Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1691C00003
Edition Number	1
EudraCT No	2010-019511-37

A 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients with Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy

Study dates:	First subject enrolled:	*05 Nov 2010*
	Last subject last visit:	*25 Aug 2011*
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 D1691C00003 was conducted at 53 centers in 6 European countries and South Africa. (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	
• The primary objective of this study was to compare the change from baseline in HbA1c achieved with each of the 2 twice daily (BID) doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.	Change in HbA1c from baseline to week 16
Key secondary	
(1) To compare the percent change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.	Percent change in body weight from baseline to week 16
(2) To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 1 week of double-blind treatment.	Change in FPG from baseline to week 1.
(3) To compare the change from baseline in FPG achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.	Change in FPG from baseline to week 16
(4) To compare the proportion of subjects with HbA1c <7.0% achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in subjects with an HbA1c ≥7.0% at baseline.	Proportion of subjects with HbA1c <7.0% at week 16, in subjects who had HbA1c ≥7.0% at baseline

Objectives	Outcome variables
Safety	
To examine the safety and tolerability of dapagliflozin co-administered with metformin versus placebo co-administered with metformin by assessment of adverse events (AEs), laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycemic events, cardiovascular events calculated creatinine clearance, estimated glomerular filtration rate (eGFR), and physical examination findings.	AEs, laboratory values, ECG, pulse, BP, hypoglycemic events, cardiovascular events, calculated creatinine clearance, eGFR, and physical examination findings.

The primary and all key secondary objectives/variables were efficacy objectives/variables. For a complete list of other secondary objectives/variables see the Clinical Study Report (CSR).

Study design

This was a 16-week, international, multicenter, randomized, double-blind, double dummy, parallel-group, placebo-controlled, pivotal Phase III study to evaluate the efficacy and safety of dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg once daily (QD) in subjects with type 2 diabetes. The dapagliflozin 10 mg QD arm was included as a measure of assay sensitivity, and not contributory to the primary objective and key secondary objectives. Dapagliflozin or placebo was added to the therapy of subjects who had inadequate glycemic control on metformin therapy alone.

Target subject population and sample size

Subjects with type 2 diabetes mellitus (T2DM) were eligible to enter the study if they were treated with metformin ≥1500 mg/day monotherapy for at least 10 weeks prior to enrollment and showed inadequate glycemic control (HbA1c ≥6.7% and ≤10.5% at screening and enrollment and HbA1c ≥6.5% and ≤10.0%, based on central laboratory values obtained at Visit 3, one week prior to randomization).

Subjects eligible for the study were stratified according to their baseline HbA1c and within each stratum they were randomized to dapagliflozin or placebo treatment. One recruitment stratum (Stratum 1) was characterized by HbA1c levels at randomization of <7.0% (blood samples taken at Visit 3, or one week before randomization). When Stratum 1 had met its goal for randomized subjects, communication was sent out to all sites that screening and enrollment was only allowed to continue for subjects in Stratum 2 characterized by HbA1c levels ≥7.2% and ≤10.5%. For these subjects in Stratum 2, randomization criteria of HbA1c ≥7.0% and ≤10.0% applied. Globally, subjects were randomized to ensure a 1:1:1:1 ratio of subjects in the 4 arms. Recruitment was competitive between sites and countries.

In order to detect a 0.5% difference in mean change from baseline in HbA1c between one of the dapagliflozin treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo using a 2-sample t-test at a 0.025, two-sided significance level with 90% power, 95 evaluable subjects were required per treatment group in the Full Analysis Set. If one assumed 3% of the subjects did not have a baseline and post-baseline efficacy measurement, 98 subjects per group (392 total subjects) were needed to be randomized. Further, if 40% of subjects failed to meet entry

criteria for randomization (as seen in study MB102014), then approximately 654 subjects had to be enrolled.

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

The investigational product dapagliflozin (2.5 mg and 5 mg) or matching placebo had to be taken twice daily, the investigational product dapagliflozin (10 mg) or matching placebo had to be taken once daily in the morning. Metformin had to be taken orally with food, once with breakfast and once with the evening meal, during the study period.

Duration of treatment

According to the protocol, subjects were to be treated with study medication for 16 weeks.

Statistical methods

The primary outcome variable, change from baseline to week 16 in HbA1c, was analyzed using an analysis of covariance (ANCOVA) model with treatment group as fixed effect 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. Treatment effects were determined through pair-wise treatment group comparisons: each dapagliflozin dose group versus placebo. No statistical comparisons were made amongst the three dapagliflozin groups (2.5 mg BID, 5 mg BID, and 10 mg QD).

The dapagliflozin 10 mg QD treatment group is provided as a measure of assay sensitivity. Comparisons of dapagliflozin 10 mg QD to placebo were performed with nominal p values, outside of the controls, for multiplicity for the two dapagliflozin BID groups.

A Hochberg procedure was used to control the overall Type I error rate for the two treatment group comparisons (dapagliflozin 2.5 mg BID and 5 mg BID) versus placebo for the primary efficacy variable. Nominal p-values for the differences between the two dapagliflozin dose groups (2.5 mg BID and 5 mg BID) and the placebo group were determined. If the largest of the two p-values was ≤0.050 (two-sided), then the two treatment group comparisons (2.5 mg BID and 5 mg BID) versus placebo were declared statistically significant. If the largest of the p-values was >0.050 (two-sided), then the corresponding treatment group comparison (2.5 mg BID or 5 mg BID) versus placebo was not significant. Then, the smaller p-value was assessed for significance at a 0.025 level (two-sided). Further testing of treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo for key secondary variables was performed using a hierarchical, fixed sequence testing procedure, but only with respect to the treatment group(s) found significant for the primary efficacy variable. The testing of the key secondary variables was performed in the order listed below. The level of significance used for key secondary variables was 0.050. The following key secondary efficacy variables had been identified: (1) Percent change in body weight from baseline to week 16, (2) Change in FPG from baseline to week 1, (3) Change in FPG from baseline to week 16, (4) Proportion of subjects with HbA1c <7.0%, in subjects with HbA1c ≥7.0% at baseline.

For outcome variables other than HbA1c, an ANCOVA model with treatment group as a fixed effect, HbA1c at randomization stratum and the baseline measurement as a covariate was used.

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 safety analysis set was used in all summaries of safety data.

Subject population

In total, 520 subjects were enrolled and 428 completed the enrollment period. In total, 428 subjects entered the lead-in period. Most common reasons for not entering the lead-in period were incorrect enrollment and withdrawal of consent. In most cases, incorrect enrollment included subjects that developed an exclusion criterion or violated an inclusion criterion during the lead-in period after they were correctly enrolled, i.e., their diabetes improved so much that they could not be included in the study any more. In total, 400 subjects were randomized.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were 58 years old. The proportions of men and women were similar in all groups: approximately 45% men and 55% women. Around two thirds of the subjects were obese (body mass index [BMI] $\geq$30 kg/m^2). Around 38% of the subjects had at least one history of cardiovascular disease (CVD) other than hypertension. A total of 4.3% of subjects had a congestive heart failure defined as New York Heart Association (NYHA) Class I and II.

Mean duration of T2DM was 5.23 years and 12.0% of the subjects had a duration over 10 years. At baseline, mean HbA1c was 7.80%. Mean FPG at baseline amounted to approximately 155 mg/dL. The mean background dose of metformin at enrollment and at randomization was around 1900 mg/daily and showed no difference between treatment groups.

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 + MET N=101	DAPA 2.5MG BID + MET N=100	DAPA 5MG BID + MET N=99	DAPA 10MG QD + MET N=99
Primary endpoint				
HbA1c (%) at week 16 (LOCF)				
Adjusted mean change from baseline (SE)	-0.30 (0.0593)	-0.52 (0.0594)	-0.65 (0.0600)	-0.59 (0.0598)
p-value vs. PLA + MET		0.0106 *	<.0001 *	0.0007
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-0.22 (0.0840)	-0.35 (0.0843)	-0.29 (0.0844)
Key secondary endpoints				
Percent change in body weight (%) at week 16 (LOCF)				
Adjusted mean percent change from baseline (SE)	-1.04 (0.3105)	-2.84 (0.3099)	-3.20 (0.3125)	-2.76 (0.3086)
p-value vs. PLA + MET		<.0001 *	<.0001 *	<.0001
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-1.82 (0.3630)	-2.18 (0.3636)	-1.73 (0.3635)
Fasting plasma glucose (mg/dL) at week 1				
Adjusted mean change from baseline (SE)	2.0 (2.584)	-13.7 (2.657)	-14.7 (2.672)	-15.5 (2.634)
p-value vs. PLA + MET		<.0001 *	<.0001 *	<.0001
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-15.7 (3.040)	-16.7 (3.039)	-17.5 (3.044)
Fasting plasma glucose (mg/dL) at week 16 (LOCF)				
Adjusted mean change from baseline (SE)	-10.4 (2.669)	-20.8 (2.738)	-25.6 (2.759)	-20.4 (2.720)
p-value vs. PLA + MET		0.0010 *	<.0001 *	0.0015
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-10.4 (3.132)	-15.3 (3.139)	-10.0 (3.145)
Proportion of subjects with HbA1c <7.0% after 16 weeks of double-blind treatment, in subjects with an HbA1c ≥7.0% at baseline				
Percent adjusted (SE)	21.4% (4.170)	33.6% (4.567)	38.2% (4.651)	28.1% (4.619)
p-value vs. PLA + MET		0.0518	0.0079 *	0.2874
Difference vs. PLA + MET, percent		12.2% (6.270)	16.8% (6.339)	6.7% (6.299)

* Significant p-value: Hochberg's method was used to control the overall Type I error rate ≤0.05 for primary endpoint for Dapa 2.5 mg BID and Dapa 5 mg BID, and secondary endpoints were tested following a sequential testing procedure at alpha=0.05.. Comparisons of dapagliflozin 10 mg QD versus placebo yielded nominal p-values only. LOCF Last observation carried forward, SE standard error

Primary endpoints

Regarding the primary objective, dapagliflozin treatment of 2.5 and 5 mg BID co-administered with metformin-immediate release (IR) over 16 weeks achieved a statistically significant reduction in HbA1c by approximately -0.52% and -0.65 % compared to placebo (-0.30%) co-administered with metformin-IR at week 16 (last observation carried forward [LOCF]). The respective placebo-adjusted values were -0.22% and -0.35%, respectively.

Key secondary endpoints

Since the tests of the primary endpoints yielded a significant result in the dapagliflozin 2.5 and 5 mg BID groups, the secondary endpoints were tested following a sequential testing procedure. The testing sequence was applied separately for each dose group (2.5 mg BID and/or 5 mg BID) with an α=0.05 for each testing stream.

The mean percent change in body weight from baseline to week 16 (LOCF) was -2.84% and -3.20% in the dapagliflozin 2.5 and 5 mg BID groups compared to the placebo group (-1.04%). The difference from placebo (-1.82% and -2.18% placebo-adjusted mean change, respectively) was statistically significant in both dapagliflozin BID groups. In the dapagliflozin groups, the percent decrease in total body weight occurred faster during the first week, and then continued in a slower fashion.

The reduction in FPG from baseline to week 1 was -13.7 and -14.7 mg/dL in the dapagliflozin 2.5 and 5 mg BID groups compared to the placebo group (2.0 mg/dL). The difference from placebo (-15.7 and -16.7 mg/dL placebo-adjusted mean change, respectively) was statistically significant in both dapagliflozin BID groups.

The reduction in FPG from baseline to week 16 (LOCF) was -20.8 and -25.6 mg/dL in the dapagliflozin 2.5 and 5 mg BID groups compared to the placebo group (-10.4 mg/dL). The difference from placebo (-10.4 and -15.3 mg/dL placebo-adjusted mean change, respectively) was statistically significant in both dapagliflozin BID groups.

The proportion of subjects with HbA1c below 7% at week 16 (LOCF) who had an HbA1c $\geq$7% at baseline was larger in the dapagliflozin treatment groups (33.6% and 38.2% in the dapagliflozin 2.5 and 5 mg BID groups) than in the placebo group (21.4%). However, the difference was statistically significant only in the dapagliflozin 5 mg BID group (p=0.0079) and not in the dapagliflozin 2.5 mg BID group (p=0.0518).

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

	PLA + MET N=101	DAPA 2.5MG BID + MET N=100	DAPA 5MG BID + MET N=100	DAPA 10MG QD + MET N=99
At least one AE	37 (36.6)	40 (40.0)	33 (33.0)	46 (46.5)
At least one event of hypoglycemia	0	1 (1.0)	0	2 (2.0)
Death	0	0	0	0
At least one SAE	0	4 (4.0)	1 (1.0)	2 (2.0)
AE leading to discontinuation*	3 (3.0)	5 (5.0)	3 (3.0)	4 (4.0)
SAE leading to discontinuation*	0	0	0	0
Hypoglycemia leading to discontinuation*	0	0	0	0
At least one AE of genital infection	1 (1.0)	0	5 (5.0)	3 (3.0)
At least one AE of urinary tract infection	1 (1.0)	2 (2.0)	4 (4.0)	2 (2.0)

* Discontinuation of study medication;

Adverse events and events of hypoglycemia

Proportions of subjects with at least one AE were slightly higher in the dapagliflozin 2.5 mg BID and 10 mg QD groups (40.0% and 46.5%, respectively) than in the dapagliflozin 5 mg BID and placebo groups (33.0% and 36.6%, respectively). A higher proportion of subjects in the dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD groups compared to placebo experienced at least one serious adverse event (SAE) (4.0%, 1.0%, and 2.0%, respectively, vs. 0.0%). None of the SAEs was assessed as related to the double-blind study medication as assessed by the investigator. A similar proportion of subjects in the dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD groups compared to placebo was discontinued from study medication due to an adverse event (DAE) (5.0%, 3.0%, and 4.0%, respectively, vs. 3.0%). No AE leading to discontinuation of double-blind study medication was assessed as serious.

No deaths were reported during the 16-week double-blind treatment period.

One subject in the dapagliflozin 2.5 mg BID group and 2 subjects in the dapagliflozin 10 mg QD 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) and events of genital infections or UTI were identified using pre-specified lists of preferred terms (PTs). These events 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 with at least one event suggestive of genital infection was higher in the dapagliflozin 5 mg BID (5.0%) and 10 mg QD groups (3.0 %) than in the dapagliflozin 2.5 mg BID (0.0%) and placebo groups (1.0%). The proportion of subjects with at least one

event suggestive of UTI in the dapagliflozin groups (2.0%, 5.0%, and 3.0% in the dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD groups, respectively) was comparable to the placebo group (3.0%). In all treatment groups, the proportion of subjects with events suggestive of UTI was higher in women than in men. No kidney infections were reported.

The proportion of subjects with AEs of renal impairment or failure was similar in the dapagliflozin groups (5.0%, 3.0%, and 3.0% in the dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD groups, respectively) and in the placebo group (4.0%).

One subject in the placebo group reported an AE of hepatic disorder (hepatic steatosis).

AEs of urinary stones were reported for one subject each in the dapagliflozin 10 mg QD and placebo groups.

No AEs of the categories hypotension/dehydration/hypovolemia, and fracture were reported (categories defined according to pre-specified lists of PTs).

Laboratory evaluation

Two subjects in the dapagliflozin 5 mg BID group showed a marked abnormality (MA) of hematocrit >55%. No MA of hematocrit was associated with a thromboembolic event. There was a small mean increase in hematocrit until week 16 in all dapagliflozin groups. In the placebo group, hematocrit did not show a meaningful mean change during the 16-week double-blind treatment period.

Small mean decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed from baseline to week 16 in all dapagliflozin treatment groups. A few subjects in each dapagliflozin group (approximately 1%) had individual elevations in ALT >3 x upper limit of normal (ULN) or total bilirubin (TB) >1.5 x ULN. No subject had a combined measurement of ALT or AST >3 x ULN and TB >1.5 x ULN.

No subject showed an MA of blood urea nitrogen (BUN). Two subjects each in the dapagliflozin 2.5 and 5 mg BID groups and 3 subjects in the placebo group showed at least one measurement of creatinine ≥1.5 x baseline concentration. One subject in the placebo group showed a creatinine concentration ≥2.5 mg/dL. In the dapagliflozin groups, a mean increase in BUN and a mean decrease in calculated creatinine clearance were observed from baseline to week 16. No such changes were observed in the placebo group. Subjects in the dapagliflozin treatment groups showed a slight mean decrease in eGFR from baseline to week 16 between -3.5and -0.3 mL/min/1.73m^2.

MAs of electrolytes were rare: MAs of calcium below 7.5 mg/dL were observed in one subject each in the dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD groups. MAs of potassium ≥6.0 mEq/L were observed in 2, 3, 1, and 3 subjects in the dapagliflozin 2.5 mg BID, 5 mg BID, 10 mg QD, and placebo groups. One subject in the dapagliflozin 5 mg BID group showed at least one MA of sodium >150 mEq/L, whereas no subject showed an MA of sodium <130 mEq/L. At least one measurement of inorganic phosphorus equal or below the low MA limit was observed in one subject each in the dapagliflozin 2.5 mg BID and placebo

groups. One subject each in the dapagliflozin 2.5 and 5 mg BID groups showed at least one measurement of inorganic phosphorus equal or above the high MA limit. Except for a slight mean increase in magnesium and inorganic phosphorus in the dapagliflozin groups, serum electrolytes did not show any meaningful mean changes from baseline to week 16 in any treatment group. Furthermore, subjects in all dapagliflozin groups showed a mean decrease in serum uric acid. No such changes were observed in the placebo group.

Three subjects in the dapagliflozin 5 mg BID group and 1 subject in the placebo group showed at least one MA of creatine kinase (CK) >5 x ULN. Thereof, 2 subjects in the dapagliflozin 5 mg BID group showed at least one MA of CK >10 x ULN.

Vital signs

Subjects in the dapagliflozin groups showed a slight mean decrease in seated SBP but no meaningful change in seated DBP from baseline to week 16. In the placebo group, no meaningful mean change in either seated SBP or seated DBP was observed. Neither dapagliflozin nor placebo treatment showed any mean change of seated heart rate.