2. SYNOPSIS

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Title of study: Pharmacodynamics, pharmacokinetics, safety and tolerability of ultra low doses of dapagliflozin in healthy subjects

Investigator: [redacted]

Study site: [redacted]

Publication (reference): None

Studied period (years): 11 June 2010 to 14 June 2010	**Phase of development**: 1

Objectives: The primary objective was to assess the effect of a single 0.001- to 2.5-mg oral dose of dapagliflozin on urinary glucose excretion in healthy subjects.

Secondary objectives were:

- To assess the safety and tolerability of a single 0.001- to 2.5-mg oral dose of dapagliflozin in healthy subjects.
- To characterize the pharmacokinetics of low doses of dapagliflozin and dapagliflozin 3-O-glucuronide (0.1 to 2.5 mg).

Exploratory objectives were:

- To assess the palatability of dapagliflozin in oral solution (0.001- to 0.3-mg doses).
- To assess dapagliflozin dose(s) at which glucose can be detected in urine by a commercially available glucose dipstick test after the administration of a single 0.001- to 2.5-mg oral dose of dapagliflozin.
- To assess the effect of dapagliflozin on urinary glucose clearance and the percent inhibition of renal glucose reabsorption.
- To compare the change of plasma glucose AUC_{0-3} from Baseline after the administration of a single 0.001- to 2.5-mg oral dose of dapagliflozin with a liquid meal.

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Methodology: This was an open-label, randomized, parallel-group, single-dose, pharmacokinetic (PK) and pharmacodynamic (PD) study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days before Day 1. On the evening of Day −2, subjects were admitted to the clinical facility. Assessments performed on Day −1 included vital sign measurements, 12-lead ECG, laboratory tests including serum creatinine and PD sampling, calculation of estimated glomerular filtration rate (eGFR), urine glucose dipstick test and urine interval PD sampling, liquid Meal Tolerance Test (MTT), and palatability assessment (for subjects receiving dapagliflozin solution). On Day 1, subjects received a single oral dose (solution or tablet) of dapagliflozin as follows:

- Dapagliflozin solution (0.001 mg [Cohort 1], 0.01 mg [Cohort 2], 0.1 mg [Cohort 3], and 0.3 mg [Cohort 4]).
- Dapagliflozin tablet (1.0 mg [Cohort 5] and 2.5 mg [Cohort 6]).

Blood samples for PK analysis were collected for up to 24 hours after study drug administration. Blood and urine samples for PD analysis were collected for up to 24 hours starting on Day −1 until Day 1 and from predose on Day 1 until Day 2. A liquid MTT was administered 1 hour after drug administration, and eGFR was calculated on Days −1 and 1. A urine glucose dipstick test was performed at selected times starting at Screening, on Day −2, on Day −1 to Day 1, and from predose on Day 1 to Day 2. Subjects randomly assigned to receive oral solutions of 0.001, 0.01, 0.1-, or 0.3-mg dapagliflozin underwent palatability assessments using a questionnaire on Day −1 (vehicle only) and after dosing on Day 1. The results of the palatability assessment will be used to guide liquid formulation development.

Subjects were closely monitored for adverse events (AEs) throughout the study, and clinical laboratory evaluations, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECG) were performed at selected times throughout the study. Subjects were discharged from the clinical facility on Day 2 after all study evaluations were completed.

Number of subjects (planned and analyzed): A total of 36 subjects were planned; 35 subjects were randomly assigned, and 33 subjects completed the study. Thirty-three subjects were included in the PK, PD, and safety populations. However, PK parameters were not calculated for dapagliflozin doses below 0.1 mg as concentrations were below the limit of quantification (BLQ), therefore data for only 22 subjects were included in the PK analyses.

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Diagnosis and main criteria for inclusion: Healthy male and female subjects as determined by medical history, physical examination, 12-lead ECG, and clinical laboratory evaluations were eligible to participate in the study. Female subjects of childbearing potential were not nursing or pregnant and were using an acceptable method of contraception for at least 4 weeks before dosing and throughout the study. All female subjects had a negative pregnancy test within approximately 48 hours before dosing.

Test product, dose and mode of administration, batch number:

Dapagliflozin powder (for solution), single dose administered orally, [redacted]

Dapagliflozin 1.0-mg tablet, single dose administered orally, [redacted]

Dapagliflozin 2.5-mg tablet, single dose administered orally, [redacted]

Duration of treatment: Subjects received a single oral dose of study drug. The duration of participation for each subject, including Screening, was approximately 23 days.

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Criteria for evaluation:

Pharmacodynamics and Pharmacokinetics: Blood samples for the determination of plasma concentrations of dapagliflozin and its inactive metabolite (dapagliflozin 3-O-glucuronide) were collected before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing on Day 1. The lower limit of quantitation (LLOQ) was 0.100 and 0.200 ng/mL for dapagliflozin and dapagliflozin 3-O-glucuronide, respectively. Blood samples were also collected for determination of plasma glucose on Days −1 (Baseline) and 1 at 0, 0.5, 1, 1.5, 2, 3, 4, and 24 hours. The 24-hour sample on Day −1 was the same as the 0-hour sample on Day 1. On Days −1 (Baseline) and 1, urine samples were collected for determination of urinary glucose excretion at intervals of 0 to 1, 1 to 4, and 4 to 24 hours. In addition, a commercially available urine glucose dipstick test (Multistix® 10 SG Reagent Strips for Urinalysis) was used to test for the presence of glucose in

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spot urine samples at 0 (predose), 1, 8, and 24 hours on Days −1 and 1.

The following PD parameters were calculated for plasma and urine glucose:

BAe_{0-24}	change in 24-hour urinary glucose excretion from Baseline after the administration of a single dose of dapagliflozin on Day 1. The 24-hour urinary glucose excretion at Baseline (Day −1) and Day 1 was calculated as the sum of the intervals collected from 0 to 1 hour, 1 to 4 hours, and 4 to 24 hours.
$BAUEC_{1-4}$	baseline-adjusted area under the plasma concentration versus time curve from 1 to 4 hours during 3-hour liquid MTT
BCLr	baseline-adjusted urinary glucose clearance
%IRR	percent inhibition of renal glucose reabsorption

The following PK parameters were calculated for dapagliflozin and dapagliflozin 3-O-glucuronide:

AUC_{0-t}	area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration
AUC_{0-inf}	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
C_{max}	maximum observed plasma concentration
T_{max}	time to achieve maximum observed plasma concentration
$t_{1/2}$	terminal half-life

Safety: Safety assessments included monitoring of AEs, clinical laboratory evaluations, vital sign measurements, physical examination findings, and 12-lead ECG results.

Statistical methods:

Pharmacodynamics and Pharmacokinetics: Plasma concentration and time deviation data for dapagliflozin and dapagliflozin 3-O-glucuronide are presented in data listings and summarized using the following descriptive statistics: number of subjects, mean, SD, coefficient of variation (CV), median, minimum, maximum, and the 25th and 75th percentiles. Mean and individual

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plasma concentration versus scheduled time profiles are presented in figures on linear and semilogarithmic scales. Urine concentration data for glucose are presented in a data listing. Results of glucose dipstick tests are listed by dose level and study day and summarized by frequency tables. All PD and PK parameters are presented in data listings and summarized by dose level using the following descriptive statistics: number of subjects, mean, SD, CV, median, and range. Geometric means are presented for PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}, and PD parameters AUEC, BAUEC, CLr, and BCLr.

To assess the effect of single oral doses of dapagliflozin on urinary glucose excretion, point estimates and 95% confidence intervals (CIs) were calculated for each dose level. These estimates were constructed from an analysis of variance model on the change from Baseline in Ae_{0-24} with dose level as the main factor level. Weighted least squares were used to estimate the means and the 95% CIs.

The frequency distribution (counts and percentages) of subjects with an increase in 24-hour urinary glucose excretion after dosing were tabulated by dose levels.

To compare the change from Baseline in plasma glucose AUC during the 3-hour MTT ($AUEC_{1-4}$) administered after a single dapagliflozin dose on Day 1, point estimates and 95% CIs were calculated for each dose level. These estimates were constructed from the analysis of covariance model on the changes from Baseline in plasma glucose AUC during the 3-hour MTT ($BAUEC_{1-4}$) with dose level as the main factor level and baseline plasma glucose AUC during 3-hour MTT as the covariate ($AUEC_{1-4}$ on Day –1).

All palatability results are presented in a data listing.

Safety: Subject disposition, demographics, and baseline characteristics are presented in data listings and summarized. All AE data are presented in data listings and summarized by system organ class, preferred term, and dose level. Vital sign measurements and clinical laboratory test results are presented in data listings and summarized by dose level. Any clinically significant clinical laboratory results are listed. Electrocardiogram and physical examination results are listed.

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SUMMARY – CONCLUSIONS

Pharmacodynamics:

The following table summarizes the results from the statistical analysis of the baseline-adjusted amount of glucose excreted in 24 hours.

Parameter (unit)	Treatment[a]	N	LS Mean	95% CI for the LS Mean
$BAe_{0\ 24}$ (mg)	1	5	50.6	154.3 , 53.0
	2	6	5.6	31.4 , 20.2
	3	5	17.1	6.5 , 40.7
	4	5	538.4	115.9 , 961.0
	5	6	19096.8	10215.2 , 27978.5
	6	6	22836.2	15486.0 , 30186.4

Abbreviations: $BAe_{0\ 24}$, baseline adjusted $Ae_{0\ 24}$; CI, confidence interval; LS, least squares.

Note: An analysis of variance model on the change from Baseline in $Ae_{0\ 24}$ with dose level as the main factor level was used. Weighted least squares were used to estimate the means and the 95% CIs.

[a] Treatment 1: single oral dose of 0.001 mg dapagliflozin solution.
Treatment 2: single oral dose of 0.01 mg dapagliflozin solution.
Treatment 3: single oral dose of 0.1 mg dapagliflozin solution.
Treatment 4: single oral dose of 0.3 mg dapagliflozin solution.
Treatment 5: single oral dose of 1.0 mg dapagliflozin tablet.
Treatment 6: single oral dose of 2.5 mg dapagliflozin tablet.

Following single oral administration of dapagliflozin, the amount of glucose excreted in 24 hours increased with dapagliflozin dose from 0.3 to 2.5 mg. The mean absolute amount of glucose excreted in urine in response to dapagliflozin treatment (as measured by $BAe_{0\text{-}24}$) ranged from 538 mg at the 0.3-mg dapagliflozin dose level to more than 20000 mg at the 2.5-mg dapagliflozin dose level. All subjects who received 1.0- and 2.5-mg dapagliflozin (6 subjects per dose) exhibited an increase in 24-hour urinary glucose amount excreted. Urinary glucose clearance was less than 1 mL/min at doses ranging from 0.001 to 0.3 mg and increased to 24 and 36 mL/min at the 1.0- and 2.5-mg dose levels, respectively.

Urinary glucose reabsorption was close to 100% for doses ranging from 0.001 to 0.3 mg.

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However, glucose reabsorption was reduced to 79% and 75% at the 1.0- and 2.5-mg dapagliflozin dose levels, respectively. There was 21% and 25% inhibition of renal glucose reabsorption at the 1.0- and 2.5-mg dapagliflozin dose levels, respectively. At doses below 1.0 mg, there was minimal or no inhibition of glucose reabsorption.

The following table summarizes the results from the statistical analysis of plasma glucose following the administration of dapagliflozin with a liquid meal (MTT).

Parameter (unit)	Treatment[a]	N	LS Mean	95% CI for the LS Mean
$BAUEC_{1\ 4}$ (mg•h/dL)	1	5	2.4	19.9 , 15.1
	2	6	16.7	32.9 , 0.5
	3	5	28.4	47.0 , 9.8
	4	5	26.1	43.7 , 8.4
	5	6	25.7	41.7 , 9.7
	6	6	25.5	41.5 , 9.6

Abbreviations: $BAUEC_{1\ 4}$, baseline adjusted $AUEC_{1\ 4}$; CI, confidence interval; LS, least squares; MTT, meal tolerance test.

Note: An analysis of covariance model on the change from baseline in plasma glucose AUC during 3 hour MTT with dose level as the main factor level and baseline plasma glucose AUC during 3 hour MTT as the covariate, was used for this analysis.

[a] Treatment 1: single oral dose of 0.001 mg dapagliflozin solution.
Treatment 2: single oral dose of 0.01 mg dapagliflozin solution.
Treatment 3: single oral dose of 0.1 mg dapagliflozin solution.
Treatment 4: single oral dose of 0.3 mg dapagliflozin solution.
Treatment 5: single oral dose of 1.0 mg dapagliflozin tablet.
Treatment 6: single oral dose of 2.5 mg dapagliflozin tablet.

Oral administration of dapagliflozin reduced the plasma glucose levels when given with a liquid meal. The change from Baseline of plasma glucose AUC following the administration of a single dose of dapagliflozin with a liquid meal was greater at the 0.1-mg dapagliflozin dose and above, but with no apparent difference between the dose levels.

All subjects who received the 1.0- and 2.5-mg treatments (6 subjects per dose) showed a positive

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result in the glucose dipstick test by 8 hours. Glucose dipstick test results were negative at all time points in doses of 0.1 mg and below.

Pharmacokinetics:

All plasma concentrations of dapagliflozin were BLQ from all subjects (a total of 5) who received the dapagliflozin 0.001-mg solution dose. Four of 6 subjects who received the dapagliflozin 0.01-mg solution dose had 1 measurable concentration for dapagliflozin. Also, at both of these dose levels, dapagliflozin 3-O-glucuronide concentrations were BLQ in all of the subjects.

The following table summarizes the PK parameters for dapagliflozin.

	Treatment			
Parameter (unit)	**0.1 mg Solution (N=5)**	**0.3 mg Solution (N=5)**	**1.0 mg Tablet (N=6)**	**2.5 mg Tablet (N=6)**
$AUC_{0\ t}$ (ng•h/mL)	3.22 (20%)	11.17 (23%)	49.24 (37%)	131.07 (23%)
$AUC_{0\ inf}$ (ng•h/mL)[a]	3.87 (18%)	12.51 (25%)	54.00 (39%)	142.92 (23%)
C_{max} (ng/mL)	1.19 (25%)	3.06 (19%)	13.21 (38%)	42.51 (24%)
T_{max} (h)	0.50	0.50	1.00	0.58
	(0.50 1.00)	(0.50 1.00)	(1.00 1.00)	(0.50 1.00)
$t_{1/2}$ (h)	3.51 (0.34)	7.34 (2.36)	8.16 (1.14)	8.32 (1.64)

Note: Geometric means (CV) are reported only for AUCs and C_{max}. Arithmetic mean (SD) is presented for $t_{1/2}$. For T_{max}, median (minimum maximum) is presented.
[a] Without Subject [redacted] who had a percent extrapolated area greater than 20%, geometric mean (CV) value in the 0.1 mg dose group is 3.93 (20).

Geometric mean peak exposure of dapagliflozin as assessed by C_{max} increased with dose from 1.19 ng/mL to 42.51 ng/mL as the dapagliflozin dose increased from 0.1 to 2.5 mg. Geometric mean total exposure of dapagliflozin as assessed by $AUC_{0\text{-}inf}$ increased with dose from 3.87 ng•h/mL to 142.92 ng•h/mL as the dapagliflozin dose increased from 0.1 mg to 2.5 mg. Median T_{max} for dapagliflozin occurred at 0.5 to 1 hour at all dose levels, and $t_{1/2}$ was 7 to 8 hours for the 0.3-, 1-, and 2.-5mg dapagliflozin dose levels. However, mean $t_{1/2}$ was only 3.5 hours for the 0.1-mg dose level reflecting that the assay sensitivity did not allow for the final elimination phase to be accurately characterized.

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The following table summarizes the PK parameters for dapagliflozin 3-O-glucuronide:

	Treatment			
Parameter (unit)	**0.1 mg Solution (N=5)**	**0.3 mg Solution (N=5)**	**1.0 mg Tablet (N=6)**	**2.5 mg Tablet (N=6)**
$AUC_{0\ t}$ (ng•h/mL)	3.22 (34%)	12.65 (37%)	60.35 (23%)	172.59 (49%)
$AUC_{0\ inf}$ (ng•h/mL) [a]	3.93 (36%)	17.19 (15%)	67.52 (22%)	191.44 (47%)
C_{max} (ng/mL)	1.26 (25%)	3.49 (43%)	17.19 (24%)	46.21 (63%)
T_{max} (h)	1.50	1.50	1.50	1.25
	(1.00 1.50)	(1.00 1.50)	(1.00 1.50)	(1.00 1.50)
$t_{1/2}$ (h)	1.98 (0.98)	5.58 (1.58)	8.60 (2.22)	9.59 (2.07)

Note: Geometric means (CV) are reported only for AUCs and C_{max}. Arithmetic mean (SD) is presented for $t_{1/2}$. For T_{max}, median (minimum maximum) is presented.
N=4 for $t_{1/2}$ and $AUC_{0\ inf}$ in 0.3 mg solution treatment.
[a] Without Subject [redacted] who had a percent extrapolated area greater than 20%, geometric mean (CV) value in the 0.1 mg dose group is 3.67 (41).

Geometric mean C_{max} of dapagliflozin 3-O-glucuronide increased with dose from 1.26 ng/mL to 46.21 ng/mL as the dapagliflozin dose increased from 0.1 mg to 2.5 mg. Geometric mean total exposure of dapagliflozin 3-O-glucuronide increased with dose from 3.93 ng•h/mL to 191.44 ng•h/mL as the dapagliflozin dose increased from 0.1 mg to 2.5 mg, probably reflecting the assay limits such that the final elimination phase was not accurately characterized at the lower doses. Median T_{max} for dapagliflozin 3-O-glucuronide occurred at 1.25 to 1.50 hours at all dose levels, and $t_{1/2}$ was 6 to 10 hours for the 0.3-, 1-, and 2.5-mg dapagliflozin dose levels. However, mean $t_{1/2}$ was only 2 hours for the 0.1-mg dose level, probably reflecting the assay limits such that the final elimination phase was not accurately characterized; thus, the $t_{1/2}$ estimate for the 0.1-mg dose should be interpreted with caution.

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Safety:

Subject disposition is summarized in the following table:

	Treatment						
No. of subjects (%)	**0.001 mg Solution (N=6)**	**0.01 mg Solution (N=6)**	**0.1 mg Solution (N=6)**	**0.3 mg Solution (N=5)**	**1.0 mg Tablet (N=6)**	**2.5 mg Tablet (N=6)**	**Overall (N=35)**
Safety population[a]	5 (83.3)	6 (100.0)	5 (83.3)	5 (100.0)	6 (100.0)	6 (100.0)	33 (94.3)
PK population[b]	5 (83.3)	6 (100.0)	5 (83.3)	5 (100.0)	6 (100.0)	6 (100.0)	33 (94.3)
PD population[c]	5 (83.3)	6 (100.0)	5 (83.3)	5 (100.0)	6 (100.0)	6 (100.0)	33 (94.3)
Completed	5 (83.3)	6 (100.0)	5 (83.3)	5 (100.0)	6 (100.0)	6 (100.0)	33 (94.3)
Discontinued	1 (16.7)	0	1 (16.7)	0	0	0	2 (5.7)
Reasons for discontinuation							
Other	1 (16.7)	0	1 (16.7)	0	0	0	2 (5.7)

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic.

Note: Percentages were based on the number of subjects who were randomly assigned in each treatment and overall.

[a] The safety population included all enrolled subjects who received study drug. Two subjects discontinued from the study prior to receiving dapagliflozin and were not included in the safety population for analyses.

[b] The PK population included all subjects who had adequate PK profiles. All available derived PK parameter values were included in the PK data set and reported, but only subjects with adequate PK profiles were included in the summary statistics and statistical analysis. Pharmacokinetic parameters were not calculated for dapagliflozin doses below 0.1 mg as concentrations were below the limit of quantification, therefore data for only 22 subjects were included in the PK analyses.

[c] The PD population included all subjects who had a baseline value and at least 1 other value after dapagliflozin administration.

A total of 35 subjects were randomly assigned in the study. Of these, 33 subjects (94.3%) completed the study. Two (5.7%) subjects discontinued from the study prior to receiving dapagliflozin. Subject MB102088-1-96 received the vehicle, and the next day experienced mild diarrhea, abdominal pain, and nausea, which resolved without treatment within 24 hours. This subject changed his mind regarding study participation; the subject was scheduled to receive dapagliflozin 0.001-mg solution. Subject [redacted] was discontinue due to out-of-range

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clinical laboratory results (elevated aspartate aminotransferase and creatine kinase); the subject was scheduled to receive dapagliflozin 0.1-mg solution.

Subject demographics and baseline characteristics are summarized in the following table:

	Treatment						
	0.001-mg Solution (N 5)	**0.01-mg Solution (N 6)**	**0.1-mg Solution (N 5)**	**0.3-mg Solution (N 5)**	**1.0-mg Tablet (N 6)**	**2.5-mg Tablet (N 6)**	**Overall (N 33)**
Age (years)							
Mean (SD)	28.8 (10.23)	30.8 (8.18)	29.2 (5.97)	36.6 (10.92)	30.0 (6.54)	30.7 (11.79)	31.0 (8.82)
Median	27.0	31.0	26.0	43.0	28.5	26.5	28.0
Min, Max	19, 46	21, 45	23, 37	20, 46	22, 40	20, 52	19, 52
Sex, No. (%)							
Male	2 (40.0)	2 (33.3)	2 (40.0)	2 (40.0)	3 (50.0)	1 (16.7)	12 (36.4)
Female	3 (60.0)	4 (66.7)	3 (60.0)	3 (60.0)	3 (50.0)	5 (83.3)	21 (63.6)
Race, No. (%)							
White	4 (80.0)	4 (66.7)	5 (100.0)	4 (80.0)	4 (66.7)	4 (66.7)	25 (75.8)
Black or African American	1 (20.0)	2 (33.3)	0	1 (20.0)	2 (33.3)	2 (33.3)	8 (24.2)
Ethnicity, No. (%)							
Hispanic or Latino	2 (40.0)	2 (33.3)	3 (60.0)	3 (60.0)	3 (50.0)	2 (33.3)	15 (45.5)
Not Hispanic or Latino	3 (60.0)	4 (66.7)	2 (40.0)	2 (40.0)	3 (50.0)	4 (66.7)	18 (54.5)
Height (cm)							
Mean (SD)	168.26 (8.599)	164.17 (10.454)	168.22 (15.109)	169.34 (14.561)	163.75 (11.537)	168.20 (9.703)	166.84 (11.042)
Median	168.90	165.00	162.40	167.70	160.85	163.25	163.50
Min, Max	157.1, 180.9	147.6, 178.9	154.0, 187.3	153.0, 187.5	148.5, 178.3	160.7, 185.4	147.6, 187.5
Weight (kg)							
Mean (SD)	74.08 (15.655)	70.68 (7.240)	75.76 (18.640)	78.12 (15.623)	68.72 (9.829)	78.52 (13.626)	74.16 (13.081)

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Median	72.10	72.10	74.60	69.60	69.90	75.50	72.10
Min, Max	59.8, 99.0	57.8, 79.2	54.7, 103.7	63.1, 100.0	54.8, 81.2	60.3, 94.8	54.7, 103.7
BMI (kg/m^2)							
Mean (SD)	25.96 (3.186)	26.22 (1.273)	26.54 (3.831)	27.08 (2.887)	25.55 (1.435)	27.60 (2.842)	26.49 (2.548)
Median	26.50	26.05	24.80	25.30	25.20	27.65	25.90
Min, Max	21.8, 30.3	24.7, 28.3	22.4, 31.5	24.5, 30.7	24.2, 28.2	22.6, 31.2	21.8, 31.5

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum.

Note: Percentages were based on the number of subjects in the safety population who were randomly assigned in each treatment and overall.

Overall AEs are summarized in the following table:

	Treatment						
No. of subjects (%)	**0.001 mg Solution (N=5)**	**0.01 mg Solution (N=6)**	**0.1 mg Solution (N=5)**	**0.3 mg Solution (N=5)**	**1.0 mg Tablet (N=6)**	**2.5 mg Tablet (N=6)**	**Overall (N=33)**
Total number of AEs	0	0	0	1	2	0	3
Number of subjects with at least 1 AE	0	0	0	1 (20.0)	1 (16.7)	0	2 (6.1)

Abbreviation: AE, adverse event.

Note: At each level of subject summarization, a subject was counted once if he or she reported 1 or more events. Adverse events were summarized by treatment at onset of the event and were coded using MedDRA Version 12.1. Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.

Two subjects (6.1%) reported AEs after receiving study drug. One subject (1/5, 20.0%) in the dapagliflozin 0.3-mg solution group experienced presyncope, and 1 subject (1/6, 16.7%) in the dapagliflozin 1.0-mg tablet group experienced abdominal pain and diarrhea. No AE was

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considered related to study drug, and all AEs were considered mild in severity. All AEs resolved without treatment by the end of the study. There were no deaths, SAEs, or AEs that led to study drug discontinuation. No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, physical examination findings, or 12-lead ECG results.

CONCLUSIONS:

[redacted]

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[redacted]		
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