24-week Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1690C00018
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A 24-week, multicentre, randomised, double-blind, age-stratified, placebo-controlled phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycaemic control on usual care

Report for the 24-week short-term treatment period

This synopsis is revised based on the CSR Errata list No 1 dated on 9 November 2011 and Errata list No 2 dated on 7 August 2012. The revision was done due to minor corrections on page 8 (Key secondary endpoints) and page 12 (vital signs) in this synopsis.

Study dates:	First subject enrolled: *10 February 2010* Last subject last visit for the 24-week period: *26 May 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 D1690C00018 was conducted at 171 centers in Europe, North America, Latin America, and Asia/the Pacific Region. (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	
There were 2 independent primary objectives of equal weight in this study:	
• To assess the glycemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes mellitus (T2DM) subjects with cardiovascular disease (CVD) and hypertension, measured as the mean change in glycosylated hemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Change in HbA1c from baseline to week 24
• To assess the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in T2DM subjects with CVD and hypertension at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as: - an absolute drop of 0.5% or more from baseline HbA1c, and - a relative drop of 3% or more from baseline for total body weight, and - an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure (SBP), in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Proportion of subjects achieving: - an absolute reduction in HbA1c of ≥0.5% from baseline to week 24, and - a relative reduction in total body weight of ≥3% from baseline to week 24, and - an absolute reduction in seated SBP of ≥3 mmHg from baseline to week 24
Key secondary	
1st To compare the mean change in seated SBP from baseline to week 8 between dapagliflozin 10 mg versus placebo in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Change in seated SBP from baseline to week 8
2ndTo compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Percent change in body weight from baseline to week 24

Objectives	Outcome variables
3rd To compare the mean change in seated SBP from baseline to week 24 between dapagliflozin 10 mg versus placebo, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Change in seated SBP from baseline to week 24
4th To compare the proportion of subjects with baseline body mass index (BMI) ≥27 kg/m^2 with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24 in the overall population and in the two predefined age subgroups (<65 years, ≥65 years)	Proportion of subjects achieving a reduction in body weight of ≥5% from baseline to week 24 in subjects with a baseline BMI ≥27 kg/m^2
Safety	
To evaluate the safety and tolerability of dapagliflozin by assessment of adverse events (AEs) including cardiovascular (CV) events, laboratory values, electrocardiogram (ECG), pulse, blood pressure (BP), hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate (eGFR), and physical examination findings	AEs including CV events, laboratory values, ECG, pulse, BP, hypoglycemic 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 multicenter, randomized, double-blind, age-stratified, placebo-controlled Phase III study with a 24-week short-term treatment period followed by a 28-week extension period to evaluate the effect of dapagliflozin 10 mg once daily (qd) in combination with pre-existing anti-hyperglycemic treatment on HbA1c and on the proportion of subjects who achieved a clinical benefit in adult subjects with T2DM, CVD, and hypertension who have inadequate glycemic control.

Note that this synopsis includes only results from the 24-week short-term treatment period.

Target subject population and sample size

The study entry criteria specified enrollment of male subjects ≥45 years of age and female subjects ≥50 years of age diagnosed with T2DM, CVD, and hypertension who received mono-therapy or dual combination therapy with oral anti-diabetic drugs (OADs), insulin therapy in combination with OADs, or insulin monotherapy on a daily basis for 8 weeks and stable for at least 4 weeks before enrollment and who showed inadequate glycemic control (7.2% ≤ HbA1c ≤ 10.5%). Subjects on anti-hypertensive treatment should have used this treatment uninter-ruptedly on a daily basis in the last 4 weeks before enrollment.

Subjects eligible for the study were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying CV event (>1 year or ≤1 year [i.e., within 12 months] before enrollment). A total of 8 strata were formed for the purposes of randomization by each combination of the three factors, and within each stratum subjects were randomized to dapagliflozin or placebo at a ratio of 1:1.

A total of 362 subjects (181 per group) provided 90% power to detect a difference in proportions of subjects who achieved a clinical benefit of 25% versus 10% (Δ = 15%) within a given age stratum at a significance level of 0.0125 using a chi-square test. Assuming that 3.7% of the randomized subjects were not evaluable in the full analysis set, a total of 376 randomized subjects at minimum were required for each age stratum. The smaller age stratum could contain as few as 40% of the total randomized subjects. Therefore, 940 subjects had to be randomized in total, and the larger age stratum contained 564 randomized subjects (60% of total) at most.

A total of 181 evaluable subjects (full analysis set) for each treatment group within a given age stratum provided >99% power to detect a difference of 0.5% between dapagliflozin and placebo for mean change in HbA1c from baseline to week 24 at a significance level of 0.0125, assuming a standard deviation of 0.9%, using a two-sample t-test.

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

Subjects administered dapagliflozin 10 mg qd or matching placebo according to their assignment to treatment groups as add-on therapy to pre-existing anti-hyperglycemic treatment during the 24-week short-term treatment period. Dapagliflozin or matching placebo was taken orally once daily within 30 minutes before breakfast and at approximately the same time of the day. 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.

Pre-existing anti-hyperglycemic treatment comprised monotherapy or dual combination therapy with OADs, insulin therapy in combination with OADs, or insulin monotherapy. In subjects treated with insulin, the average daily insulin dose was reduced by 25% on the day of randomization (Visit 4). Apart from that, the dose of anti-hyperglycemic medications should not have been changed during the 24-week short-term treatment period unless rescue criteria or a definition of hypoglycemia were met.

Subjects received pre-existing anti-hypertensive, anti-platelet, and lipid lowering treatment. No changes in anti-hypertensive medications were allowed during the 24-week short-term treatment period, except when rescue criteria for SBP or diastolic blood pressure (DBP) were exceeded or the subject experienced symptomatic or orthostatic hypotension. Subjects were instructed to keep anti-platelet and lipid lowering treatment constant throughout the 24-week short-term treatment period. Anti-hypertensive, anti-platelet, and lipid lowering treatment could be changed if in the subject's best interest according to the investigator's judgment.

Duration of treatment

According to the protocol, subjects were to be treated with study medication for 52 weeks (24-week short-term treatment period plus 28-week extension period). Note that this synopsis includes only results from the 24-week short-term treatment period.

Statistical methods

A hierarchical testing procedure was used to control the type I error rate across the two primary and four key secondary endpoints, both in the overall population as well as within individual age strata. Initially, a Bonferroni multiplicity correction was applied to the two tests associated with the primary efficacy variables in the overall study population so that each variable was tested at a significance level of 0.025 (two-sided). Only if the given primary efficacy variable proved significant for the overall population, an additional Bonferroni correction was applied so that each test within age strata was performed at a significance level of 0.0125 (two-sided).

Testing of the key secondary variables was performed in a fixed order sequence and applied separately for the overall population and for each of the two age strata. If both primary variables were statistically significant, the alpha level of 0.05 (two-sided) was used; if only one of the primary variables was statistically significant, testing was done at a significance level of 0.025 (two-sided). If none of the primary variables was statistically significant, no testing was done.

The primary efficacy variables and key secondary efficacy variables were analyzed overall and in each age stratum. For the overall evaluation of the first primary efficacy variable and the continuous secondary efficacy variables an analysis of covariance (ANCOVA) model with treatment group and age-by-insulin use-by-time from most recent qualifying CV event group (8 levels) as fixed effects and baseline value as a covariate was used. For the analysis within each age stratum, the ANCOVA model included terms (fixed effects) for treatment group, insulin use-by-time from most recent qualifying CV event group (4 levels), and baseline covariate. The model was used to derive a least squares estimate of the treatment difference with corresponding p-value and two-sided confidence interval. The level applied to the respective test was determined by the Bonferroni correction. Further, two-sided 95% confidence intervals for the mean change within each treatment group were calculated. For variables analyzed as percent change from baseline, the ANCOVA model was applied to logarithm-transformed data, and resulting least-squares means and confidence intervals were back-transformed to provide estimates in the original scale. The second primary efficacy variable was analyzed by the Cochran-Mantel-Haenszel (CMH) method. For the overall analysis, the CMH model included age-by insulin use-by- time from most recent qualifying CV event group as a strata variable. For the analysis within each age stratum, the CMH model included insulin use-by-time from most recent qualifying CV event as a strata variable. The difference in the response rates between treatment groups was displayed along with a confidence interval derived from asymptotic theory. The level applied to the respective test was determined by the Bonferroni correction. P-values were calculated from a chi-square test using the appropriate CMH model.

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, 1429 subjects were enrolled out of which 922 were randomized. The most common reason for not being randomized was not fulfilling all the inclusion criteria and fulfilling at least one exclusion criterion (454 subjects). Around 88% of the randomized subjects completed the 24-week short-term treatment period and around 86% continued into the 28-week extension period. Primary reason for not continuing into the 28-week extension period was occurrence of a discontinuation criterion (44 subjects). Two subjects in the dapagliflozin and 1 subject in the placebo group died during the 24-week short-term treatment period. Another death for a subject in the placebo group occurred more than 30 days after the last dose of study medication and was not included in the analysis of the 24-week short-term treatment period. All treated subjects were included in the safety analysis set. The full analysis set included 914/922 subjects (526/530 subjects in age stratum <65 years and 388/392 subjects in age stratum ≥65 years).

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 63 years of age with around 42% aged ≥65 years. There were about 68% male and 32% female subjects in both treatment groups. Around 94% of the subjects were at least overweight (BMI ≥25 kg/m^2), and almost two thirds were obese (BMI ≥30 kg/m^2).

Mean duration of T2DM was 12.4 years, and around 56% of the subjects had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%. Around 52% of the subjects reported the use of insulin. Subjects had been on insulin treatment for about 3 years, and the average calculated mean daily insulin dose was slightly higher in the dapagliflozin (57 IU) than in the placebo (49 IU) group. Around 83% of the subjects were on OAD treatment with or without concomitant insulin use.

Most subjects reported coronary heart disease (75.2%) or stroke/transient ischemic attack (20.7%). The median time from diagnosis or occurrence of the most recent qualifying CV event was 4.2 years, and 80% of the subjects had their most recent qualifying CV event diagnosed more than 1 year ago.

All subjects had hypertension according to the inclusion criteria. The duration of hypertension was ≥3 years in almost 90% of the subjects and ≥10 years in 50% of the subjects. Hypertension was well controlled as indicated by a mean seated SBP and DBP of 133.2 mmHg and 76.9 mmHg, respectively. Almost 13% of the subjects had congestive heart failure.

Summary of efficacy results

Primary and key secondary efficacy endpoints are summarized for all subjects in the full analysis set in Table S2.

Note: The following rules applied to the analysis of the primary and key secondary efficacy variables: the LOCF approach was used for all primary and key secondary efficacy variables. The change in HbA1c and the HbA1c item of the 3-item endpoint of clinical benefit was

analyzed excluding data after glycemic rescue and including data after anti-hypertensive rescue. The change in total body weight and the total body weight item of the 3-item endpoint of clinical benefit was analyzed including data after glycemic rescue and including data after anti-hypertensive rescue. The change in seated SBP and the seated SBP item of the 3-item endpoint of clinical benefit was analyzed including data after glycemic rescue and excluding data after anti-hypertensive rescue.

Table S2 Summary of primary and key secondary efficacy endpoints - full analysis set

	PLA N = 459	DAPA 10 MG N = 455
Primary endpoints		
HbA1c (%) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	0.08 (0.0400), 451	-0.38 (0.0403), 448
p-value vs. PLA		<0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent, N#	0.9%, 451	11.7%, 444
p-value vs. PLA		<0.0001 *
Key secondary endpoints		
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N#	-0.99 (0.6651), 459	-2.96 (0.6755), 451
p-value vs. PLA		0.0126 *
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N#	-0.30 (0.1645), 459	-2.56 (0.1630), 455
p-value vs. PLA		<0.0001 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	-1.03 (0.6908), 459	-2.99 (0.7016), 451
p-value vs. PLA		0.0174 *
Subjects with total body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI $\geq$27 kg/m^2		
Percent adjusted (SE), N#	4.0% (0.986), 397	16.5% (1.884), 388
p-value vs. PLA		<0.0001 *

N: number of subjects in the full analysis set.
N#: number of subjects in the full analysis set with non-missing baseline and week t (LOCF) values.
BMI: body mass index; HbA1c: glycosylated hemoglobin; PLA: placebo; DAPA: dapagliflozin; LOCF: last observation carried forward; SBP: systolic blood pressure; SE: standard error.
* Significant p-value: the primary endpoints were tested at $\alpha = 0.025$ (two-sided); the secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$ (two-sided).

Primary endpoints

Subjects in the dapagliflozin group showed a statistically significant mean reduction in HbA1c from baseline to week 24 (last observation carried forward [LOCF]) compared to placebo in all subjects of the full analysis set (-0.46%) and in both age strata (<65 years: -0.42%; ≥65 years: -0.53%).

The proportion of subjects with a clinical benefit based on response for a 3-item endpoint of clinical benefit at week 24 (LOCF) was significantly larger in the dapagliflozin group compared to placebo in all subjects of the full analysis set (9.9%) and in both age strata (<65 years: 10.0%; ≥65 years: 9.9%).

Key secondary endpoints

Since the tests of both primary endpoints yielded a significant result in all subjects in the full analysis set and in both age strata, the secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$ (two-sided).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in seated SBP from baseline to week 8 (LOCF) compared to placebo in all subjects of the full analysis set (-1.97 mmHg) and in the age stratum <65 years (-3.12 mmHg). The placebo-corrected mean change in seated SBP from baseline to week 8 (LOCF) in the age stratum ≥65 years (-0.48 mmHg) was not statistically significant.

Subjects in the dapagliflozin group showed a statistically significant mean percent reduction in total body weight from baseline to week 24 (LOCF) compared to placebo in all subjects of the full analysis set (-2.27%) and in the age stratum <65 years (-2.29%). In age stratum ≥65 years, statistical testing stopped with the previous key secondary endpoint because the result for the comparison between treatment groups was not significant.

Subjects in the dapagliflozin group showed a statistically significant mean reduction in seated SBP from baseline to week 24 (LOCF) compared to placebo in all subjects of the full analysis set (-1.95 mmHg) and in the age stratum <65 years (-2.99 mmHg). In age stratum ≥65 years, statistical testing stopped with the first key secondary endpoint.

The proportion of subjects with a baseline BMI ≥27 kg/m^2 and with a total body weight reduction of at least 5% from baseline to week 24 (LOCF) was significantly larger in the dapagliflozin group compared to placebo in all subjects of the full analysis set (**12.5%)** and in age stratum <65 years (12.4%). In age stratum ≥65 years, statistical testing stopped with the first key secondary endpoint.

Summary of safety results

Numbers (%) of subjects with AEs are summarized by categories of AEs for all subjects in the safety analysis set in Table S3.

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

	Number (%) of subjects	
	PLA N = 462	**DAPA 10 MG N = 460**
At least one AE	268 (58.0)	271 (58.9)
At least one event of hypoglycemia	84 (18.2)	89 (19.3)
Death	1 (0.2)	2 (0.4)
At least one SAE	26 (5.6)	27 (5.9)
AE leading to discontinuation*	21 (4.5)	31 (6.7)
SAE leading to discontinuation*	3 (0.6)	5 (1.1)
Hypoglycemia leading to discontinuation*	0	1 (0.2)
At least one event suggestive of genital infection	5 (1.1)	30 (6.5)
At least one event suggestive of urinary tract infection	18 (3.9)	19 (4.1)

* of study medication.

Adverse events and events of hypoglycemia

Similar proportions of subjects in the dapagliflozin and placebo group experienced at least one AE or serious adverse event (SAE) in all subjects of the safety analysis set (AEs: 58.9% vs. 58.0%; SAEs: 5.9% vs. 5.6%) and in both age strata. Proportions of subjects discontinued from study medication due to an AE or with an AE assessed as related to the study medication were larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (AE leading to discontinuation: 6.7% vs. 4.5%; related AE: 16.3% vs. 11.7%) and in age stratum ≥65 years and similar in both treatment groups in age stratum <65 years.

There were 3 deaths during the 24-week short-term treatment period: one subject in the dapagliflozin group ≥65 years suffered a sudden death, another subject in the dapagliflozin group <65 years died from cardiogenic shock and septic shock, and 1 subject in the placebo group <65 years died from a cerebrovascular accident.

One further subject in the placebo group ≥65 years died from an acute pulmonary edema more than 30 days after the last dose of study medication but before the scheduled follow-up visit. Death of this subject is not included in the analysis of the 24-week short-term treatment period.

Proportions of subjects with an event of hypoglycemia were similar in both treatment groups in all subjects of the safety analysis set (19.3% vs. 18.2%) and in age stratum ≥65 years and larger in the dapagliflozin than in the placebo group in age stratum <65 years. No hypoglycemic event was classified as major. One subject in the dapagliflozin group in age stratum <65 years was discontinued from double-blind study medication due to a hypoglycemic event.

Overall, proportions of subjects with an event of hypoglycemia were larger in subjects receiving background treatment with insulin with or without OAD(s) compared to subjects receiving OAD(s) only. Proportions of subjects with an event of hypoglycemia were larger in the dapagliflozin than in the placebo group in subjects receiving background treatment with insulin plus OAD(s) (OAD(s) excluding SU: 23.8% vs. 18.0%; OAD(s) including SU: 35.9% vs. 22.2%) and did not show a difference between treatment group in subjects receiving insulin alone (36.8% vs. 38.5%).

Events suggestive of genital infection or urinary tract infection (UTI) and events of genital infectionsor 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.

Proportions of subjects with AEs suggestive of genital infections and AEs of genital infections were larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (AEs suggestive of genital infections: 6.5% vs. 1.1%; AEs of genital infections: 5.0% vs. 0.6%) and in both age strata. Around two thirds of the subjects with an AE suggestive of genital infection and almost 60% of the subjects with an AE of genital infection were female.

Proportions of subjects with AEs suggestive of UTI and AEs of UTI were similar in both treatment groups in all subjects of the safety analysis set (AEs suggestive of UTI: 4.1% vs. 3.9%; AEs of UTI: 2.8% vs. 3.2%) and in both age strata. Around two thirds of the subjects reporting at least one AE suggestive of UTI and at least one AE of UTI were female. One subject in the dapagliflozin group reported an AE of costovertebral angle tenderness which was on the pre-specified list of PTs indicating kidney infection but kidney infection was not confirmed.

The proportion of subjects with AEs of hypotension, dehydration, or hypovolemia was small but larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (2.2% vs. 0.4%) and in both age strata.

The proportion of subjects with AEs of renal impairment or failure (predominantly laboratory abnormalities) was small but larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (7.4% vs. 3.9%) and in age stratum ≥65 years and did not show a meaningful difference between treatment groups in age stratum <65 years.

The proportion of subjects with AEs of cardiac disorders was small and similar in both treatment groups in all subjects of the safety analysis set (5.2% vs. 4.8%) and in both age strata.

No subject in the dapagliflozin and 5 subjects in the placebo group (2 in age stratum <65 years and 3 in age stratum ≥65 years) experienced an AE of fracture.

Four subjects in the dapagliflozin and 1 subject in the placebo group experienced an AE of malignant and unspecified neoplasms.

Laboratory evaluation

Four subjects in the dapagliflozin and 2 subjects in the placebo group showed at least one marked abnormality (MA) of hematocrit >55%. Two subjects in the placebo group showed at least one MA of hemoglobin >18 g/dL. All MAs of hematocrit and hemoglobin were observed in age stratum <65 years. None of these subjects showed a thromboembolic AE. There was a small increase in mean hematocrit, hemoglobin, and red blood cell count (RBC) from baseline to week 16 in the dapagliflozin group. Thereafter, the 3 hematology parameters remained almost stable. In the placebo group, mean hematocrit, hemoglobin, and RBC did not show a meaningful change during the 24-week short-term treatment period.

Proportions of subjects with MAs of liver function tests were smaller in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (1.3% vs. 2.2%) and in age stratum <65 years and similar in both treatment groups in age stratum ≥65 years. No subject in either treatment group showed a combined MA of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and total bilirubin (TB). Subjects in the dapagliflozin group showed a decrease in mean AST and ALT and no meaningful change in mean alkaline phosphatase (ALP) and TB from baseline to week 24. In the placebo group, no meaningful change in mean AST, ALT, ALP, and TB was observed from baseline to week 24.

Proportions of subjects with an MA of creatinine ≥1.5 x baseline concentration were larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (3.1% vs. 1.7%) and in age stratum ≥65 years and similar in both treatment groups in age stratum <65 years. Subjects in the dapagliflozin group showed an increase in mean BUN and a slight decrease in mean calculated creatinine clearance from baseline to week 24. Mean serum creatinine, eGFR and cystatin-C did not show a meaningful change from baseline to week 24 in the dapagliflozin group. In the placebo group no meaningful change in any of these renal laboratory parameters was observed from baseline to week 24.

Proportions of subjects with an MA of potassium ≥6.0 mEq/L were larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (4.2% vs. 2.6%) and in age stratum <65 years and did not show a meaningful difference between treatment groups in the age stratum ≥65 years. Proportions of subjects with an MA of inorganic phosphorus above age related numbers were larger in the dapagliflozin than in the placebo group in all subjects of the safety analysis set (2.6% vs. 1.1%) and in age stratum ≥65 years and did not show a meaningful difference between treatment groups in the age stratum <65 years. Subjects in the dapagliflozin group showed an increase in mean magnesium, a slight increase in mean inorganic phosphorus, and a decrease in mean uric acid from baseline to week 24. The other electrolytes did not show a meaningful change from baseline to week 24 in the dapagliflozin group. In the placebo group, no meaningful change in any serum electrolyte was observed from baseline to week 24.

No subject in the dapagliflozin and 3 subjects in the placebo group showed at least one MA of CK >5 x upper limit of normal. All subjects with an MA of CK were included in age stratum <65 years. Subjects in the dapagliflozin group showed a decrease in mean CK from baseline

to week 24. In the placebo group, no meaningful change in mean CK was observed from baseline to week 24.

Vital signs

Subjects in the dapagliflozin group showed a mean decrease in seated SBP and DBP from baseline to week 24 (LOCF) compared to placebo in all subjects of the safety analysis set and in age stratum <65 years and no meaningful difference in the mean change of seated SBP and DBP between treatment groups in age stratum ≥65 years. Seated heart rate did not show a meaningful mean change in either treatment group from baseline to week 24.

Proportions of subjects with a measured orthostatic hypotension were larger in the dapagliflozin than in the placebo group overall (17.2% vs. 13.2%) and in both age strata: <65 years (16.7% vs. 11.5%); ≥65 years (18.0% vs. 15.5%).