Evaluation Methods on Oral Hypoglycemic Agents, suggesting at least 100 subjects each for monotherapy and combination therapies considered at higher risk of hypoglycemia and at least 50 subjects each for other combination therapies. Ten percent marginal subjects were added considering drop-out through the study.

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

Investigational product had to be taken once daily in the morning.

- Dapagliflozin 5 mg dose: Dapagliflozin 5 mg 1 tablet
- Dapagliflozin 10 mg dose: Dapagliflozin 10 mg 1 tablet

**Duration of treatment**

According to the protocol, subjects were to be treated with study medication for 52 weeks.

**Statistical methods**

Unless otherwise specified, for all changes (or percent changes) from baseline to a specific timepoint post-baseline as well as for glycemic therapeutic response definitions, analyses were based on measurements available at that timepoint or the last post-baseline measurement prior to the timepoint, if no measurement was available at that timepoint, i.e., last observation carried forward (LOCF). For rescued subjects, values collected after initiation of rescue medication were not considered for calculating the LOCF values of HbA1c, fasting plasma glucose (FPG), fasting insulin, C-peptide and fasting lipids.

Descriptive statistics at each timepoint including week 52 (LOCF) were presented by subgroups as well as for the total population for all efficacy variables.

The safety evaluations included analyses of adverse events (AEs), laboratory values, electrocardiogram (ECG), vital signs (pulse and blood pressure [BP]), hypoglycemic events, estimated glomerular filtration rate (eGFR), and physical examination findings.

The analysis of safety was based on the safety analysis set. Safety data gained during the 52-week treatment period as well as during the 3-week safety follow-up period were evaluated. Safety data were presented by subgroups as well as for the total population. Safety data were also presented by final titration status. Safety variables were summarized descriptively.

**Subject population**

In total, 1030 subjects enrolled, 792 subjects entered the lead-in period, thereof 768 subjects skipped the wash-out period and 24 subjects underwent the wash-out period. The most common reasons for not entering the lead-in period were incorrect enrollment (i.e., the subject did not meet all inclusion and exclusion criteria) (224 subjects) and withdrawal of consent (7 subjects). In total, 728 subjects received treatment with study medication. The most common reasons for not being treated were incorrect enrollment (i.e., the subject did not meet all inclusion and exclusion criteria) (274 enrolled subjects) and withdrawal of consent (15 enrolled subjects). Approximately 87% of the subjects completed the 52-week treatment period. The most common reasons for not completing the 52-week treatment period were withdrawal of consent (39 subjects), occurrence of an AE (27 subjects), and not meeting the study criteria (25 subjects).

On average, subjects were 58-years-old with approximately 25% of the subjects aged above 65 years. There were about 57% male and 43% female subjects. All subjects were Japanese. Mean duration of T2DM was 5.86 years with 17.0% of the subjects diagnosed for T2DM for longer than 10 years. At baseline, mean HbA1c was 7.72% and 11.3% of the subjects had a baseline HbA1c ≥9%. Mean FPG at baseline was 144.93 mg/dL. On average, subjects weighed 67.52 kg and approximately 15% had a body mass index (BMI) ≥30 $kg/m^2$.

Overall, demographic characteristics were similar in subjects with monotherapy and combination therapy. However, this was not a randomized study, and subjects with ongoing, antidiabetic treatment in the combination therapy groups clearly represent a different history of T2DM compared with subjects in the monotherapy group. The following differences were observed between the study subgroups:

- Duration of T2DM was longer in subjects with combination therapy (6.94 years) compared with subjects with monotherapy (3.78 years). Baseline HbA1c and FPG were slightly higher in subjects with combination therapy (7.82% and 147.35mg/dL) than with monotherapy (7.53% and 140.29 mg/dL).

- Duration of T2DM was higher in up-titrated subjects (7.26 years) compared with non-titrated subjects (5.23 years). The same applied to HbA1c (8.44% vs 7.40%) and FPG (161.78 md/dL vs. 137.25 mg/dL).

**Summary of efficacy results**

The main efficacy endpoints are summarized in Table S2.

**Table S2 Summary of main efficacy endpoints - full analysis set**

| | Monotherapy N=249 | All Combination Therapies N=477 | Total N=726 |
|---|---|---|---|
| **Change from baseline to week 52 (LOCF), mean (SD)** | | | |
| HbA1c | -0.66 (0.711) | -0.68 (0.699) | -0.68 (0.702) |
| FPG | -14.3 (21.44) | -17.4 (26.23) | -16.3 (24.72) |
| Total body weight (kg) | -2.58 (2.290) | -2.06 (2.757) | -2.24 (2.616) |
| Seated SBP | -5.228 (11.6825) | -3.902 (13.0311) | -4.367 (12.5809) |
| **Change from last pre-titration until week 24 after up-titration (LOCF), mean (SD)** | **N#=50** | **N#=177** | **N#=227** |
| HbA1c | -0.12 (0.548) | -0.11 (0.493) | -0.11 (0.504) |
| FPG | -1.8 (16.71) | -2.2 (22.45) | -2.1 (21.28) |

FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin, LOCF: last observation carried forward, N# number of subjects with final up-titration in the full analysis set, SBP: systolic blood pressure, SD: standard deviation.

Subjects showed a consistent reduction in mean HbA1c of -0.68% at week 52 (LOCF) (-0.66% in the monotherapy group and -0.68% in the combination therapy group). Subjects

showed a consistent reduction in FPG of -16.3 mg/dL at week 52 (LOCF) (-14.3 mg/dL in the monotherapy group and -17.4 mg/dL in the combination therapy group). Subjects showed a consistent reduction in total body weight of -2.24 kg at week 52 (LOCF) (-2.58 kg in the monotherapy group and -2.06 kg in the combination therapy group). Subjects showed a consistent reduction in seated systolic BP (SBP) of -4.37 mmHg at Week 52 (-5.23 mmHg in the monotherapy group and -3.90 mmHg in the combination therapy group).

Up-titration of dapagliflozin showed additional improvement of glycemic control within 24 weeks (LOCF). Subjects showed a further reduction in mean HbA1c of -0.11% at week 24 (LOCF) after up-titration (-0.12% in the monotherapy group and -0.11% in the combination therapy group). Subjects showed a small further reduction in mean FPG of -2.1 mg/dL at week 24 (LOCF) after up-titration (-1.8 mg/dL in the monotherapy group and -2.2 mg/dL in the combination therapy group).

**Summary of safety results**

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

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

| | Monotherapy N=249 | All Combination Therapies N=479 | Total N=728 |
|---|---|---|---|
| At least one AE | 197 (79.1) | 347 (72.4) | 544 (74.7) |
| At least 1 event of hypoglycemia | 6 (2.4) | 19 (4.0) | 25 (3.4) |
| Death | 0 | 0 | 0 |
| At least 1 SAE | 14 (5.6) | 15 (3.1) | 29 (4.0) |
| AE leading to discontinuation[a] | 15 (6.0) | 30 (6.3) | 45 (6.2) |
| SAE leading to discontinuation[a] | 4 (1.6) | 4 (0.8) | 8 (1.1) |
| Hypoglycemia leading to discontinuation[a] | 0 | 0 | 0 |
| At least 1 AE of genital infection | 7 (2.8) | 12 (2.5) | 19 (2.6) |
| At least 1 AE of UTI | 9 (3.6) | 11 (2.3) | 20 (2.7) |

AE: adverse event, SAE: serious adverse event, UTI: urinary tract infection.
[a] of study medication

Adverse events and events of hypoglycemia

The overall proportions of subjects with AEs, serious AEs (SAEs), related AEs, and discontinuation of investigational product due to an AE (DAE) were similar in the monotherapy and combination therapy groups. In total, 74.7% of subjects experienced at least 1 AE, 79.1% in subjects receiving monotherapy and 72.4% in subjects receiving combination therapy. Overall, the proportion of subjects with hypoglycemia was low (3.4%) and showed no meaningful difference between the monotherapy group (2.4%) and the combination

therapy group (4.0%). There were no events of major hypoglycemia in this study. No event of hypoglycemia led to discontinuation.

There were no deaths during the 52-week, open-label treatment period. Overall, the proportion of subjects with at least 1 SAE was low (4.0%) and showed no relevant difference between the monotherapy group (5.6%) and combination therapy group (3.1%).

The proportion of subjects who experienced a DAE was 6.2% and similar in the monotherapy group (6.0%) and the combination therapy group (6.3%).

AEs of renal impairment or failure, diagnosed based on laboratory results and not on clinical findings, were rare (2.9%) but slightly more common in the combination therapy group (3.3%) compared with the monotherapy group (2.0%). This concerned especially the MET subgroup (14.1%). However, in this subgroup, evaluation criteria for an AE of renal impairment or failure and discontinuation criteria were different (eGFR <60 mL/min compared to <45 mL/min in the other subgroups).

In this study, the proportion of subjects who reported events suggestive of/events of urinary tract infection (UTI) was overall low and comparable in the monotherapy and combination therapy groups. A comparison by gender showed that events suggestive of UTI were mainly reported by females. Events suggestive of/events of genital infection were rare and comparable in the monotherapy and combination therapy groups. Events suggestive of genital infection were mostly reported by females. All events suggestive of UTI and genital infection were of mild or moderate intensity. No subject experienced an infection of the kidney.

AEs of hepatic disorder were reported in 9 subjects (1.2%) and were balanced between the monotherapy and combination therapy groups.

For other AEs of special interest (such as events of volume depletion and AEs of fractures), the proportions of subjects affected were low and did not show any particular pattern.

Laboratory evaluation

Eight subjects (1.1%) showed marked abnormalities (MAs) of increased hematocrit and 9 subjects (1.3%) showed MAs of increased hemoglobin that were balanced between the monotherapy and combination therapy groups. Furthermore, subjects showed slight mean increases in hemoglobin and hematocrit until week 52, which were reversible at follow-up.

MAs of elevated liver tests were balanced between the monotherapy and combination therapy groups. Twenty subjects (2.7%) showed at least 1 MA of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin (TBL). Eleven subjects (1.5%) showed a single value of TBL >1.5 × upper limit of normal (ULN). In no subject did ALT or 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 drug induced liver injury.

No subject showed an MA of blood urea nitrogen (BUN), and 1 subject showed an MA of serum creatinine. Subjects showed a slight mean increase in BUN from baseline to week 52 that was reversible at follow-up. Subjects did not show a meaningful change in mean eGFR from baseline to week 52.

Few subjects showed at least 1 MA of serum electrolytes, including inorganic phosphorus. Subjects showed a slight increase in mean magnesium from baseline to week 52 that was reversible at follow-up.

Vital signs

Subjects showed a slight mean decrease in seated SBP and no meaningful mean change in seated DBP from baseline to week 52. The change in SBP was reversible at follow-up.

During the 52-week, open-label treatment period, 20.8% of subjects had measurements of orthostatic hypotension and the proportion of subjects with orthostatic hypotension was slightly larger in the combination therapy group (23.1%) than in the monotherapy therapy group (16.2%).