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

SYNOPSIS

Clinical Study Report for Study MB102035

TITLE OF STUDY: An Exploratory Phase 2 Study to Assess the Effect of Dapagliflozin on Glomerular Filtration Rate (GFR) in Subjects with Type 2 Diabetes who have Inadequate Glycemic and Blood Pressure (BP) Control

INVESTIGATORS/STUDY CENTERS: [redacted] sites in Canada, the Netherlands and the United States participated in the study.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 29-December-2009 **CLINICAL PHASE:** 2b
Study Completion Date: 30-November-2010

OBJECTIVES: This study has no primary or secondary objectives.

Exploratory Objectives:

- To assess the percent change from baseline in glomerular filtration rate (GFR) achieved with dapagliflozin 10 mg plus metformin and/or sulfonylurea (SU) versus placebo plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment
- To assess the percent change from baseline in GFR achieved with dapagliflozin 10 mg plus metformin and/or SU versus hydrochlorothiazide (HCTZ) 25 mg plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment
- To assess the changes from baseline in the mean 24-hour, daytime (0900 to 2100 hours), and nighttime (0100 to 0600 hours) ambulatory systolic blood pressure (SBP) achieved with dapagliflozin 10 mg plus metformin and/or SU versus placebo plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment
- To assess the changes from baseline in the mean 24-hour, daytime (0900 to 2100 hours), and nighttime (0100 to 0600 hours) ambulatory SBP achieved with dapagliflozin 10 mg plus metformin and/or SU versus HCTZ 25 mg plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment

Sub-study exploratory objective (selected sites only):

- To assess the percent change from baseline in red cell mass (RCM) and plasma volume (PV) achieved with dapagliflozin 10 mg plus metformin and/or SU versus HCTZ 25 mg plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment

- To assess the percent change from baseline in RCM and PV achieved with dapagliflozin 10 mg plus metformin and/or SU versus placebo plus metformin and/or SU, after 12 weeks of oral administration of double-blind treatment

METHODOLOGY: This was a randomized, double-blind, 3-arm, parallel-group, placebo and active-controlled study of subjects receiving metformin and/or SU randomized to receive: dapagliflozin 10 mg daily dose (QD); HCTZ 25 mg QD; or placebo. Allowing approximately 8 months for subject recruitment, this study was to be conducted over 12 months. The study consisted of the following:
Qualification Period (≤ 14 days): Subjects were to maintain their stable dose of commercially available metformin and/or SU. If applicable, subjects also were to maintain their stable dose of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).
Lead-in Period (1 week): Subjects receiving metformin and/or SU were to have pre-randomization glycosylated hemoglobin (HbA1c) values ≥ 6.6 % and ≤ 9.5 %. Subjects maintained their stable dose of commercially available metformin and/or SU and, if applicable, their stable dose of ACEI or ARB. Subjects received diet and exercise counseling during the lead-in period and for the duration of the study. Upon entry in the lead-in period, subjects were also given a blood glucose meter and instructed on self-monitoring of blood glucose technique and protocol requirements. Twenty-four-hour ambulatory BP monitoring (ABPM) was to be initiated upon completion of all other Day -7 visit procedures, and the subjects were scheduled to return to the site following completion of the 24-hour ABPM recording.
Double-blind Treatment Period (12 weeks): Subjects maintained their stable dose of commercially available metformin and/or SU and, if applicable, their stable dose of ACEI or ARB. Subjects also continued to take single-blind lead-in study medication throughout any randomization procedures performed on days prior to Day 1 randomization. On Day 1, subjects were randomly assigned to receive dapagliflozin 10 mg QD and HCTZ 25 mg matching placebo QD, dapagliflozin 10 mg matching placebo QD and HCTZ 25 mg QD, or dapagliflozin 10 mg matching placebo QD and HCTZ 25 mg matching placebo QD in a 1:1:1 ratio. Randomization was stratified globally by prior antihypertensive drug use (ACEI or ARB, or no antihypertensive drug) as well as by participation in the sub-study (participating or not participating). Dose titration of double-blind study medication was not permitted at any time during the treatment period, and doses of the commercially available metformin and/or SU, as well as ACEI or ARB (if applicable), were to remain unchanged for the duration of the treatment period.
Sub-Study: The sub-study consisted of the measurement of RCM and PV at selected sites, which randomized consenting subjects. Enrollment into the sub-study was to continue until a minimum of 30 subjects had been enrolled, or once enrollment into the main study was completed or terminated, whichever occurred last.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 75 subjects (25 subjects in each treatment arm); **Enrolled:** 154; **Randomized:** 75; **Treated:** 24 treated with dapagliflozin 10 mg, 26 treated with HCTZ 25 mg, 25 treated with placebo.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women with type 2 diabetes, ages ≥ 18 to ≤ 70 years, who had inadequate glycemic control, defined as HbA1c ≥ 6.6% and ≤ 9.5%, and who were receiving a stable dose of metformin and/or an SU, for at least 4 weeks prior to the enrollment visit. Subjects had an enrollment C-peptide ≥ 0.8 ng/mL, an estimated GFR > 60 mL/min/1.73m^2 and < 150 mL/min/1.73m^2, urine albumin:creatinine ratio < 300 mg/g, BMI ≤ 45.0 kg/m^2, and inadequate BP control (SBP ≥ 130 and < 165 mmHg, and/or diastolic BP (DBP) ≥ 80 and < 105 mmHg at enrollment). Subjects receiving an ACEI or an ARB were receiving a stable dose for at least 4 weeks prior to enrollment. Subjects did not need to be receiving an antihypertensive treatment to be eligible for the study.

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

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Matching placebo for dapagliflozin tablets 10 mg administered QD [redacted]

HCTZ tablets 25 mg QD, [redacted] or matching placebo for HCTZ tablets QD, administered orally for the 12-week double-blind treatment period [redacted].

CRITERIA FOR EVALUATION:

Efficacy: The key exploratory efficacy endpoint was the change from baseline in the mean 24-hour, daytime (0900 to 2100 hours), and nighttime (0100 to 0600 hours) ambulatory SBP at Week 12 (last observation carried forward [LOCF]).

Safety: General safety endpoints included the number of subjects with adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, cardiovascular events, and marked abnormalities (MAs) in clinical laboratory tests, as well as summaries of vital signs, electrocardiograms and safety laboratory tests.

The key exploratory safety endpoint was the percent change from baseline in GFR at Week 12, as determined by plasma clearance of the radiocontrast agent iohexol, using the modified last observation carried forward (MLOCF) approach.

The sub-study exploratory endpoint was the percent change from baseline in RCM and PV at Week 12 (MLOCF).

STATISTICAL CONSIDERATIONS: Given that this was a pilot study designed for exploratory analysis, formal statistical hypothesis testing was not performed. The sample size for this study was not based on any formal power considerations. The sample size target was 20 subjects per treatment group. Assuming a 20% dropout rate, 75 subjects (25 per treatment arm) were randomized.

Mean change from baseline at the Week 12 LOCF in 24-hour, daytime, and nighttime ambulatory SBP was analyzed using an analysis of covariance (ANCOVA) model with treatment group and prior drug use (i.e., ACEI or ARB, or no antihypertensive drug) as an effect. In addition, the change from baseline in fasting plasma glucose (FPG) and body weight over time and the change from baseline in HbA1c, FPG, and body weight at Week 12 LOCF were summarized.

For analysis of percent change from baseline at Week 12 in GFR, values were first transformed to logarithms and the changes from baseline were expressed as geometric mean percent changes from baseline. An ANCOVA of the logarithms of the post-baseline to baseline ratios was performed. Treatment group and prior drug use (i.e., ACEI or ARB, or no antihypertensive drug) were considered as a fixed effect. The natural logarithm of the baseline measurement was included as covariate. The model provided least squares mean estimates and 2-sided 95% confidence intervals (CIs) for (geometric) mean percent changes from baseline within treatment groups and for the difference in mean percent change from baseline between the dapagliflozin plus metformin and/or SU treatment group and the other treatment groups.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: All but 1 subject completed the study (Table 1). In all treatment groups, the majority of subjects were male, white, and under 65 years of age (Table 2). Subjects in the placebo group were slightly older than those in the other 2 groups. Mean BMI and weight were lower for subjects in the dapagliflozin 10 mg group than for those in the other 2 groups.

Table 1: Subject Disposition – End of 12-Week Double-blind Treatment Period

	Number (%) of Subjects			
	Placebo	**DAPA 10 mg**	**HCTZ 25 mg**	**Overall**
Subjects completing the period	25 (100.0)	23 (95.8)	26 (100.0)	74 (98.7)
Subjects not completing the period	0	1 (4.2)	0	1 (1.3)
Reason for not completing the period				
Subject withdrew consent	0	1 (4.2)	0	1 (1.3)

This table includes all randomized subjects 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. N = number of randomized subjects, DAPA = dapagliflozin, HCTZ = hydrochlorothiazide

Table 2: Baseline and Demographic Characteristics – Randomized Subjects

	Placebo	**DAPA 10 mg**	**HCTZ 25 mg**	**Overall**
Age (yr)				
Mean	58.0	53.7	54.8	55.5
Median	62.0	53.5	56.0	56.0
Min, Max	37, 70	35, 68	36, 68	35, 70
Age Category (n, %)				
< 65 yr	19 (76.0)	22 (91.7)	21 (80.8)	62 (82.7)
65 – 75 yr	6 (24.0)	2 (8.3)	5 (19.2)	13 (17.3)
Gender (n, %)				
Male	18 (72.0)	16 (66.7)	15 (57.7)	49 (65.3)
Female	7 (28.0)	8 (33.3)	11 (42.3)	26 (34.7)
Race (%)				
White	17 (68.0)	19 (79.2)	20 (76.9)	56 (74.7)
Black or African American	4 (16.0)	4 (16.7)	4 (15.4)	12 (16.0)
Asian	3 (12.0)	0	2 (7.7)	5 (6.7)
Other	1 (4.0)	1 (4.2)	0	2 (2.7)
BMI Category (%)				
< 25 kg/m^2	2 (8.0)	6 (25.0)	0	8 (10.7)
≥ 25 kg/m^2	23 (92.0)	18 (75.0)	26 (100.0)	67 (89.3)
≥ 27 kg/m^2	20 (80.0)	18 (75.0)	22 (84.6)	60 (80.0)
≥ 30 kg/m^2	15 (60.0)	11 (45.8)	16 (61.5)	42 (56.0)

This table includes all randomized subjects 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.
DAPA = dapagliflozin, HCTZ = hydrochlorothiazide, BMI = body mass index

Efficacy Results: Adjusted mean (± SE) decreases from baseline in 24-hour and daytime ambulatory SBP were observed at the Week 12 LOCF in both active treatment groups (-3.28 ± 1.77 and -6.55 ± 1.68 mmHg for 24-hour SBP and -5.93 ± 1.87 and -6.83 ± 1.77 mmHg for daytime SBP in the dapagliflozin 10 mg and HCTZ 25 mg groups, respectively), whereas a substantial decrease in nighttime ambulatory SBP occurred only in the HCTZ 25 mg group (-7.76 ± 1.99 mmHg). Adjusted mean changes from baseline in 24-hour, daytime, and nighttime SBP for the placebo group were 0.88 ± 1.64, 1.55 ± 1.73, and 0.61 ± 1.95 mmHg, respectively.

Improvement in HbA1c, FPG, and total body weight were observed at the Week 12 LOCF relative to baseline in randomized subjects treated with dapagliflozin 10 mg as compared with those treated with placebo or HCTZ 25 mg. Mean (± SD) changes from baseline in HbA1c were -0.73 ± 0.78% for dapagliflozin 10 mg, versus -0.37 ± 0.72% for placebo and +0.14 ± 0.91% for HCTZ 25 mg. Mean changes from baseline in FPG were -23.9 ± 33.78 mg/dL in the dapagliflozin 10 mg group, compared with +7.7 ± 29.12 and +3.4 ± 38.50 mg/dL in the placebo and HCTZ 25 mg groups, respectively. Mean changes from baseline in total body weight were -2.27 ± 2.63 kg in the dapagliflozin 10 mg group, compared with +0.30 ± 1.82 and +1.12 ± 2.51 kg in the placebo and HCTZ 25 mg groups, respectively.

Safety Results: In general, dapagliflozin 10 mg was safe and well tolerated (Table 3).

Table 3: Overall Adverse Events Summary – Treated Subjects

	Number (%) of Subjects		
	Placebo N = 25	**Dapagliflozin 10 mg N = 24**	**HCTZ 25 mg N = 26**
At least 1 AE	12 (48.0)	15 (62.5)	17 (65.4)
At least 1 hypoglycemia event	3 (12.0)	1 (4.2)	1 (3.8)
At least 1 AE or hypoglycemia	13 (52.0)	15 (62.5)	17 (65.4)
At least 1 related AE	4 (16.0)	9 (37.5)	9 (34.6)
Deaths	0	0	0
At least 1 SAE	0	3 (12.5)	0
At least 1 related SAE	0	0	0
SAE leading to discontinuation of study medication	0	0	0
AE leading to discontinuation of study medication	0	0	0
Hypoglycemia leading to discontinuation of study medication	0	0	0

MedDRA Version: 13.1

N is the number of treated subjects.

Includes non-serious adverse events and hypoglycemia 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 serious adverse events 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 a 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.

Summary of Safety Outcome Results:

- The proportion of subjects reporting at least 1 AE was higher in the active treatment groups than in the placebo group. The proportions of subjects for whom AEs were considered related to treatment were higher in the active treatment groups than in the placebo group (9 of 24, 37.5% for dapagliflozin 10 mg and 9 of 26, 34.6% for HCTZ 25 mg, versus 4 of 25, 16.0% for placebo).
- Three subjects in the dapagliflozin 10 mg group had SAEs, versus none in the HCTZ 25 mg or placebo groups. These 3 subjects had SAEs of right-leg cellulitis; surgery for lumbar disc strain; and pleuritic chest pain (CT pulmonary angiogram negative for pulmonary embolism), respectively.
- No event of hypoglycemia was an SAE, and none led to discontinuation of the study medication.
- No deaths were reported.

- No AEs led to discontinuation of study treatment during the study.
- The following other AEs of significant medical interest were identified: hypoglycemia in 3 subjects in the placebo group, 1 subject in the dapagliflozin 10 mg group, and 1 subject in the HCTZ 25 mg group; genital infection in 2 subjects in the dapagliflozin 10 mg group (1 of whom had a mycotic genital infection); urinary tract infection in 1 subject in the dapagliflozin 10 mg group and 2 subjects in the HCTZ 25 mg group; hypotension/dehydration/hypovolemia (syncope) in 1 subject in the dapagliflozin 10 mg group; and urinary stones in 1 subject in the HCTZ 25 mg group. These events were not considered SAEs and did not result in discontinuation of treatment. No AEs in the other categories of significant medical interest (renal impairment/failure, fractures, infections of the kidney, or hepatic disorder) were reported for any subject.
- Marked abnormalities were reported for 2 subjects in the dapagliflozin 10 mg group and 5 subjects in the HCTZ 25 mg group. One subject in the dapagliflozin 10 mg group had decreased fasting plasma glucose recorded on Day 56 only and the other subject had elevated serum potassium and decreased serum calcium concentrations recorded on Day 15 only. Of those in the HCTZ 25 mg group with MAs, 3 had elevated serum creatinine levels that met the criterion for an MA (≥ 1.5 times the baseline value), 1 had a creatine kinase level 5 times the upper limit of normal at lead-in and during the study, and 1 had serum sodium concentrations < 130 mEq/L during the study. No MAs were reported for hematocrit, hemoglobin, AST, ALT, ALP, total bilirubin, blood urea nitrogen, albumin, total protein, bicarbonate, magnesium, or albumin/creatinine ratio.
- There were no clinically relevant mean changes from baseline in laboratory values, including hepatic function tests, renal function tests, serum creatine kinase level, total protein, serum albumin, and serum electrolyte levels. Slight mean increases from baseline in mean hematocrit occurred in the dapagliflozin 10 mg treatment group.
- Mean decreases from baseline at Week 12 in seated, supine, and standing in-office SBP and DBP were generally greater in the dapagliflozin 10 mg group than in the placebo and HCTZ 25 mg groups, without an increase in the proportions of subjects with orthostatic hypotension, dehydration, hypovolemia, or syncope. The mean changes from baseline for seated SBP and DBP were -3.96 and -3.08 mmHg, respectively, for the placebo group, -12.32 and -5.09 mmHg for the dapagliflozin 10 mg group, and -7.19 and -1.58 mmHg for the HCTZ 25 mg group.

The key exploratory endpoint of this study was safety-related (i.e., the percent change from baseline in GFR, as determined by plasma clearance of the radiocontrast agent iohexol, after 12 weeks of study drug administration). Decreases in the adjusted mean percent change from baseline in GFR were observed at the Week 12 MLOCF in all treatment groups, with greater decreases in the dapagliflozin 10 mg group (difference versus placebo and HCTZ 25 mg (± SE): -8.07 ± 2.72% and -7.62 ± 2.71%, respectively (Table 4). Subgroup analysis of the adjusted mean percent change from baseline in GFR at Week 12 MLOCF by prior antihypertensive drug use showed similar results for dapagliflozin 10 mg, regardless of prior antihypertensive drug use (-9.65 ± 3.44% for those with no prior treatment versus -11.17 ± 2.30% for those with prior ACEI/ARB treatment). In contrast, adjusted mean percent changes from baseline in GFR at Week 12 MLOCF observed in the placebo and HCTZ 25 mg groups were different, depending on prior treatment (-7.27 ± 3.30% without prior treatment versus -0.68 ± 2.42% with prior treatment for placebo and -0.69 ± 3.52% without prior treatment versus -4.47 ± 2.26% with prior treatment for HCTZ 25 mg).

In a sub-study of 30 subjects, numerical median percent changes from baseline at the Week 12 MLOCF in RCM were -1.17% (95% CI -3.64, 3.27), +6.59% (95% CI -9.86, 61.53), and -6.52% (95% CI -17.82, 2.72) for the placebo, dapagliflozin 10 mg, and HCTZ 25 mg groups, respectively. Numerical median changes from baseline in PV at the Week 12 LOCF were +5.2% (95% CI -4.4, 13.3), -7.3% (95% CI -16.5, -1.8), and +2.8% (95% CI -9.3, 29.0) for the placebo, dapagliflozin 10 mg, and HCTZ 25 mg groups, respectively. The results should be interpreted with caution due to the limited number of subjects in the

sub-study population. The results should be interpreted with caution due to the limited number of subjects in the sub-study population.

Table 4: GFR (mL/min/1.73 mg^2) Adjusted Mean Percent Change from Baseline at Week 12 (MLOCF) – Treated Subjects

	Placebo N = 25	Dapagliflozin 10 mg N = 24	HCTZ 25 mg N = 26
N#	25	22	26
Baseline mean (SD)	100.56 (17.701)	100.59 (14.278)	101.92 (17.604)
Week 12 mean (SD)	97.48 (14.802)	90.50 (16.695)	97.77 (13.122)
Mean percent change from baseline (SD)	-2.70 (7.656)	-10.67 (10.309)	-3.48 (12.471)
Adjusted percent change from baseline			
Mean (SE)	-2.92 (2.0133)	-10.76 (1.9684)	-3.40 (1.9756)
95% confidence interval	(-6.86, 1.18)	(-14.60, -6.74)	(-7.26, 0.63)
Difference in adjusted percent change from baseline vs. placebo			
Mean (SE)		-8.07 (2.7177)	
95% confidence interval		(-13.34, -2.49)	
Difference in adjusted percent change from baseline vs. HCTZ 25 mg			
Mean (SE)		-7.62 (2.7068)	
95% confidence interval		(-12.87, -2.06)	

N is the number of treated subjects.

N# is the number of treated subjects with non-missing baseline and Week 12 (MLOCF) values.

Based on an ANCOVA model for log (Week 12 value) – log (baseline value) with treatment group and prior antihypertensive drug use as an effect and log (baseline value) as a covariate.

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DATE OF REPORT: 12-Aug-2011