52-week Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1690C00004
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A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III study with a 52-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination with Metformin compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Therapy Alone

Report for the 52-week short-term treatment period.

This synopsis is revised based on the CSR Errata list dated 2 November 2010. The revision was done due to one minor correction in the date for FSI.

Study dates:

First subject enrolled: ***28** March 2008*
Last subject last visit first 52-week period: *15 December 2009*

Phase of development:

Therapeutic confirmatory (III)

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

Study centre(s)

Study D1690C00004 was conducted at 95 centers in 10 countries. (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 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	
To examine whether, after 52 weeks of oral administration of double-blind treatment, the absolute change from baseline in HbA1c level with dapagliflozin plus metformin was non-inferior to glipizide (sulphonylurea) plus metformin in subjects with T2DM who had inadequate glycemic control on 1500 mg/day or higher doses of metformin therapy alone.	Change in HbA1c from baseline to week 52
Key secondary	
To show that dapagliflozin plus metformin reduces body weight compared to glipizide plus metformin after 52 weeks of treatment.	Absolute change in body weight from baseline to week 52
To show that dapagliflozin plus metformin treatment leads to fewer subjects with hypoglycemic events compared to glipizide plus metformin after 52 weeks of treatment.	Proportion of subjects reporting at least one episode of hypoglycemia over 52 weeks
To show that higher percentage of subjects treated with dapagliflozin plus metformin reduces their baseline body weight for at least 5% compared to subjects treated with glipizide plus metformin after 52 weeks of treatment.	Proportion of subjects with body weight decrease ≥5% from baseline to week 52
Safety	
To evaluate the safety and tolerability by assessment of adverse events (AE), laboratory values, electrocardiogram (ECG), pulse, blood pressure, hypoglycemic events, calculated creatinine clearance and physical examination findings.	AEs, laboratory values, ECG, pulse, blood pressure, hypoglycemic events, calculated creatinine clearance and physical examination findings

The primary and all key secondary objectives/variables were efficacy objectives/variables. For other secondary objectives/variables and tertiary objectives/variables see the Clinical Study Report (CSR). Results of other secondary objectives/variables and tertiary objectives/variables are not included in this Synopsis, but can be found in the CSR.

Study design

This was an international, multi-center, randomized, parallel-group, double-blind, active-controlled Phase III study with a 52-week short-term treatment period followed by a 52-week

extension period to evaluate the efficacy and safety of dapagliflozin as add-on therapy to metformin compared with glipizide as add-on therapy to metformin in adult subjects with T2DM who have inadequate glycemic control (HbA1c >6.5% and ≤10.0%) on metformin therapy alone. Note that this synopsis includes only results from the 52-week short-term treatment period.

Target subject population and sample size

The study entry criteria specified enrollment of male or female subjects ≥18 years of age, diagnosed with T2DM, and treated with a maximum of 2 OADs that included metformin for at least 8 weeks prior to enrollment. At the start of the metformin dose-stabilization period, subjects had to show inadequate glycemic control, defined as HbA1c >6.5% and ≤10.0%, a FPG level ≤270 mg/dL, and a C-peptide level ≥1.0 ng/mL to be eligible for the study. At the start of the placebo lead-in period, subjects had to be treated with metformin alone on a stable dose of ≥1500 mg/day for at least 8 weeks.

To demonstrate non-inferiority of dapagliflozin in comparison with glipizide as add-on therapy to metformin for changes from baseline to week 52 in HbA1c within a non-inferiority margin of 0.35%, assuming a standard deviation SD = 1.25%, and at a one-sided significance level of 0.025, 280 evaluable subjects were needed in each treatment group to provide approximately 90% power (given a true difference of zero between the 2 treatment groups). Assuming a 5% exclusion rate from the full analysis set, 295 subjects per treatment group were needed for the full analysis set.

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

Subjects in both treatment groups had to receive open-label metformin at a dose of 1500, 2000 or 2500 mg/day during the 52-week short-term treatment period. The subject's metformin dose during the 52-week short-term treatment period was to be based on his/her metformin dose and other OAD therapy during the last 8 weeks prior to enrollment (for details see the CSR). Subjects who did not receive metformin monotherapy at a stable dose of 1500, 2000 or 2500 mg/day already during the last 8 weeks prior to the enrollment visit had to pass through a dose stabilization period.

The 52-week short-term period consisted of a titration period (week 0 to week 18) and a maintenance treatment period (week 19 to week 52). During the titration period, subjects were up-titrated to the optimal effect (FPG <110 mg/dL, <6.1 mmol/L,) or the highest tolerable dose. All subjects started with the investigational product at dose level 1 (dapagliflozin 2.5 mg or glipizide 5 mg). They could be up-titrated in 3 week intervals to dose level 2 (dapagliflozin 5 mg or glipizide 10 mg) and 3 (dapagliflozin 10 mg or glipizide 20 mg). During the maintenance treatment period subjects continued on the dose level they have reached at the end of the titration period.

At any time during the study, the investigational product could be down-titrated to mitigate recurrent hypoglycemic events. Subjects who experienced recurrent hypoglycemic events at dose level 1 could be down-titrated to zero at the investigator's discretion. Subjects could be

up-titrated again to the maximum tolerable dose until the end of the titration period; thereafter, no up-titration was allowed until the end of the maintenance treatment period.

Duration of treatment

According to the original protocol, subjects were treated with study medication for 104 weeks (52-week short-term treatment period plus 52-week long-term extension period). Note that this synopsis includes only results from the 52-week short-term treatment period.

Statistical methods

A hierarchical closed testing procedure was used to control the type I error rate ≤0.050 (two-sided) across the primary and key secondary efficacy variables. The non-inferiority of the primary variable was tested first (one-sided 0.025 significance level) followed by the key secondary variables in the order as shown above (test for superiority of dapagliflozin plus metformin over glipizide plus metformin at a two-sided 0.050 significance level). The primary efficacy variable was analyzed with an analysis of covariance model (ANCOVA) which was used to derive a least squares estimate of the treatment difference in mean change with the corresponding two-sided 95% confidence interval. If the upper limit of the 95% confidence interval was <0.35%, then dapagliflozin as add-on therapy to metformin was considered to be non-inferior to glipizide as add-on therapy to metformin. Other continuous key secondary efficacy variables were analyzed using an ANCOVA yielding a least squares estimate of the treatment difference in mean change with corresponding p-value and two-sided 95% confidence interval. Further, two-sided 95% confidence intervals for the mean change within each treatment group were calculated. 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 baseline value. Efficacy was evaluated using the full analysis set. The primary efficacy variable was analyzed with both the full analysis set and the per-protocol analysis set. The non-inferiority conclusion pertaining to the primary efficacy variable was drawn primarily based on results from the full analysis set. The safety analysis set was used in all summaries of safety data.

Subject population

In total, 1217 subjects were enrolled out of which 816 were randomized. The most common reason for not being randomized was not fulfilling all the inclusion criteria and fulfilling at least one exclusion criterion (344 subjects). More than 75% of the subjects completed the 52-week short-term treatment period and continued into the 52-week extension period. Withdrawal of consent was the most common reason for not completing the short-term treatment period (55 subjects) and not continuing into the extension period (63 subjects). The full analysis set included 801/816 randomized subjects. The safety analysis set included 814/816 randomized subjects.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 58 years of age with around 75% aged below 65 years and less than 4% aged over 75 years. There were around 55% male and 45% female subjects in both treatment groups. 81% of the subjects were white and 75% were of

non-Hispanic/Latino ethnicity. Mean duration of T2DM was 6.3 years with around 20% of the subjects suffering from T2DM over 10 years. At baseline, mean HbA1c was around 7.7% and around 10% of the subjects had a baseline HbA1c ≥9%. At baseline, around two thirds of the subjects received a metformin monotherapy, and around one third received metformin combined with another OAD. Both in monotherapy and in combinations with another OAD, the majority of subjects received metformin at a dosage ≥1500 mg/day.

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

	DAPA + MET N = 400	GLIP + MET N = 401
Primary endpoint		
HbA1c (%) at week 52 (LOCF)		
Adjusted mean change from baseline (SE)	-0.52 (0.0403)	-0.52 (0.0402)
non-inferiority p-value vs. GLIP + MET	<0.0001 *	
Key secondary endpoints		
Total body weight (kg) at week 52 (LOCF)		
Adjusted mean change from baseline (SE)	-3.22 (0.1756)	1.44 (0.1754)
p-value vs. GLIP + MET	<0.0001 *	
Subjects with at least one episode of hypoglycemia at week 52 (LOCF)		
Percent adjusted	3.5% (0.919)	40.8% (2.403)
p-value vs. GLIP + MET	<0.0001 *	
Subjects with body weight reduction of at least 5% at week 52 (LOCF)		
Percent adjusted	33.3% (2.354)	2.5% (0.779)
p-value vs. GLIP + MET	<0.0001 *	

* Significant p-value: the primary endpoint was tested for non-inferiority at $\alpha = 0.025$ (one-sided) applying a non-inferiority margin of 0.35%. The secondary endpoints were tested for superiority following a sequential testing procedure at $\alpha = 0.05$ (two-sided).

Subjects in the dapagliflozin and the glipizide group showed a similar mean decrease of 0.52% in HbA1c at week 52 (LOCF), compared to baseline. The mean decrease in HbA1c at week 52 (LOCF) was statistically significantly non-inferior in the dapagliflozin group compared to glipizide (upper limit of the 95% CI of the difference in adjusted mean change from baseline between treatment groups: 0.11%; pre-specified non-inferiority margin: 0.35%).

Subjects in the dapagliflozin group showed a mean decrease of 3.22 kg in total body weight from baseline to week 52 (LOCF), while in the glipizide group, total body weight increased by 1.44 kg during the same period of time. The difference in change of body weight at week 52 (LOCF) between dapagliflozin and glipizide treated subjects was statistically significant and clinically relevant ($p < 0.0001$).

A statistically significant and clinically relevant lower proportion of subjects in the dapagliflozin group (3.5%), compared to glipizide (40.8%), experienced at least one event of hypoglycemia over 52 weeks of treatment ($p < 0.0001$).

A statistically significant and clinically relevant higher proportion of subjects in the dapagliflozin group (33.3%), compared to glipizide (2.5%), reduced their body weight by at least 5% from baseline to week 52 (LOCF) ($p < 0.0001$).

Summary of safety results

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

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

	DAPA + MET N = 406	GLIP + MET N = 408
At least one AE	318 (78.3)	318 (77.9)
At least one event of hypoglycemia	14 (3.4)	162 (39.7)
Death	0	3 (0.7)**
At least one SAE	35 (8.6)	46 (11.3)
AE leading to discontinuation*	37 (9.1)	24 (5.9)
SAE leading to discontinuation*	9 (2.2)	8 (2.0)
Hypoglyc. leading to discontinuation*	0	6 (1.5)
At least one event suggestive of genital infection	50 (12.3)	11 (2.7)
At least one event suggestive of urinary tract infection	44 (10.8)	26 (6.4)

* of study medication; ** one subject each died from mesenteric infarction and acute myocardial infarction, in one subject a sudden death was reported.

The overall proportions of subjects experiencing any AE (78.3% vs. 77.9%) or SAE (8.6% vs. 11.3%) were similar in dapagliflozin and glipizide treated subjects. A higher proportion of subjects in the dapagliflozin group (9.1%), compared to glipizide (5.9%) was discontinued from study medication due to an AE.

There were 3 deaths (due to mesenteric infarction, myocardial infarction and sudden death) in the glipizide group. One further subject in the dapagliflozin group died more than 30 days after the last dose of double-blind study medication and one further subject in each treatment group died after the follow-up visit was performed. Death of these subjects is not included in the analysis of the 52-week short-term treatment period (for details see the CSR).

Hypoglycemic events were reported for 3.4% of subjects in the dapagliflozin group compared to 39.7% in the glipizide group. In the glipizide group, there were 3 major hypoglycemic events and 6 subjects in the glipizide group were discontinued from study treatment due to a

hypoglycemic event. No subject in the dapagliflozin group experienced a major hypoglycemic event or was discontinued due to a hypoglycemic event.

Events suggestive of genital infections (GI) or urinary tract infections (UTI) were identified using pre-specified lists of PTs. Events suggestive of GIs 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.

The proportion of subjects reporting events suggestive of GIs or UTIs was higher in females than in males, and both in males and in females the proportion of subjects reporting events suggestive of GIs or UTIs was higher in the dapagliflozin (GI: males: 5.3%, females: 21.1%; UTI: males: 8.0%, females: 14.4%) than in the glipizide group (GI: males: 0.4%, females: 5.4%; UTI: males: 4.0%, females: 9.2%).

Proportions of subjects reporting AEs of renal impairment or failure were higher in the dapagliflozin group (5.9%), compared to glipizide (3.4%). The difference between treatment groups was primarily caused by the higher number of subjects with an AE of creatinine renal clearance decreased in the dapagliflozin group (4.2%), compared to glipizide (1.7%).

Overall, 10 subjects in the dapagliflozin and 6 subjects in the glipizide group showed an AE of hepatic disorder.

Five subjects in the dapagliflozin and no subject in the glipizide group showed a MA of hematocrit >55%. The MAs of hematocrit were not associated with any thromboembolic events. There was a small mean increase in hematocrit over the first 26 weeks in the dapagliflozin group. Thereafter, hematocrit remained almost stable (change from baseline to week 52: 2.86%). In the glipizide group, hematocrit did not show any meaningful mean change during the 52-week short-term treatment period (change from baseline to week 52: 0.39%).

MAs of ALT and AST were balanced between the two treatment groups. One subject in the dapagliflozin group developed ALT and AST values >20 x ULN in combination with bilirubin >2 x ULN and was later diagnosed with acute hepatitis. In one subject in the glipizide group, ALT reached values >10 x ULN and AST reached values >5 x ULN, but no AE specific for a hepatic disease was documented. In the dapagliflozin group, compared to glipizide, a mean decrease in ALT (-5.0 U/L) and a slight mean decrease in AST (-1.7 U/L) was observed.

There was no subject with a MA of ALP in any treatment group and only the subject later diagnosed with acute hepatitis showed a MA of total bilirubin. Subjects in both treatment groups showed a slight mean decrease in ALP and no mean change in total bilirubin during the 52-week short-term treatment period.

Renal MAs were balanced between the two treatment groups. Subjects in the dapagliflozin and the glipizide group did not show any clinically meaningful mean changes in serum creatinine (-0.002 mg/dL vs. 0.041 mg/dL) and BUN (1.4 mg/dL vs. 0.4 mg/dL), while a mean decrease in calculated creatinine clearance (-6.2 mL/min vs. -4.6 mL/min) was observed in both treatment groups and a mean decrease in eGFR (-0.5 mL/min/1.73m^2 vs.

-5.4 mL/min/1.73m^2) was observed only in the glipizide group. Subjects in both treatment groups showed a similar mean increase in serum cystatin-C (0.076 mg/L vs. 0.083 mg/L) from baseline to week 52.

Subjects in the dapagliflozin group showed small mean decreases in systolic (-4.0 mmHg) and diastolic (-1.6 mmHg) blood pressure from baseline to week 52 (LOCF), while no relevant changes in systolic (0.5 mmHg) and diastolic (-0.4 mmHg) blood pressure were observed in the glipizide group. In subjects with systolic blood pressure >140 mmHg at baseline, systolic (-8.0 mmHg) and diastolic (-3.2 mmHg) blood pressure also decreased in the glipizide group and decreases in systolic (-13.0 mmHg) and diastolic (-3.8 mmHg) blood pressure in the dapagliflozin group were more pronounced than in the overall study population. No increase in orthostatic hypotension was observed under dapagliflozin treatment.