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

24-Week ST and ST + LT Data Up to 09-Aug-2010 Clinical Study Report for Study MB102029

TITLE OF STUDY: A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase 2/3 Trial to Evaluate the Glycemic Efficacy, Renal Safety, Pharmacokinetics, and Pharmacodynamics of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Moderate Renal Impairment Who Have Inadequate Glycemic Control

INVESTIGATORS/STUDY CENTERS: [redacted] sites ([redacted] in the United States, [redacted] in Canada, [redacted] in Italy, [redacted] in Mexico, [redacted] in Argentina, [redacted] in India, [redacted] in Australia, [redacted] in France, [redacted] in Peru, [redacted] in Spain, [redacted] in Denmark, [redacted] in Puerto Rico, and [redacted] in Singapore) participated in the study.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 19-Jun-2008 **CLINICAL PHASE:** 2/3

Long-term, at least 52-week, Data Cut-off Date: 25-Jun-2010

Long-term Extension Period: Ongoing

Primary Efficacy Objective: To compare the change from baseline in hemoglobin A1c (HbA1c) achieved with each dapagliflozin treatment group versus placebo, after 24 weeks of oral administration of double-blind treatment.

Secondary Objectives:

- To compare the change from baseline in estimated glomerular filtration rate (eGFR) in each dapagliflozin treatment group versus placebo, after 52 weeks of oral administration of study treatment
- To compare the change from baseline in estimated creatinine clearance (eCrCl) in each dapagliflozin treatment group versus placebo, after 52 weeks of oral administration of study treatment
- To compare the change from baseline in fasting plasma glucose (FPG) achieved with each dapagliflozin treatment group versus placebo, after 24 weeks of oral administration of double-blind treatment
- To compare the change from baseline in body weight achieved with each dapagliflozin treatment group versus placebo, after 24 weeks of oral administration of double-blind treatment.

Safety Objectives:

- To assess the safety and tolerability of each dose of dapagliflozin after up to 24 weeks of oral administration of double-blind treatment
- To assess the safety and tolerability of each dose of dapagliflozin after up to 52 weeks of oral administration of study treatment
- To assess the safety and tolerability of dapagliflozin after up to 104 weeks of oral administration of study treatment.

Pharmacokinetic and Pharmacodynamic Objectives:

- To explore plasma concentration-time data for dapagliflozin and metabolites, including its major metabolite (M15)
- To explore protein binding data for dapagliflozin
- To assess the change from baseline in the quantity of glucose excreted in a 24-hour collection of urine achieved with each dapagliflozin treatment group relative to placebo, after 6 and 52 weeks of oral administration of double-blind treatment.

METHODOLOGY: Following screening, subjects entered the qualification period. Qualified subjects then entered a 7-day placebo lead-in period during which they received diet and exercise counseling that was provided for the duration of the study. Single-blind placebo was used to assess subject's compliance with treatment and eligibility for entry into the double-blind treatment period.

Subjects entered the 24-week double-blind treatment period on the Day 1 visit. Subjects were randomized in a blinded manner to 1 of 3 treatment groups consisting of placebo, dapagliflozin 5 mg, or dapagliflozin 10 mg daily. Randomization was stratified by pre-enrollment anti-hyperglycemic therapy (insulin-based regimen, sulfonylurea-based regimen, thiazolidinedione-based regimen, or other regimen). Dose titration of dapagliflozin was not permitted at any time during the study. However, subjects with lack of glycemic control during the double-blind treatment period were eligible to receive open-label rescue medication with any approved, appropriate antihyperglycemic medication, except metformin, in addition to their current double-blind treatment, in accordance with the approved label and conventional standards of care and based on central laboratory fasting plasma glucose (FPG) and confirmatory FPG results. Subjects who received a first rescue medication and subsequently met the criteria for lack of glycemic control, could have had other rescue medications, except for metformin, added or substituted according to the judgment of the investigator. Subjects received anti-diabetic medication according to their baseline regimen without modification unless the baseline regimen was modified for rescue treatment, or for prevention of hypoglycemia in all treatment periods. Titration of open-label rescue medication was permitted during the double-blind treatment period.

Eligible subjects completing the 24-week short-term, double-blind treatment period continued into the double-blind, 28-week long-term treatment period. Subjects with a lack of glycemic control during the long-term treatment period were eligible to receive open-label rescue medication in addition to their double-blind treatment based on central laboratory HbA1c values. If subjects met the protocol-specified glycemic criteria based on HbA1c, they were recommended for open-label rescue medication. Subjects who received a first rescue medication and subsequently fulfilled the criteria for lack of glycemic control could have other rescue medications added or substituted according to the judgment of the investigator.

Eligible subjects completing the 28-week long-term double-blind treatment period continued into the 52-week site and subject blinded long-term extension period (cumulative study data reported here could range from 53 to 102 weeks). Subjects with lack of glycemic control were eligible, based on pre-specified

criteria, to receive open-label rescue medication. During the extension period, all rescue decisions were based on central laboratory HbA1c.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 252 (84 per dapagliflozin treatment group); **Enrolled:** 631; **Randomized:** 252; **Treated in Short-term period:** 252: 84 treated with placebo; 83 treated with dapagliflozin 5 mg; and 85 treated with dapagliflozin 10 mg. **Treated in Long-term period:** 202: 62 treated with placebo; 71 treated with dapagliflozin 5 mg; and 69 treated with dapagliflozin 10 mg.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Males and females , ≥ 18 years old, with Type 2 diabetes mellitus (T2DM) and moderate renal impairment, defined as an eGFR 30 mL/min/1.73m^2 to 59 mL/min/1.73m^2, who have inadequate glycemic control, defined as HbA1c ≥ 7.0% and ≤ 11.0%. Subjects had a body mass index (BMI) ≤ 45.0 kg/m^2.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dapagliflozin tablets, 5 mg and 10 mg, oral administration; 52 weeks up to 09-Aug-2010. [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Placebo for dapagliflozin tablets, oral administration 52 weeks up to 09-Aug-2010. [redacted]

CRITERIA FOR EVALUATION: Efficacy: The primary endpoint was the change from baseline in HbA1c at Week 24, last observation carried forward (LOCF). Secondary efficacy assessments (LOCF) were the change from baseline in FPG at Week 24 and the change from baseline in total body weight at Week 24.

Safety: Safety outcomes included changes from baseline in eGFR, eCrCl, and measured creatinine clearance (mCrCl) at Week 52; reported serious and non-serious adverse events (AEs); discontinuations due to AEs, worsening renal insufficiency or end stage renal disease (ESRD), or elevated potassium levels; reported hypoglycemia events and events of special interest; laboratory abnormalities and standard safety laboratory tests; electrocardiograms (ECGs); and vital signs.

STATISTICAL CONSIDERATIONS: The primary efficacy analysis compared the change in HbA1c from baseline at Week 24 (or the last post baseline observation prior to rescue and prior to Week 24 if no Week 24 assessment was available or rescue medication was taken prior to the Week 24 assessment) for the dapagliflozin 5 mg and the dapagliflozin 10 mg treatment groups with placebo. This analysis was based on an analysis of covariance (ANCOVA) model with treatment group and pre-enrollment anti-hyperglycemic therapy stratum as fixed effects and the baseline value as a covariate. A hierarchical closed testing procedure was performed to control the familywise type I error rate at 0.05 within each treatment group across the primary and secondary efficacy endpoints.

SUMMARY OF RESULTS:

Disposition: Of the 631 subjects who enrolled in the study, more than half of subjects did not complete the qualification period. The most common reason for non-completion of the qualification period was that a subject no longer met study criteria. Of the 277 subjects who entered the lead-in period, 26 subjects discontinued prior to randomization into the short-term period. The most common reason for not being randomized was subject no longer met study criteria; the second most common reason was adverse event (Table 1).

Of 252 subjects randomized to the 24-week short-term, double-blind treatment period, 48 subjects did not complete the short-term period (Table 2). The most common reason for non-completion of the short-term period was due to AEs of sustained elevated serum potassium and 'other'. The completion rate was lower for the placebo group than for the dapagliflozin groups (Table 2). This difference was largely due to more

subjects in the placebo group who had AEs of sustained elevated serum potassium during the 24-week short-term period than in the dapagliflozin groups. Of the 202 subjects who continued into the 28-week long-term, double-blind treatment period, 19 subjects did not complete the period. The most common reason for not completing the 28-week, long-term double-blind treatment period was other AEs; the second most common reason was subject withdrew consent (Table 2).

Of 171 subjects entering the supplemental long-term site and subject blinded extension period up to data-base cut-off, 9 subjects did not complete the extension period (Table 3). The completion rate was lower for the placebo group than for the dapagliflozin groups (Table 3). This difference was largely due to more subjects in the placebo group who had AEs of "other" during the 24-week short-term period than in the dapagliflozin groups. The most common reason for non-completion of the long-term extension period was due to AEs, mainly, sustained elevated serum potassium. Of the 15 subjects who entered into the follow-up period, 1 subject did not complete the period due to other AEs (Table 3).

Table 1: Subject Disposition - Pre-randomization Subject Status Summary, Enrolled Subjects (MB102029)

	Total
Subjects enrolled	631
Subject completing the qualification period (%)	276 (43.7)
Subjects not completing the qualification period (%)	355 (56.3)
Reason not completing the qualification period (%)	
Adverse event	0
Subject withdrew consent	13 (2.1)
Lost to follow-up	1 (0.2)
Subject no longer meets study criteria	341 (54.0)
Subjects continuing to the lead-in period	277
Subjects randomized (%)	252 (91.0)
Subjects not randomized (%)	26 (9.4)
Reason for not being randomized (%)	
Adverse event	3 (1.1)
Subject withdrew consent	2 (0.7)
Lost to follow-up	1 (0.4)
Administrative reason by Sponsor	1 (0.4)
Subject no longer meets study criteria	19 (6.9)

Percentages reported are based on enrolled subjects or on subjects receiving at least one dose of treatment in the lead-in period. Randomization status based on IVRS information.

Table 2: Subject Disposition - End of 52-Week Short-term Plus Long-term Double-blind Treatment Period (MB102029)

	Number (%) of Subjects			
	Placebo	**DAPA 5 mg**	**DAPA 10 mg**	**Total**
Subjects randomized	84	83	85	252
Short-term double-blind treatment period				
Subjects completing period (%)	63 (75.0)	72 (86.7)	69 (81.2)	204 (81.0)
Subjects not completing period (%)	21 (25.0)	11 (13.3)	16 (18.8)	48 (19.0)
Reason not completing the period (%)				
Lack of efficacy	2 (2.4)	0	0	2 (0.8)
Adverse event	12 (14.3)	7 (8.4)	6 (7.1)	25 (9.9)
Other	2 (2.4)	5 (6.0)	2 (2.4)	9 (3.6)
Sustained elevated serum potassium	10 (11.9)	2 (2.4)	4 (4.7)	16 (6.3)
Subject withdrew consent	3 (3.6)	1 (1.2)	6 (7.1)	10 (4.2)
Death	1 (1.2)	0	1 (1.2)	2 (0.8)
Lost to follow-up	0	1 (1.2)	0	1 (0.4)
Poor/non-compliance	0	1 (1.2)	1 (1.2)	2 (0.8)
No longer meets study criteria	3 (3.6)	0	01 (1.2)	4 (1.6)
Administrative reason by Sponsor	0	0	1 (1.2)	1 (0.4)
Other	0	1 (1.2)	0	1 (0.4)
Subjects continuing in the study (%)	62 (73.8)	71 (85.5)	69 (81.2)	202 (80.2)
Subjects not continuing in the study (%)	22 (26.2)	12 (14.5)	16 (18.8)	50 (19.8)
Long-term double-blind treatment period				
Subjects entering the period (%)	62	71	69	202
Subjects completing period (%)	54 (87.1)	64 (90.1)	64 (92.8)	182 (90.1)
Subjects not completing period (%)	8 (12.9)	7 (9.9)	4 (5.8)	19 (9.4)
Reason not completing the period (%)				
Adverse event	5 (8.1)	4 (5.6)	2 (2.9)	11 (5.4)
Other	4 (6.5)	1 (1.4)	1 (1.4)	6 (3.0)
Worsened chronic renal insufficiency	0	1 (1.4)	0	1 (0.5)
Sustained elevated liver function tests	0	0	1 (1.4)	1 (0.5)
Sustained elevated serum potassium	1 (1.6)	2 (2.8)	0	3 (1.5)
Subject withdrew consent	2 (3.2)	1 (1.4)	1 (1.4)	4 (2.0)
Death	0	1 (1.4)	0	1 (0.5)
Lost to follow-up	1 (1.6)	1 (1.4)	1 (1.4)	3 (1.5)
Subjects continuing in the study (%)	53 (85.5)	59 (83.1)	59 (85.5)	171 (84.7)
Subjects not continuing in the study (%)	9 (14.5)	12 (16.9)	10 (14.5)	31 (15.3)

This table includes all randomized subjects who took at least 1 dose of double-blind study medication and entered the long-term period. Percentages reported are based on the total number of subjects in each treatment group.

DAPA = dapagliflozin; N = number of treated subjects

Table 3: Subject Disposition - Long-term Extension Period (up to 09-Aug-2010) Site- and Subject-blinded Period (MB102029)

	Number (%) of Subjects			
	Placebo	**DAPA 5 mg**	**DAPA 10 mg**	**Total**
Subjects randomized	84	83	85	252
Extension				
Subject entering extension	53 (63.1)	59 (71.1)	59 (69.4)	171 (67.9)
Subjects completing extension	0	0	0	0
Subjects not completing extension	3 (3.6)	1 (1.2)	5 (5.9)	9 (3.6)
Reason not completing extension				
Lack of efficacy	0	0	1 (1.2)	1 (0.4)
Adverse event	2 (2.4)	1 (1.2)	3 (3.5)	6 (2.4)
Other	0	1 (1.2)	0	1 (0.4)
Worsened chronic renal insufficiency	0	0	1 (1.2)	1 (0.4)
Sustained elevated liver function tests	1 (1.2)	0	0	1 (0.4)
Sustained elevated serum potassium	1 (1.2)	0	2 (2.4)	3 (1.2)
Death	0	0	1 (1.2)	1 (0.4)
Other	1 (1.2)	0	0	1 (0.4)
Subjects continuing to follow-up (%)	2 (2.4)	0	4 (4.7)	6 (2.4)
Subjects not continuing to follow-up (%)	1 (1.2)	1 (1.2)	1 (1.2)	3 (1.2)
Follow-up				
Subjects entering follow-up (%)	3 (3.6)	5 (6.0)	7 (8.2)	15 (6.0)
Subjects not completing follow-up (%)	1 (1.2)	0	0	1 (0.4)
Reason for not completing follow-up (%)				
Other	1 (1.2)	0	0	1 (0.4)

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; N = number of treated subjects

Demographics and Other Pertinent Baseline Characteristics: In general, the treatment groups were balanced with respect to demographic and baseline characteristics (Table 4).

Table 4: Baseline and Demographic Characteristics Summary, Randomized Subjects (MB102029)

	Placebo N = 84	DAPA 5 mg N =83	DAPA 10 mg N = 85	Total N = 252
Age (yr)				
Mean	67	66	68	67
Median	67	66	68	67
Min, Max	46, 84	32, 92	52, 83	32, 92
Age Category (n, %)				
< 65 yr	36 (42.9)	39 (47.0)	29 (34.1)	104 (41.3)
≥ 65 yr	48 (57.1)	44 (53.0)	56 (65.9)	148 (58.7)
≥ 75 yr	19 (22.6)	9 (10.8)	16 (18.8)	44 (17.5)
Gender (n, %)				
Male	53 (63.1)	55 (66.3)	56 (65.9)	164 (65.1)
Female	31 (36.9)	28 (33.7)	29 (34.1)	88 (34.9)
Race (n, %)				
White	69 (82.1)	65 (78.3)	77 (90.6)	211 (83.7)
Black/African-American	1 (1.2)	7 (8.4)	4 (4.7)	12 (4.8)
Asian	6 (7.1)	4 (4.8)	3 (3.5)	13 (5.2)
Other	8 (9.5)	7 (8.4)	1 (1.2)	16 (6.3)
Geographic Region (%)				
North America	41 (48.8)	51 (61.4)	48 (56.5)	140 (55.6)
Latin America	23 (27.4)	15 (18.1)	17 (20.0)	55 (21.8)
Europe	11 (13.1)	9 (10.8)	9 (10.6)	29 (11.5)
Asia/Pacific	9 (10.7)	8 (9.6)	11 (12.9)	28 (11.1)
Body Mass Index Categorization (%)				
< 25 kg/m^2	9 (10.7)	6 (7.2)	5 (5.9)	20 (7.9)
≥ 25 kg/m^2	75 (89.3)	77 (92.8)	80 (94.1)	232 (92.1)
≥ 27 kg/m^2	68 (81.0)	69 (83.1)	75 (88.2)	212 (84.1)
≥ 30 kg/m^2	50 (59.5)	59 (71.1)	54 (63.5)	163 (64.7)
Pre-enrollment Anti-hyperglycemic Therapy (%)				
Insulin-based regimen	55 (65.5)	54 (65.1)	55 (64.7)	164 (65.1)
Sulfonylurea-based regimen	21 (25.0)	21 (25.3)	21 (24.7)	63 (25.0)
Thiazoliinedione-based regimen	1 (1.2)	1 (1.2)	2 (2.4)	4 (1.6)
Other regimen	7 (8.3)	7 (8.4)	7 (8.2)	21 (8.3)

This table includes all evaluable subjects. Percentages reported are based on the total number of subjects in each treatment group. The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.

Efficacy Results: In this study, the mean decreases in HbA1c produced by dapagliflozin compared to placebo at Week 24 (LOCF) were small, and did not attain statistical significance (Table 5). Consequently, the secondary efficacy endpoints, including decreases from baseline at Week 24 in FPG and in body weight were not subject to statistical hypothesis testing. Taken together, however, mean reduction from baseline at Week 24 in body weight for dapagliflozin treatment groups compared to placebo was suggested. The proportion of subjects rescued or discontinued due to lack of glycemic control was higher for the placebo group than for either dapagliflozin treatment groups during the double-blind treatment period.

Table 5: Primary and Secondary Efficacy Endpoints (LOCF), Excluding Data After Rescue, Randomized Subjects

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
PRIMARY EFFICACY ENDPOINT			
HBA1C (%) AT WEEK 24 (LOCF)			
N#	82	83	82
BASELINE MEAN (SD)	8.53 (1.285)	8.30 (1.040)	8.22 (0.973)
WEEK 24 LOCF MEAN (SD)	8.18 (1.204)	7.97 (1.150)	7.90 (0.930)
MEAN CHANGE FROM BASELINE (SD)	-0.35 (1.260)	-0.33 (0.997)	-0.32 (0.856)
ADJ. MEAN CHANGE FROM BSL. (SE)	-0.32 (0.1701)	-0.41 (0.1701)	-0.44 (0.1708)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	(-0.66, 0.01)	(-0.74, -0.07)	(-0.77, -0.10)
DIFFERENCE FROM PLACEBO (SE)		-0.08 (0.1448)	-0.11 (0.1457)
95% CI FOR DIFFERENCE FROM PLACEBO		(-0.37, 0.20)	(-0.40, 0.17)
P-VALUE VS. PLACEBO (*)		0.561	0.435

N is the number of randomized subjects who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with non-missing baseline and Week t (LOCF) values.
(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.
Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a covariate.

Table 5: Primary and Secondary Efficacy Endpoints (LOCF), Excluding Data After Rescue, Randomized Subjects

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
SECONDARY EFFICACY ENDPOINT			
FPG (MG/DL) AT WEEK 24 (LOCF)			
N#	83	83	84
BASELINE MEAN (SD)	150.2 (48.19)	161.4 (55.88)	164.8 (66.81)
WEEK 24 LOCF MEAN (SD)	158.0 (50.01)	147.4 (54.12)	153.0 (58.38)
MEAN CHANGE FROM BASELINE (SD)	7.8 (53.80)	-14.0 (59.32)	-11.8 (83.55)
ADJ. MEAN CHANGE FROM BSL. (SE)	8.4 (9.621)	-5.2 (9.548)	-0.6 (9.524)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	(-10.5, 27.4)	(-24.0, 13.6)	(-19.3, 18.2)
DIFFERENCE FROM PLACEBO (SE)		-13.6 (8.142)	-9.0 (8.136)
95% CI FOR DIFFERENCE FROM PLACEBO		(-29.7, 2.4)	(-25.0, 7.0)

N is the number of randomized subjects who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with non-missing baseline and Week t (LOCF) values.
(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.
Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a covariate.

Table 5: Primary and Secondary Efficacy Endpoints (LOCF), Excluding Data After Rescue, Randomized Subjects

EFFICACY ENDPOINT STATISTICS	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL BODY WEIGHT (KG) AT WEEK 24 (LOCF)			
N#	84	83	85
BASELINE MEAN (SD)	89.61 (20.046)	95.23 (20.909)	93.25 (17.309)
WEEK 24 LOCF MEAN (SD)	90.04 (19.776)	93.82 (21.268)	91.51 (17.658)
MEAN CHANGE FROM BASELINE (SD)	0.43 (2.425)	-1.41 (3.010)	-1.74 (3.088)
ADJ. MEAN CHANGE FROM BSL. (SE)	0.27 (0.4872)	-1.54 (0.4815)	-1.89 (0.4693)
95% CI FOR ADJ. MEAN CHANGE FROM BSL.	(-0.69, 1.23)	(-2.48, -0.59)	(-2.81, -0.96)
DIFFERENCE FROM PLACEBO (SE)		-1.81 (0.4435)	-2.16 (0.4395)
95% CI FOR DIFFERENCE FROM PLACEBO		(-2.68, -0.94)	(-3.03, -1.29)

N is the number of randomized subjects who took at least one dose of double-blind study medication.
N# is the number of randomized subjects with non-missing baseline and Week t (LOCF) values.
(*) Significant p-value: Primary endpoint is tested at alpha=0.027 applying Dunnett's adjustment, and secondary endpoints are tested following a sequential testing procedure at alpha=0.05.
Analysis of continuous outcomes based on separate ANCOVA models with treatment group and stratum as effects and baseline values as a covariate.

A few Week 24 efficacy endpoints and all efficacy analyses of the 52-week short-term plus long-term period data are exploratory, and no statistical hypothesis tests were performed. The exploratory efficacy analyses for the short-term plus long-term period are based on longitudinal repeated measures analyses using observed data across visits without any data imputation. The following is a brief summary of the exploratory efficacy results for the 52-week short-term plus long-term period overall, excluding data after rescue unless otherwise indicated:

- The small, statistically insignificant mean reductions in HbA1c observed in subjects in the dapagliflozin treatment groups at the end of the 24-week short-term period persisted throughout the 28 week long term period, with adjusted mean reductions at Week 52 slightly greater than those seen at Week 24. At Week 52, the placebo subtracted adjusted mean changes from baseline in HbA1c, excluding data after rescue, were -0.29% (95% CI: -0.76, 0.18) in the dapagliflozin 5 mg group and -0.30% (95% CI: -0.77, 0.17) in the dapagliflozin 10 mg group. This numeric increase is due to a notable deterioration in HbA1c in placebo over time.
- At Week 1, the placebo-subtracted adjusted mean changes from baseline in FPG, excluding data after rescue, were -16.72 mg/dL (95% CI: -31.39, -2.05) in the dapagliflozin 5 mg group and -9.32 mg/dL (95% CI: -23.89, 5.25) in the dapagliflozin 10 mg group.
- At Week 52, the placebo-subtracted adjusted mean changes from baseline in FPG, excluding data after rescue, were -6.89 mg/dL (95% CI: -30.88, 17.09) in the dapagliflozin 5 mg group and -8.75 mg/dL (95% CI: -32.31, 14.80) in the dapagliflozin 10 mg group.
- At Week 24 (LOCF), numerical decreases in the waist circumference of subjects in the dapagliflozin 5 and 10 mg (-0.62 cm and -1.58 cm) treatment groups were observed compared to an increase in the placebo group (0.48 cm), when adjusted for baseline.
- The effects of dapagliflozin on weight loss was clinically meaningful and was observed in all dapagliflozin groups during the study, with an adjusted mean reduction in total body weight for the dapagliflozin 5 mg and 10 mg groups compared with an increase in the placebo group, including data after rescue. The magnitude of the treatment-related difference relative to placebo was greater at later time points during the long-term period when data after rescue were included due to a mean weight gain seen for the placebo group. At Week 52, the placebo subtracted differences in adjusted mean changes from baseline for the dapagliflozin 5 and 10 mg treatment groups were -2.44 kg (95% CI = -3.88, -1.00) and -2.98 kg (95% CI = -4.43, -1.53), respectively.
- At Week 24, the overall proportion of subjects discontinued or rescued for failing to achieve pre specified glycemic targets was numerically lower in the dapagliflozin treatment groups compared with the placebo groups, when adjusted for baseline HbA1c. The placebo-subtracted differences in the adjusted proportion for the dapagliflozin 5 and 10 mg treatment groups were -5.8% (95% CI = -16.4, 4.8) and -14.5% (95% CI = -23.4, -5.5), respectively.
- At Week 52, numerically greater proportions of subjects achieved a therapeutic glycemic response, defined as HbA1c < 7.0%, when adjusted for baseline HbA1c, in the dapagliflozin 5 or 10 mg treatment groups (15.5% and 11.7%, respectively) than in the placebo group (3.7%). Similar proportions were observed at Week 24 (LOCF) across dapagliflozin treatment groups and placebo.

Safety Results: The analysis of safety data for the 52-week short-term plus long-term period supports the conclusion that daily administration of dapagliflozin was generally safe and well-tolerated in subjects with T2DM and moderate renal impairment. No serious safety signals associated with the administration of dapagliflozin were identified in this population. The safety results for the 52-week period were generally consistent with those seen for the 24-week short-term period, and no new risks were identified during the long-term extension period up to data cutoff.

Mean reductions in eGRF and eCrCl were observed in the dapagliflozin and placebo groups at Week 52 (Table 6). For eGFR, the adjusted mean reduction at Week 52 was larger for the dapagliflozin 10 mg group than for the placebo group and similar for dapagliflozin 5 mg and placebo. For eCrCl, the adjusted mean reduction from baseline at Week 52 was larger in both the dapagliflozin 5 and 10 mg groups than in the placebo group, with an apparent dose-dependent trend. The pattern of change over the 52-week short-term plus long-term period differed among the groups. In both dapagliflozin treatment groups, there were initial mean decreases in eGFR and eCrCl at Week 1 that were larger than those observed in the placebo group, followed by stabilization in the eGFR and eCrCl over the remainder of the 52-week short-term plus long-term period. In contrast, a gradual decreasing trend in mean eGFR and eCrCl values was seen in the placebo group.

The overall AE summary for the 52-week short-term plus long-term period is provided in Table 7.

Table 6: Estimated GFR (mL/min/1.73 m^2) and Estimated CrCl (mL/min): Adjusted Mean Change from Baseline at Week 52 (Observed), Including Data After Rescue, Treated Subjects

	PLA N = 84	DAPA 5 mg N = 83	DAPA 10 mg N = 85
N#			
Estimated Glomerular Filtration Rate	49	64	63
Baseline Mean (SD)	47.39 (10.592)	44.21 (9.020)	43.46 (8.956)
Adjusted Mean (SE) Change from Baseline	-1.35 (1.5705)	-2.00 (1.4426)	-4.47 (1.4501)
Difference from Placebo		-0.65	-3.12
95% CI for difference vs Placebo		(-3.52, 2.22)	(-6.00, -0.24)
Estimated Creatinine Clearance Rate[a]			
Baseline Mean (SD)	63.11 (17.318)	62.27 (17.823)	60.50 (18.087)
Adjusted Mean (SE) Change from Baseline	-1.89 (1.8405)	-3.95 (1.7094)	-7.19 (1.7236)
Difference from Placebo		-2.06	-5.30
95% CI for difference vs Placebo		(-5.43, 1.31)	(-8.67,-1.93)

[a] Weight changes are observed with dapagliflozin treatment and may interfere with the interpretation of eCrCl data.

N# is the number of randomized subjects with non-missing baseline and Week 52 (observed) values.
Based on an ANCOVA model with treatment group and stratum as effects and baseline value as a covariate.
DAPA = dapagliflozin; N = number of subjects treated; PLA = placebo.

Table 7: Overall Adverse Events Summary - 52-Week Short-term Plus Long-term Double-blind Period, Including Data After Rescue

	Number (%) of Subjects		
	PLA N = 84	**DAPA 5 mg N = 83**	**DAPA 10 mg N = 85**
At least one AE	73 (86.9)	78 (94.0)	74 (87.1)
At least 1 hypoglycemia event	41 (48.8)	36 (43.4)	32 (37.6)
At least 1 AE or hypoglycemia event	74 (88.1)	78 (94.0)	76 (89.4)
At least 1 related AE	34 (40.5)	35 (42.2)	37 (43.5)
Deaths	3 (3.6)	1 (1.2)	1 (1.2)
At least 1 SAE	18 (21.4)	14 (16.9)	20 (23.5)
At least 1 related SAE	2 (2.4)	4 (4.8)	6 (7.1)
SAE leading to disc. of study medication	5 (6.0)	4 (4.8)	4 (4.7)
AE leading to disc. of study medication	18 (21.4)	11 (13.3)	8 (9.4)
Hypoglycemia event leading to disc of study medication	1 (1.2)	1 (1.2)[a]	0

[a] Discontinuation due to hypoglycemia was recorded in error on the case report form for this subject.
Includes all randomized subjects who took at least one dose of blinded study medication.
Includes non-serious adverse events and hypoglycemia with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 4 days, or before the start of long-term extension treatment if earlier.
Includes serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term plus long-term treatment plus 30 days, or before the start of long-term extension treatment if earlier. 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 are included in the hypoglycemia line.
AE = adverse event; DAPA = dapagliflozin; disc = discontinuation; N = number of subjects treated; PLA = placebo; SAE = serious adverse event

- The proportion of subjects who reported at least 1 AE, as well as the proportion who had at least 1 AE considered by the investigator to be related to study medication, across the 52-week short-term plus long-term period were similar for the dapagliflozin and placebo groups, when data after rescue were included. More subjects in the placebo group had AEs that led to discontinuation.
- For most subjects, AEs were of mild and moderate intensity. AEs of severe or very severe intensity were reported during the 52-week short-term plus long-term period for a higher proportion of subjects in the placebo group (22.7%) compared with either dapagliflozin group (13.2% and 15.3%).
- Five deaths were reported during the 52-week short-term period, 3 in the placebo group (acute myocardial infarction [n=2], traumatic brain injury), 1 in the dapagliflozin 5 mg (myocardial infarction) and 1 in the dapagliflozin 10 mg group (myocardial infarction). Three of the deaths occurred during the 24-week short-term period. One additional death occurred during the additional 52-week long-term extension period in the dapagliflozin 10 mg group (cardiac failure). Results of adjudicated cardiovascular events will be provided separately.
- While the proportions of subjects with serious adverse events (SAEs) during the 52-week short-term plus long-term period were similar for the dapagliflozin and placebo groups, the proportion of subjects with SAEs considered related to study medication was higher for the dapagliflozin 10 mg group than for the other 2 groups. The same pattern was seen for the

24-week short-term period. During the additional 52-week long-term extension period, the types of SAEs were generally consistent with those reported for the 52-week short-term plus long-term period.

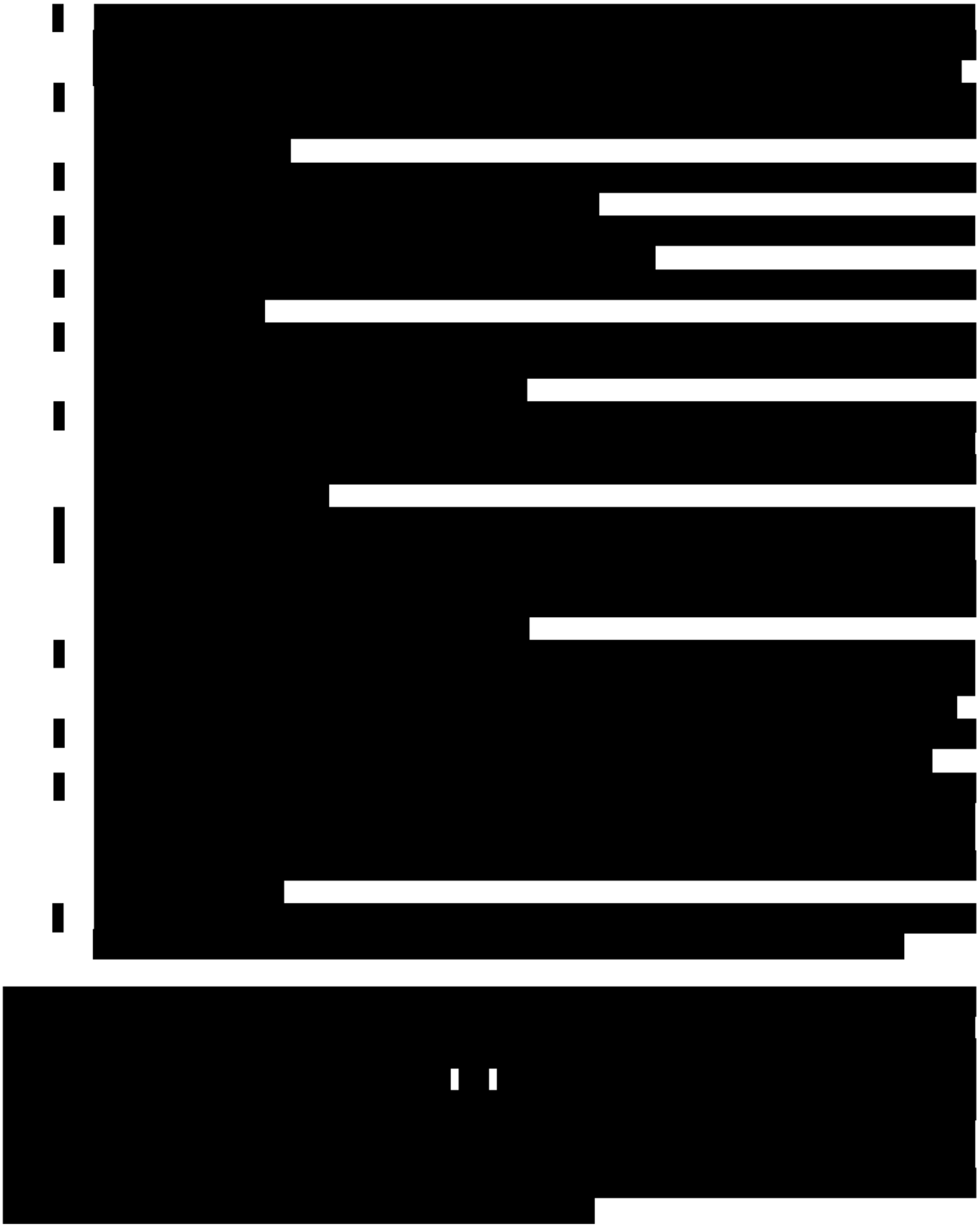
- There were 6 subjects with major episodes of hypoglycemia during the 52-week short-term period, including 4 in the placebo group and 2 in the dapagliflozin 10 mg group. Three of these events were reported as SAEs of hypoglycemia (2 subjects in dapagliflozin 10 mg group) or hypoglycemic coma (placebo subject); study medication was discontinued in 1 placebo subject with a major episode of hypoglycemia. A subject in the dapagliflozin 5 mg group who completed the double-blind treatment period and entered the long-term extension period was erroneously identified on Table 7 as being discontinued due to hypoglycemia. Minor and other episodes of hypoglycemia, including data after rescue, were reported during the 52-week short-term plus long-term period for a similar proportion of subjects in the placebo and dapagliflozin 5 mg groups, and for a lower proportion of subjects in the dapagliflozin 10 mg group.
- Based on a pre-specified list of preferred terms, signs, symptoms, and other reports, events suggestive of genital infection were reported for 15 subjects, and were reported during the 52-week short-term plus long-term period for a greater proportion of subjects treated with dapagliflozin 5 mg (7.2%) and 10 mg (7.1%) compared with placebo (3.6%). In two of the 15 subjects with events suggestive of genital infection, the presence of mycotic infection was specified. A higher proportion of females than males had events suggestive of genital infection in all groups. Most subjects (75%) with an event suggestive of genital infection had a single event across the 52-week short-term plus long-term period, with most of these events having an onset during the short-term period. One event suggestive of genital infection was serious and resulted in discontinuation (balanoposthitis in the dapagliflozin 5 mg group). The remaining events were mild or moderate in intensity and did not result in discontinuation.
- Based on a pre-specified list of preferred terms, signs, symptoms, and other reports, events suggestive of urinary tract infection (UTI) were reported during the 52-week short-term plus long-term period for 23 subjects. The proportion of subjects with these events was similar for the placebo (9.5%) and dapagliflozin (8.4% and 9.4%) groups, and were higher among females than males in all groups. Among those with an event suggestive of UTI, most in the placebo group and approximately one-half of subjects in the dapagliflozin groups had an event with an onset during the 24-week short-term period. Approximately 60% of subjects with an event suggestive of UTI in all groups had a recurrent event during the 52-week short-term plus long-term period. None of the events suggestive of UTI were serious or resulted in discontinuation, and all but 1 were mild or moderate in intensity. There were no events of pyelonephritis reported in this study.
- Events of renal impairment or renal failure were infrequent during the 52-week short-term plus long-term period, but occurred in a higher proportion of subjects in the dapagliflozin 10 mg group (5.9%) compared with the placebo (2.4%) or dapagliflozin 5 mg (1.2%) groups. Most events in this category consisted of reports of increased blood creatinine; renal failure was reported for 1 subject each in the placebo and dapagliflozin 5 mg groups, and was serious and led to discontinuation in both cases. One subject in the dapagliflozin 10 mg group had a SAE of acute renal failure during the long-term extension period. The subject with renal failure in the dapagliflozin 5 mg group was the only subject discontinued for worsening chronic renal insufficiency during the supplemental short-term plus long-term period up to data cutoff; this subject had a history of decompensated chronic congestive heart failure.
- AE reports in the hypotension/dehydration/hypovolemia category were more frequent in the dapagliflozin groups (8.4% and 9.4%) than in the placebo group (4.8%) during the 52-week short-term plus long-term period, and consisted mainly of reports of hypotension. No event in this category led to discontinuation; 2 subjects in the dapagliflozin 10 mg group had events in this category (hypotension and syncope) that were serious.

- During the 52-week short-term plus long-term period, fractures were reported for 10 subjects in the dapagliflozin groups (3 in 5 mg group, 7 in 10 mg group). Most of the fractures (70%) occurred during the 28-week long-term period. No subject in the placebo group had a reported fracture during this 52-week period. There was no apparent pattern with respect to the site of fracture, or with the reported occurrence of hypoglycemia or hypotension, and all were assessed as mild or moderate in intensity and did not lead to discontinuation.
- There was a single AE report of urinary stones in a placebo subject during the 52-week short-term plus long-term period.
- Overall, marked abnormalities (MAs) were infrequent during the 52-week short-term plus long-term period, and were generally balanced between the dapagliflozin treatment groups. The pattern of laboratory MAs was consistent with that observed for the 24-week short-term period. No MAs were reported for creatine kinase > 10X ULN, serum albumin, total serum protein, or magnesium during the 52-week short-term plus long-term period.
- The proportion of subjects with a serum creatinine value ≥ 2.5 mg/dL during the 52-week short-term plus long-term period was slightly greater for the dapagliflozin 10 mg (11.9%) group compared with the dapagliflozin 5 mg (9.6%) or placebo group (9.6%). Almost all subjects with MAs in serum creatinine had elevated values at baseline.
- Mean reductions from baseline in serum uric acid were seen in all 3 groups during the 52-week short-term plus long-term period, but were generally larger in the dapagliflozin groups compared with the placebo group beginning at Week 22. Changes from baseline in the urinary albumin to creatinine and urinary protein to creatinine ratios were generally small and inconsistent among the treatment groups.
- Dose-related increases in mean hemoglobin and hematocrit were observed at Week 12, and remained stable throughout Week 52. Marked abnormalities related to elevated hematocrit or hemoglobin were reported for a larger proportion of subjects treated with dapagliflozin than placebo. One dapagliflozin-treated subject with an increase in hematocrit levels had an ischemic stroke; the subject had a history of high hematocrit levels prior to study entry, and recovered fully from the stroke while on dapagliflozin. All other changes in hematocrit and hemoglobin occurred in the absence of associated thrombotic or thromboembolic AEs.
- Mean increases in serum levels of inorganic phosphorus and magnesium were seen in the dapagliflozin groups, although mean values remained within normal range for these analytes and the magnitude of the mean changes were stable across the 52-week short-term plus long-term period. More subjects experienced MAs of hyperphosphatemia on dapagliflozin than on placebo; no MAs in magnesium were observed. Most of the MAs in the dapagliflozin groups had an onset in the 24-week short-term period, and for all subjects, inorganic phosphate concentrations returned to baseline values and/or within normal limits while the subject remained on dapagliflozin treatment.
- There was no evidence of clinically meaningful hyponatremia or hypokalemia. MAs of elevated sodium were more common on dapagliflozin than on placebo but all MAs were isolated occurrences and resolved while the subject remained on dapagliflozin. MAs of elevated potassium were more common on placebo than on dapagliflozin during the 52-week short-term plus long-term period. The proportion of subjects discontinued for elevated potassium was higher for the placebo group than for either dapagliflozin group.
- The occurrence of elevated liver function test values was similar for the 3 groups during the 52-week short-term plus long-term period, and no subject had a combination of elevations in alanine aminotransferase (ALT) or asparate aminotransferase (AST) > 3X upper limit of normal (ULN) plus a concurrent or subsequent (within 14 days) total bilirubin level > 2X ULN at any point up to data cutoff.

- The mean concentration of serum PTH exceeded the upper limit of normal (ULN) at baseline in all treatment groups, and there were larger mean increases in PTH in the dapagliflozin groups compared with placebo during the 52-week short-term plus long-term period.
- Mean reductions in seated systolic and diastolic blood pressure were larger in the dapagliflozin groups than in the placebo group during the 52-week short-term plus long-term period, and appeared dose dependent for the dapagliflozin groups. The magnitude of the mean reductions in blood pressure in the dapagliflozin 10 mg group was generally stable from Week 1. While the proportion of subjects with measured orthostatic hypotension at any assessment time during the 52-week short-term plus long-term period was higher for the dapagliflozin groups than for the placebo group, this difference appears to reflect the higher rate of orthostatic hypotension seen in the dapagliflozin groups at baseline.

Pharmacokinetic Results: The PK analyses will be included in a separate population PK report.

Pharmacodynamic Results: The mean value for the 24-hour urine glucose:creatinine ratio at Week 52 was higher in both dapagliflozin groups compared with placebo, consistent with the mechanism of action of dapagliflozin. The mean (95% CI) difference from placebo in the adjusted mean change from baseline at Week 52 was 27.68 g/g (21.21, 34.14) for the dapagliflozin 5 mg group and 25.08 g/g (18.62, 31.55) for the dapagliflozin 10 mg group.



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