Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: N/A		
Name of Active Ingredient: Dapagliflozin		

SYNOPSIS

Final Clinical Study Report for Study MB102077

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Subjects with Type 2 Diabetes with Inadequately Controlled Hypertension Treated with an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) and an Additional Antihypertensive Medication

INVESTIGATORS/STUDY CENTERS: [redacted] investigators at [redacted] sites [redacted] in United States, [redacted] in Canada, [redacted] in Puerto Rico, [redacted] in Colombia, [redacted] in Mexico, [redacted] in Denmark, [redacted] in Finland, [redacted] in Hungary, [redacted] in Germany, [redacted] in Czech Republic, [redacted] in Poland, [redacted] in Romania, [redacted] in United Kingdom, [redacted] in Ireland, [redacted] in Australia, and [redacted] in India)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 29-Oct-2010 **CLINICAL PHASE:** 3
Study Completion Date: 07-Feb-2013

OBJECTIVES:

Primary Efficacy Objectives:

- To compare the change from baseline in seated systolic blood pressure (SBP) after 12 weeks of double-blind treatment between the dapagliflozin 10 mg treatment group and the placebo treatment group.
- To compare the change from baseline in glycosolated hemoglobin (HbA1c) after 12 weeks of double-blind treatment between the dapagliflozin 10 mg treatment group and the placebo treatment group.

Secondary Efficacy Objectives:

- To compare the change from baseline in 24-hour ambulatory SBP after 12 weeks of double-blind treatment between the dapagliflozin 10 mg treatment group and the placebo treatment group.
- To compare the change from baseline in seated and 24-hour ambulatory diastolic blood pressure (DBP) after 12 weeks of double-blind treatment between the dapagliflozin 10 mg treatment group and the placebo treatment group.
- To compare the change from baseline in serum uric acid after 12 weeks of double blind treatment between the dapagliflozin 10 mg treatment group and the placebo treatment group.

There were 6 exploratory study objectives, which are described in the study report body.

METHODOLOGY: Following screening, subjects entered the qualification period in which they maintained their current treatment with a stable dose of a commercially-available oral antidiabetic agent(s) (OAD) and/or insulin plus stable therapeutic doses of a commercially-available ACEI or ARB plus an additional antihypertensive medication. [Note: prior to Protocol Amendment 8, subjects receiving insulin therapy were excluded from study participation]. Qualified subjects entered a 28-day placebo lead-in period during which they received diet and exercise counseling that was provided for the duration of the study. Subjects were given a blood glucose meter and instructed on self monitoring of blood glucose. Single-blind placebo was used to assess subject's compliance with treatment and eligibility for entry into the double-blind treatment period.

Eligible subjects who successfully completed the single-blind, placebo lead-in period and met study entry criteria for the double-blind treatment period were randomized (in a 1:1 ratio) in a blinded manner to 1 of 2 treatments groups consisting of 10 mg of dapagliflozin or dapagliflozin matching placebo, administered daily with the morning meal. Randomization was stratified according to the additional antihypertensive medication use (thiazide/thiazide-like diuretic versus calcium channel blocker, beta blocker, alpha adrenergic blocker, or central alpha adrenergic agonist) and according to insulin use at baseline. [Note: Prior to Protocol Amendment 8, randomization was stratified according to subjects' additional antihypertensive medication use only]. Subjects who completed the double-blind treatment period, or who discontinued study drug (except for withdrawal of consent), were asked to return for a follow-up visit at Week 13 (or 1 week after last dose of study medication. Scheduled visits occurred at Weeks 1, 2, 4, 8, 12, and 13. Subjects meeting prespecified criteria for severe or sustained hypertension during the double-blind treatment period were eligible to receive open-label rescue medication with an oral antihypertensive agent in addition to their current background therapy.

Changes in the blinded study medication were not permitted during the double-blind treatment period. Subjects were to maintain their stable dose of commercially-available antidiabetic agent(s), plus their stable therapeutic dose of a commercially-available ACEI or ARB plus an additional antihypertensive medication, and no new antidiabetic therapy was to be added during the double-blind treatment period. Subjects taking insulin were to maintain their insulin type and keep their insulin dose as stable as possible; those with a > 10% change (relative to Day 1) in their mean total daily insulin dose were to be discontinued from the study.

This study was originally designed with an additional double-blind treatment group, dapagliflozin 5 mg, but randomization of new subjects to this group was stopped as of Protocol Amendment 8 (implemented 01-Nov-2011). Subjects who had been randomized into the dapagliflozin 5 mg group remained on their blinded medication without change until study completion.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned to randomize: 408 (204 per treatment group [dapagliflozin 10 mg, placebo]). [Note: prior to Amendment 8, the planned number to be randomized was 765 [255 per treatment group]. **Enrolled** (signed study-specific informed consent): 2245; **Randomized and treated**: 582 (449: 224 in dapagliflozin 10 mg and 225 in placebo treatment groups; 133 in dapagliflozin 5 mg treatment group).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects with a diagnosis of type 2 diabetes (TD2M), aged ≥ 18 to ≤ 89 years, who had inadequate glycemic control, defined as HbA1c between ≥ 7.0% and ≤ 10.5% while on a stable dose of an OAD for at least 6 weeks prior to enrollment (12 weeks for a thiazolidinedione) and/or a stable daily dose of insulin during the 8 weeks prior to enrollment as monotherapy or in combination with an OAD. Subjects must have also had inadequately-controlled hypertension, defined as seated SBP ≥ 140 and < 165 mmHg, and DBP ≥ 85 and < 105 mmHg at the enrollment and Day 1 visits while on a stable, effective therapeutic dose of an ACEI or ARB, and an additional antihypertensive medication for at least 4 weeks prior to the enrollment visit. Subjects were required to have a mean 24-hour blood pressure (BP) ≥ 130/80 mmHg, as determined by ambulatory BP monitoring (ABPM) measured between Day -7 and Day -1 of the lead-in period, and a body mass index (BMI) of ≤ 45.0 kg/m^2 and central C-peptide value ≥ 0.8 ng/mL (0.30 nmol/L) at the enrollment visit.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dapagliflozin tablets 5 mg and 10 mg, oral administration, 12 weeks. Batch numbers: 5 mg: [redacted]; 10 mg: [redacted].

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Matching placebo for dapagliflozin tablets (5 and 10 mg), oral administration; 4-week lead-in period and 12-week double-blind treatment period. Batch numbers: matching 5 mg: [redacted]; matching 10 mg: [redacted], [redacted].

CRITERIA FOR EVALUATION:

Co-primary Efficacy Endpoints: The co-primary endpoints were the changes from baseline at Week 12 in seated SBP and HbA1c.

Secondary Efficacy Endpoints: The secondary endpoints were the changes from baseline at Week 12 in 24-hour mean ambulatory SBP, seated DBP, 24-hour mean ambulatory DBP, and serum uric acid.

Safety: Safety outcomes included reported serious and non-serious AEs, discontinuations due to AEs, events of special interest, laboratory abnormalities, standard safety laboratory tests, changes in electrocardiograms (ECGs), and changes from baseline in supine and standing BP; seated, supine, and standing heart rate; and 24-hour ambulatory heart rate.

Pharmacodynamics: While there was no pharmacodynamic objective, protocol-specified fasting urine glucose:creatinine ratios (UGCR) were measured before the first dose of study medication on Day 1 and at Week 12.

STATISTICAL CONSIDERATIONS: The primary efficacy analysis evaluated the change from baseline in seated SBP at Week 12 for the dapagliflozin 10 mg treatment group compared to placebo based on a longitudinal repeated measures analysis using direct likelihood with fixed categorical effects of treatment, week, treatment-by-week interaction, and randomization strata and continuous fixed covariates of baseline seated SBP value and baseline seated SBP value by week interaction. If this primary analysis was statistically significant at the 0.05 level, the statistical test for the second co-primary endpoint (change from baseline in HbA1c at Week 12) was conducted. This analysis also used a similar longitudinal repeated measures analysis except that the continuous fixed covariates were baseline HbA1c and baseline HbA1c by week interaction.

If the comparisons between the dapagliflozin 10 mg treatment group and the placebo group were significant at the 0.05 level for both co-primary endpoints, the statistical tests for the secondary efficacy endpoints were performed. The family-wise type I error rate related to the primary and secondary efficacy endpoints was controlled at the 2-sided 0.05 level by using a hierarchical closed testing procedure. Data after rescue were excluded from BP analyses.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Of the 449 subjects who were randomized to the dapagliflozin 10 mg or placebo groups and received at least 1 dose of study medication, 413 (92.0%) completed the 12-week double-blind treatment period (Table 1). The discontinuation rate was higher for the placebo group (9.8%) than for the dapagliflozin 10 mg group (5.8%).

In general, the dapagliflozin 10 mg and placebo treatment groups were balanced with respect to demographic characteristics and baseline physical measurements (Table 2). Overall, most subjects were less than 65 years of age (88.2%) and White (70.6%); 64.1% of subjects were obese (i.e., BMI ≥ 30 kg/m^2) and the mean baseline BMI was 32.01 kg/m^2. There were slightly more male (55.0%) than female (45.0%) subjects across the 2 treatment groups.

Baseline diabetes and hypertension characteristics and baseline renal function were balanced across the dapagliflozin 10 mg and placebo treatment groups. The overall median duration of T2DM was 6.4 years, and 28.1% had been diagnosed with T2DM for > 10 years. The overall mean baseline HbA1c was 8.04% and the mean baseline fasting plasma glucose (FPG) was 160.71 mg/dL. The overall median duration of hypertension was 7.5 years, and 36.7% had been diagnosed with hypertension for > 10 years. The mean baseline glomerular filtration rate, estimated using the using the Modification of Diet and Renal Disease formula (eGFR), was 84.781 and 87.014 mL/min/1.73 m^2 for the dapagliflozin 10 mg and placebo treatment groups, respectively. At baseline, 53.5% of subjects overall had mild renal impairment (defined as estimated GFR [eGFR] between 60 and < 90 mL/min/1.73m^2) and 7.8% of subjects overall had moderate renal impairment (defined as eGFR between 30 and < 60 mL/min/1.73m^2).

Most subjects in the dapagliflozin 10 mg and placebo treatment groups were receiving background metformin therapy (90.2% and 92.0%, respectively). Other OAD drugs used in at least 10% of subjects in the 2 treatment groups were the sulfonylureas, glimepiride (18.7% and 20.1%, respectively) and glyburide (14.7% and 12.9%, respectively). Insulin use was reported for 7.6% of subjects. Approximately 55% of subjects in the dapagliflozin 10 mg and placebo groups were receiving a background ACEI (56.0% and 55.4%, respectively), with the remaining 45% receiving a background ARB (44.0% and 44.2%, respectively). The additional antihypertensive drug consisted of a thiazide or thiazide-like diuretic for 200 subjects (44.5%) and a calcium channel blocker, beta blocker, central alpha adrenergic agonist or alpha adrenergic blocker for 249 subjects (55.5%).

Table 1: Subject Disposition for 12-Week Double-blind Treatment Period- MB102077

	Number (%) Subjects		
	PLA + ACEI/ARB N = 224	**DAPA 10 mg + ACEI/ARB N = 225**	**Total N = 449**
Subjects completing double-blind period	202 (90.2)	211 (93.8)	413 (92.0)
Subjects not completing double-blind period	22 (9.8)	13 (5.8) [a]	35 (7.8)
Reason for not completing double-blind period			
Adverse event	4 (1.8)	1 (0.4)	5 (1.1)
Subject withdrew consent	6 (2.7)	4 (1.8)	10 (2.2)
Subject no longer met criteria	1 (0.4)	5 (2.2)	6 (1.3)
Lost to follow-up	3 (1.3)	2 (0.9)	5 (1.1)
Administrative reason by sponsor	2 (0.9)	1 (0.4)	3 (0.7)
Lack of efficacy	2 (0.9)	0	2 (0.4)
Subject request	1 (0.4)	0	1 (0.2)
Other	3 (1.3)	0	3 (0.7)

a One subject (Subject M[redacted], received 30 days of double-blind treatment) had missing end-of-study disposition information as the site was disbanded before all final queries had been answered.
This table includes all randomized subjects in either treatment group who took at least 1 dose of double-blind study medication.
Subjects continuing in the study refers to subjects entering the follow-up period.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DAPA = dapagliflozin; PLA = placebo; N = number of randomized and treated subjects.

Table 2: Demographic Characteristics, Randomized Subjects - MB102077

	PLA + ACEI/ARB N = 224	**DAPA 10 mg + ACEI/ARB N = 225**	**Total N = 449**
Mean age, years	56.2	55.8	56.0
Age category, < 65 years, n (%)	198 (88.4)	198 (88.0)	396 (88.2)
Gender, male, n (%)	129 (57.6)	118 (52.4)	247 (55.0)
Race, n (%)			
White	157 (70.1)	160 (71.1)	317 (70.6)
Asian	38 (17.0)	34 (15.1)	72 (16.0)
Black/African-American	17 (7.6)	19 (8.4)	36 (8.0)
Other	12 (5.4)	12 (5.3)	24 (5.3)
Mean BMI, kg/m^2	32.13	31.90	32.01

This table includes all randomized subjects in either treatment group who took at least 1 dose of double-blind study medication.
Percentages reported are based on the total number of subjects in each treatment group.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DAPA = dapagliflozin; PLA = placebo; N = number of randomized and treated subjects; n = number of subjects.

Efficacy Results: Among subjects with T2DM and hypertension on background therapy with an OAD and/or insulin and an ACEI or ARB plus 1 additional antihypertensive, treatment with dapagliflozin 10 mg resulted in statistically significant and clinically relevant improvements, compared with placebo, in both BP and glycemic control, as measured by the hierarchically-ordered co-primary endpoints of change from baseline in seated SBP and HbA1c at Week 12 (Table 3). The adjusted mean changes from baseline at Week 12 showed reductions in seated SBP of -11.90 mmHg and -7.62 mmHg in the dapagliflozin 10 mg and placebo treatment groups, respectively, and reductions in HbA1c of -0.63% and -0.02% in the 2 treatment groups, respectively. The comparisons between the

dapagliflozin 10 mg and placebo treatment groups, -4.28 mmHg (95% CI: -6.54, -2.02) for seated SBP and -0.61% (95% CI: -0.76, -0.46) for HbA1c, were statistically significant.

The adjusted mean change from baseline in 24-hour mean ambulatory SBP at Week 12 (LOCF) showed a reduction of -11.33 mmHg in the dapagliflozin 10 mg treatment group compared with -6.88 mmHg in the placebo group (p=0.0012). The adjusted mean change from baseline in seated DBP at Week 12 showed a reduction of -6.30 mmHg in the dapagliflozin 10 mg treatment group compared with -5.33 mmHg in the placebo group; this comparison was not statistically significant (p=0.1619). Statistical testing of the remaining 2 secondary endpoints stopped at this point.

The adjusted mean change from baseline in 24-hour mean ambulatory DBP at Week 12 (LOCF) showed reductions of -7.56 mmHg in the dapagliflozin 10 mg treatment group and -5.57 mmHg in the placebo group, while the adjusted mean change from baseline in serum uric acid at Week 12 showed reductions of -0.43 mg/dL and -0.03 mg/dL in these 2 treatment groups, respectively (Table 3).

Table 3: Primary and Secondary Efficacy Endpoints at Week 12, Randomized Subjects - MB102077

EFFICACY ENDPOINT / TIMEPOINT		PLA + ACEI/ARB N=224	DAP 10MG + ACEI/ARB N=225
PRIMARY EFFICACY ENDPOINTS			
SEATED SYSTOLIC BLOOD PRESSURE (MMHG) (a)			
WEEK 12	n	199	205
	BASELINE MEAN (SD)	151.30 (6.749)	151.01 (7.879)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-7.62 (1.0701)	-11.90 (1.0585)
	DIFFERENCE VS. PLACEBO (SE)		-4.28 (1.1485)
	P-VALUE VS. PLACEBO		0.0002*
HBA1C (%) (a)			
WEEK 12	n	197	204
	BASELINE MEAN (SD)	8.00 (0.963)	8.09 (0.914)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-0.02 (0.0673)	-0.63 (0.0668)
	DIFFERENCE VS. PLACEBO (SE)		-0.61 (0.0773)
	P-VALUE VS. PLACEBO		<0.0001*
SECONDARY EFFICACY ENDPOINTS			
24-HOUR MEAN AMBULATORY SYSTOLIC BLOOD PRESSURE (MMHG) (LOCF) (b)			
WEEK 12	N#	186	187
	BASELINE MEAN (SD)	149.20 (12.675)	146.48 (10.436)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-6.88 (1.5793)	-11.33 (1.6031)
	DIFFERENCE VS. PLACEBO (SE)		-4.45 (1.3680)
	P-VALUE VS. PLACEBO		0.0012*
SEATED DIASTOLIC BLOOD PRESSURE (MMHG) (a)			
WEEK 12	n	199	205
	BASELINE MEAN (SD)	91.36 (4.835)	91.15 (4.829)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-5.33 (0.6377)	-6.30 (0.6308)
	DIFFERENCE VS. PLACEBO ()		-0.97 (0.6900)
	P-VALUE VS. PLACEBO		0.1619
24-HOUR MEAN AMBULATORY DIASTOLIC BLOOD PRESSURE (MMHG) (LOCF) (b)			
WEEK 12	N#	186	187
	BASELINE MEAN (SD)	88.00 (7.098)	87.51 (6.992)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-5.57 (1.0042)	-7.56 (1.0183)
	DIFFERENCE VS. PLACEBO (SE)		-1.99 (0.8635)
	95% CI FOR DIFFERENCE VS. PLACEBO		(-3.68, -0.29)
SERUM URIC ACID (MG/DL) (a)			
WEEK 12	n	198	204
	BASELINE MEAN (SD)	5.40 (1.315)	5.63 (1.596)
	ADJ. MEAN CHANGE FROM BASELINE (SE)	-0.03 (0.0890)	-0.43 (0.0883)
	DIFFERENCE VS. PLACEBO (SE)		-0.40 (0.0858)
	95% CONFIDENCE INTERVAL FOR DIFFERENCE		(-0.57, -0.23)

N is the number of randomized subjects who took at least one dose of double-blind study medication.
(*) Significant p-value: First primary endpoint is tested at alpha=0.05, second primary endpoint and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.

(a) MIXED model: post-baseline = treatment, week, treatment*week interaction, randomization strata, baseline, baseline*week
Although only Week 12 is presented, data from all weeks during the double-blind treatment period are included in the mixed model.
(b) ANCOVA model: change = treatment, baseline, randomization strata
Data after rescue are excluded from blood pressure analyses.
n is the number of randomized subjects with non-missing baseline and Week 12 values.
N# is the number of randomized subjects with non-missing baseline and Week 12 (LOCF) values.

Safety Results: Daily administration of dapagliflozin 10 mg for 12 weeks was shown to be generally safe and well tolerated in subjects with inadequately controlled T2DM and hypertension receiving background therapy with an OAD and/or insulin and an ACEI or ARB plus 1 additional antihypertensive (Table 4). The proportions of subjects reporting at least 1 AE, or 1 AE considered related to study treatment, were similar in the dapagliflozin 10 mg and placebo treatment groups when including data after rescue.

There were no deaths during the study. Few SAEs were reported, but the proportion was greater for subjects in the dapagliflozin 10 mg treatment group. Overall, SAEs were reported by subjects across various SOCs, and no malignancies were reported during the study. The single SAE considered to be related to study drug occurred in the placebo treatment group, and was the only SAE that led to discontinuation. One subject (0.4%) in the dapagliflozin 10 mg treatment group reported an AE (other than hypoglycemia) that led to discontinuation, compared with 4 subjects (1.8%) in the placebo group.

Table 4: Overall Adverse Event Summary - 12-Week Double-blind Period, Including Data After Rescue, Treated Subjects - MB102077

	Number (%) of Subjects	
	PLA + ACEI/ARB N = 224	**DAPA 10 mg + ACEI/ARB N = 225**
At least 1 AE	93 (41.5)	98 (43.6)
At least 1 hypoglycemia episode	6 (2.7)	13 (5.8)
At least 1 AE or hypoglycemia episode	94 (42.0)	101 (44.9)
At least 1 related AE	12 (5.4)	15 (6.7)
Deaths	0	0
At least 1 SAE	2 (0.9)	6 (2.7)
At least 1 related SAE	1 (0.4)	0
SAE leading to discontinuation of study drug	1 (0.4)	0
AE leading to discontinuation of study drug	4 (1.8)	1 (0.4)
Hypoglycemia leading to discontinuation of study drug	0	0

Includes non-serious AEs with onset on or after the first date of double-blind treatment and on or prior to the last day of double-blind treatment plus 4 days.
Includes SAEs with onset on or after the first date of double-blind treatment and on or prior to the last day of double-blind treatment plus 30 days.
Only hypoglycemia reported as an SAE is included in the AE, related AE, SAE, related SAE, and AE leading to discontinuation summary lines. All reported hypoglycemia events within 4 days of last day of treatment are included in the hypoglycemia line.
ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; DAPA = dapagliflozin; PLA = placebo; N = number of randomized and treated subjects; SAE = serious adverse event.

In a population receiving background OAD and/or insulin therapy to treat T2DM, a higher percentage of subjects in the dapagliflozin 10 mg group (5.8%), compared with the placebo group (2.7%), had at least 1 hypoglycemia event, but there were no major episodes of hypoglycemia. There were no reports of events of hypoglycemia that were serious or led to discontinuation of study medication in either treatment group.

The proportions of subjects with events of genital infections or UTIs were small but slightly higher for dapagliflozin 10 mg than for placebo (2.7% and 1.8%, respectively, for genital infections and 1.8% and 0.9%, respectively, for UTIs). All events of genital infections and UTI responded to therapy and none resulted in clinically relevant complications. Pyelonephritis was not reported during the study.

There were few reports of renal impairment (consisting exclusively of AEs of blood creatinine increased), with a slightly higher proportion of events in the dapagliflozin 10 mg group (1.3% vs. 0.4% for placebo). None of the subjects with events of renal impairment had excursions in serum creatinine that reached the prespecified limits for MAs. The 3 subjects in the dapagliflozin 10 mg group with an AE of blood creatinine increased all had creatinine levels elevated outside the normal range on Day 1, prior to initiation of double-blind study treatment. There were no events of renal failure during the double-blind study treatment period. There were no clinically meaningful changes

in renal function in the dapagliflozin 10 mg treatment group across the 12-week double-blind treatment period, as assessed by mean serum creatinine, CrCl, eGFR, and urinary albumin-to-creatinine ratio (UACR).

The proportion of subjects with elevated liver function tests based on laboratory values or hepatic AEs was small and balanced across the dapagliflozin 10 mg (4.0%) and placebo (3.1%) groups. Most of the hepatic laboratory abnormalities consisted of an elevation in alkaline phosphatase (ALP) to > 1.5X ULN. No subject was discontinued from study treatment due to a hepatic AE. One subject in the dapagliflozin 10 mg treatment group had clinically relevant increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin due to a viral hepatitis E infection. There were no clinically relevant mean changes from baseline in ALT, AST, or total bilirubin, and there was no signal of drug-related liver injury in the dapagliflozin 10 mg treatment group.

Small mean increases in hematocrit, magnesium, and phosphorus were seen in the dapagliflozin 10 mg treatment group that returned to pre-treatment values within 1 week after the last dose of study drug. Marked elevations in magnesium or hematocrit were infrequent (0% to < 1%) on dapagliflozin 10 mg, and were not associated with any AEs.

Mean serum sodium and potassium levels remained stable on dapagliflozin 10 mg during the 12 week treatment period. Marked laboratory abnormalities of hyperkalemia, hypernatremia, hyponatremia, or hypokalemia were infrequent (0% to < 2%), typically represented abnormalities at a single time point, and were not generally associated with AEs. Moderate hypovolemia that resolved after 3 days was reported in one subject in the dapagliflozin 10 mg group who had marked elevations in serum potassium and serum creatinine.

No laboratory marked abnormalities were reported in the dapagliflozin 10 mg treatment group for hemoglobin, blood urea nitrogen (BUN), creatinine (≥ 2.5 mg/dL), serum albumin, total serum protein, creatine kinase, or serum bicarbonate.

The statistically significant reductions in mean seated and 24-hour ambulatory SBP, and the numerically larger mean reductions in seated and ambulatory DBP in the dapagliflozin 10 mg group compared with placebo, occurred without an increase in the proportion of subjects with orthostatic hypotension, dehydration, hypovolemia, or syncope.

Pharmacodynamic Results: While the baseline values were similar for the placebo and dapagliflozin 10 mg treatment groups, consistent with the mechanism of action of dapagliflozin, a numerically higher mean UGCR was observed at Week 12 in the dapagliflozin 10 mg treatment group compared with placebo (27.74 vs. 1.76).

CONCLUSIONS: [redacted]

[redacted]

DATE OF REPORT: 21-Jun-2013