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

Final Clinical Study Report for Study MB102066

TITLE OF STUDY: Characterization of the Kinetics of Renal Glucose Reabsorption in Response to Dapagliflozin in Healthy Subjects and in Subjects with Type 2 Diabetes Mellitus

INVESTIGATORS/STUDY CENTERS: This study was conducted [redacted] in the United States of America.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 31-Aug-2010 **CLINICAL PHASE:** 1

Study Completion Date: 24-Dec-2010

OBJECTIVES:

Primary Objective: To characterize the reduction in glucose transport maximum (T_{mG}) after 7 days of oral administration of 10-mg dapagliflozin in healthy subjects and subjects with type 2 diabetes mellitus (T2DM) and to examine whether there is a difference in the renal glucosuric effect of dapagliflozin between these populations as characterized by percent change in T_{mG}.

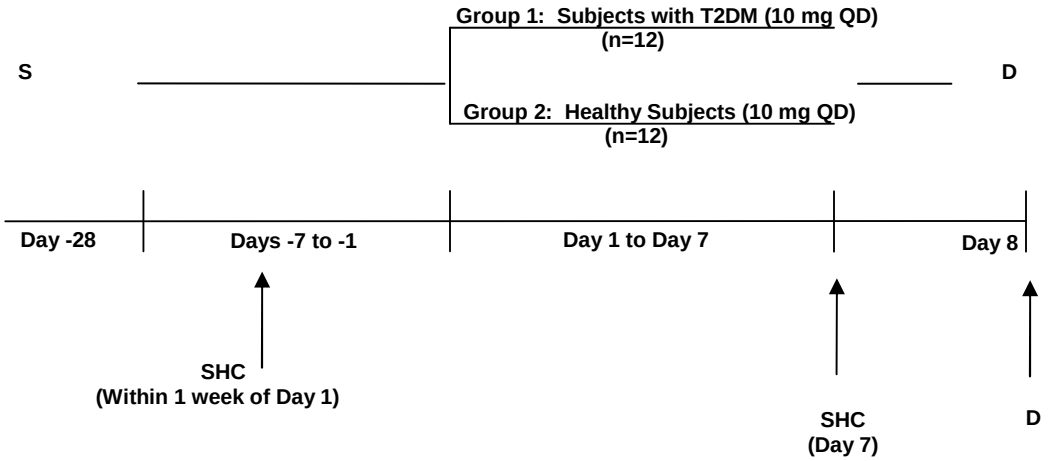
Secondary Objectives:

- To examine whether there is a difference in T_{mG} and/or splay of the glucose titration curve between healthy subjects and subjects with T2DM at baseline.
- To examine whether there is a difference in the renal glucosuric effect of dapagliflozin as characterized by percent change in the splay of the glucose titration curve in healthy subjects and in subjects with T2DM after 7 days of oral administration of 10-mg dapagliflozin daily.
- To assess the pharmacokinetic (PK) of dapagliflozin in healthy subjects and in subjects with T2DM.
- To assess the safety and tolerability of dapagliflozin in healthy subjects and subjects with T2DM.

METHODOLOGY:

This was an open-label, parallel, multiple-dose study. Twenty-four (24) subjects (12 subjects with T2DM and 12 healthy controls) were dosed on Day 1. The study scheme is shown in Figure 1.

Figure 1: Study Scheme



SHC = Stepped Hyperglycemic Clamp and Iohexol infusion
T2DM = Type 2 Diabetes Mellitus
S = Screening D = Discharge
QD = once daily

Subjects underwent screening evaluations to determine eligibility within 28 days prior to administration of study medication. The screening evaluation included a physical examination, medical history, fasting plasma glucose, glycosylated hemoglobin (HbA1C), thyroid-stimulating hormone (TSH), clinical safety labs, and estimated glomerular filtration rate (eGFR) using MDRD formula.

For screening purposes, the eGFR was estimated with the MDRD equation which was calculated as follows:

$$eGFR\ (mL/min/1.73m^2) = 175 \times (\text{standardized Scr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Black})$$

Subjects continued usual background anti-diabetic therapy throughout the study, with the exception of metformin which was held for 48 hours prior to each stepped hyperglycemic clamp procedure (due to administration of iohexol during the clamp).

The influence of dapagliflozin on the renal glucose handling capacity, in healthy subjects and subjects with T2DM, was measured by conducting a stepped hyperglycemic clamp at baseline and after 7 days of dapagliflozin administration. To sufficiently measure the maximum transport capacity, hyperglycemia was induced in 50 mg steps ranging from approximately 100 mg/dL to a target of 550 mg/dL.

In addition, a 'pancreatic clamp' approach was used to ensure that the maximal target plasma glucose concentration would be achieved in healthy subjects and that each incremental step could be attained quickly. This approach essentially 'clamps' endogenous insulin secretion using octreotide (a somatostatin analog), and by replacing key hormones to a predetermined basal level.

In addition, a novel approach was used to evaluate GFR during the clamp. Since iohexol is neither secreted nor reabsorbed in the kidney, it is a widely used exogenous marker to assess GFR. Blood and cumulative urine samples were collected for determination of iohexol concentrations at pre-dose and several time points post-dose. GFR, as estimated by renal iohexol clearance (IGFR), was used for the statistical analysis in this study. IGFR was calculated using plasma and urine iohexol concentrations with the following formula:

$$IGFR(mL/\min) = \frac{U_{io} \times V}{P_{io}}$$

where, P_{io} and U_{io} are the plasma and urine concentrations of iohexol, respectively. V is the urine volume/cumulative collection interval time.

NUMBER OF SUBJECTS (Planned and Analyzed): Twenty-four (24) subjects were administered study drug and completed the study as planned.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female healthy subjects and subjects with T2DM between the ages of 18 to 65 years were eligible to participate in this study if they met the criteria below.

Both healthy subjects and subjects with T2DM:

- Have an eGFR $\geq$ 60 and $\leq$ 160 mL/min/1.73m^2 and urinary albumin excretion less than 300 mg/g creatinine.

Subjects with T2DM:

- Have a fasting plasma glucose concentration $\leq$ 200 mg/dL and HbA1C $\leq$ 10%.
- On one of the following therapies per patient report: diet therapy alone, diet plus a sulfonylurea, diet plus metformin, or diet plus sulfonylurea plus metformin. Subjects taking metformin, and/or sulfonylurea must be on a stable dose for at least 2 months prior to study drug administration.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects received a single daily oral dose of 10-mg dapagliflozin as a tablet formulation [redacted] on Days 1 to 7 after fasting for at least 10 hours. Dapagliflozin tablets were provided by Bristol-Myers Squibb (BMS).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable.

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse events (AEs) reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. Clinical laboratory tests included serum chemistry, hematology, and urinalysis. The incidence of observed AEs were tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetics: On Day 7, PK parameters [Cmax, Tmax, Cmin, and AUC(TAU)] were derived from plasma concentration versus time data for dapagliflozin.

Pharmacodynamics: Urine was collected at specified time points during the baseline stepped hyperglycemic clamp procedure and on Day 7.

Within 1 week prior to Day 1 (Baseline) and on Day 7, at about 7:00, 7:30, and 8:00 AM (-60, -30, 0 min) blood was drawn for determination of plasma iohexol. At approximately 7:30, 7:45, and 8:00 AM (-30, -15, 0 min) blood was drawn for determination of plasma glucose. At approximately 8:00 AM (0 min) blood was drawn for determination of serum insulin.

Plasma iohexol, glucose and serum insulin concentrations were measured at 40, 80, 120, 160, 200, 240, 280, 320, 360 and 400 minutes during the stepped hyperglycemic clamp.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The sample size calculation was based on power considerations. With a one-sided test at significance level 0.05, data from 10 subjects with T2DM provided at least 99% power to conclude that 7 days of oral administration of 10-mg dapagliflozin would reduce the T_{mG} in subjects with T2DM if the true mean percent reduction from baseline in T_{mG} is 40%. Similarly, data from 10 healthy subjects provided at least 99% power to conclude that 7 days of oral administration of 10-mg dapagliflozin would reduce T_{mG} in healthy subjects if the true mean percent reduction from baseline in T_{mG} is 40%. In addition, with two one-sided tests (at significant level 0.05 for each one-sided test), data from 10 subjects in each group provided at least 87% power to conclude that the dapagliflozin effect on T_{mG} (percentage reduction in T_{mG} from baseline) would be equivalent between these two groups if 20% was used as the equivalence limit. Although the clinical relevance of any equivalence limit for changes in T_{mG} could not be defined, a 20% equivalence limit was set *a priori* as a reasonable estimate, and was similar to the criteria that would be utilized to establish bioequivalence in pharmacokinetics. These calculations assumed that T_{mG} post-treatment compared to baseline ratios were log-normally distributed and the standard deviation of log (T_{mG} post-treatment to baseline ratio) would be no greater than 0.15.

To ensure 10 completers per group, 12 subjects with T2DM meeting inclusion criteria and reaching the plasma glucose level of $\geq$ 400 mg/dL at the baseline stepped hyperglycemic clamp visit and 12 healthy subjects meeting inclusion criteria and reaching the plasma glucose level of $\geq$ 350 mg/dL at the baseline stepped hyperglycemic clamp visit were dosed on Day 1.

Statistical Analysis:

Safety: All recorded AEs were listed and tabulated by system organ class (SOC), preferred term (PT), and group. Vital signs and clinical laboratory test results were listed and summarized by group and study day. Any significant physical examination findings and clinical laboratory results were listed. Electrocardiogram readings were evaluated by the Investigator and abnormalities were listed.

Pharmacokinetics: Summary statistics were tabulated for each of the PK parameters [Cmax, Tmax, Cmin, and AUC(TAU)] by treatment group, for dapagliflozin. Geometric means and coefficients of variation (CV) were presented for Cmax, Cmin, and AUC(TAU). Medians and ranges were presented for Tmax.

GFR as Estimated by Iohexol Renal Clearance: Summary statistics were tabulated for iohexol renal clearance (IGFR) and the corresponding change from baseline and percent change from baseline by treatment group and visit.

Iohexol clearance was calculated from the infusion data collected during the entire duration of the "clamp", starting from the first hyperglycemic clamp step until the end of the duration of the clamp procedure during that study visit.

Population Pharmacodynamics Modeling:

Initially the estimation of renal glucose titration parameters T_{mG} and splay were to be estimated using a simple approach as has been described in the literature, it became evident that the original plan would not provide a rigorous approach determining these parameters. Therefore, population PD modeling was

performed to allow the development of a model that would ultimately provide a systematic approach to determining the T_{mG} and splay for each individual subject. The development of this model also allowed the determination of threshold, the plasma glucose level at which the observed renal glucose titration curve deviates from the theoretically ideal curve and glucose would begin to appear in the urine.

The relationship of the rate of glucose reabsorption in kidney (R_{ij}) for the i^{th} individual at j^{th} glucose concentration in plasma (G_{ij}) was described by a nonlinear mixed-effects population PD model in terms of maximum achievable rate of reabsorption ($T_{mG,i}$) and coefficient of glucose effect (k_i) using the following exponential function:

$$R_{ij} = T_{mG,i} \cdot \left(1 - e^{-k_i \cdot G_{ij}}\right) + \varepsilon_{ij} \qquad (1)$$

where ε_{ij} denotes the intraindividual (residual) random effect, which is assumed to have zero mean and variance σ^2.

The T_{mG} for each individual at their baseline and Day 7 visits was obtained from the individual Bayesian PD parameter estimate from the population PD model. Threshold, which is the plasma glucose concentration at which the model-projected glucose reabsorption curve deviates from the theoretical curve, was calculated by solving Equation 2 iteratively until the difference of threshold value and plasma glucose concentration (G) value was equal to zero:

$$\text{Threshold}_i = T_{mG,i} \cdot \left(1 - e^{-k_i \cdot G_{ij}}\right) \cdot \frac{100}{\text{GFR}_i} \qquad (2)$$

where GFR_i is the individual glomerular filtration rate. For this study, the infusion was kept constant during the entire duration of the clamp. Therefore, overall clearance of iohexol was utilized for calculation of GFR (also referred to as IGFR in this study)

The Splay for the i^{th} individual ($Splay_i$) was obtained by calculating the difference of the area between theoretical glucose reabsorption curve and the model-projected one:

$$\text{Splay}_i = \left\{0.5 \cdot \left(\frac{\text{GFR}_i}{100} \cdot \text{Threshold}_i + T_{mG,i}\right) \cdot (G_i - \text{Threshold}_i) + T_{mG,i} \cdot (G^*_i - G_i)\right\} - \int_{\text{Threshold}_i}^{G^*_i} T_{mG,i} \cdot \left(1 - e^{-k_i \cdot G_{ij}}\right) \qquad (3)$$

where G^*_i is the individual glucose concentration when $T_{mG,i}$ is reached.

Pharmacodynamics:

T_{mG}, Splay, and Threshold: To characterize the reduction in (T_{mG} after 7 days of oral administration of 10-mg dapagliflozin in healthy subjects and subjects with T2DM) and to examine whether there was a difference in the renal glucosuric effect of dapagliflozin between healthy subjects and subjects with T2DM (as characterized by percent change in T_{mG}), T_{mG} values were log-transformed. Percent changes from baseline at Day 7 in T_{mG} were analyzed using analysis of covariance (ANCOVA) of the logarithms of the post-treatment to baseline ratios in T_{mG}, with group as a main effect and logarithm of baseline T_{mG} value as a covariate. From that model, with some transformations (exponential back transformation and linear transformation (minus 1)), point estimates and 90% confidence intervals (CIs) for geometric mean percent change from baseline in T_{mG} within each group were constructed. P-values were provided for those assessments. From the same model and with some transformations (exponential back transformation and

linear transformation (minus 1)), the point estimate and its 90% confidence interval were calculated for subjects with T2DM to healthy subjects ratio of geometric means of the post-treatment to baseline ratios in T_{mG}. Equivalence in the dapagliflozin effect on T_{mG} between subjects with T2DM and healthy subjects was concluded if the 90% confidence interval for the subjects with T2DM to healthy subjects ratio of geometric means of the post-treatment to baseline ratios in T_{mG} was entirely contained within 80% to 125%.

T_{mG} values and their absolute change from baseline were summarized by treatment group and visit. Similar analyses were performed for splay. Although not originally planned in the protocol, similar analyses were also performed for threshold.

To examine whether there was a difference in the T_{mG} between healthy subjects and subjects with T2DM at baseline, the point estimate and its 90% confidence interval were calculated for subjects with T2DM to healthy subjects ratio of geometric means for T_{mG} at Baseline. These estimates were constructed from the results of fitting ANOVA model for log-transformed data with treatment group as a fixed effect. The point estimate of the difference and its 90% confidence interval in the log scale were exponentiated to obtain the estimate and the confidence interval for the ratio of geometric means in the original scale. No p-values were reported for the assessments. Similar analyses were performed for splay and threshold.

Urinary Glucose: Different from the plan in the original version of the protocol, the total amounts of glucose excreted in urine (absolute and corrected for iohexol) and the corresponding change from baseline were summarized by treatment group, visit and target plasma level for each collection interval instead of by treatment group, visit and collection interval. This change resulted from an amendment to the protocol after the first two subjects were studied, in whom the first planned collection interval with a target plasma glucose of 100 mg/dL was unintentionally omitted. In the first two subjects only, the first collection interval corresponded to a target plasma glucose of 150 mg/dL and corresponded to the second collection interval for the remaining subjects. In order to permit appropriate comparisons following this change in the study, the target plasma glucose was substituted for collection interval. Baseline is the time-matched value at the baseline stepped hyperglycemic visit. The mean value for the total amount of glucose excreted (absolute and corrected for iohexol) was plotted versus the corresponding target plasma glucose level for that collection interval, instead of the midpoint of each collection interval by treatment group and visit, as was initially planned.

Plasma Glucose: Different from plan in the original version of the protocol, the plasma glucose concentrations and their changes from baseline were summarized by treatment group, visit and target plasma glucose level instead of by treatment group, visit and time point. As discussed above, this change resulted from an amendment to the protocol after the first two subjects were studied in whom the first planned collection interval, with a target plasma glucose of 100 mg/dL, was unintentionally omitted. In the first two subjects only, the first collection interval corresponded to a target plasma glucose concentration of 150 mg/dL, and corresponded to the target for the second collection interval for the remaining subjects. In order to permit appropriate comparisons following this change in the study, the target plasma glucose concentration was substituted for collection interval. Baseline was the time-matched value at the baseline stepped hyperglycemic visit. The mean values for the plasma glucose concentrations were plotted versus the corresponding target plasma glucose levels by treatment group and visit.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Twenty-four (24) subjects were randomized, administered study drug and completed the study as planned. A summary of subject disposition is provided in Table 1 below. Demographic characteristics are presented in Table 2. Summary statistics for HbA1C and fasting plasma glucose at screening for both groups are presented in Table 3.

Table 1: Summary of Subject Disposition

	TRTGRP A	TRTGRP B	Dosed	Not Dosed
NO. SUBJECTS ENROLLED N =	12	12	24	37
NO. SUBJECTS DISCONTINUED N =	0	0	0	37
NO. DISCONTINUED BECAUSE :				
OTHER	0	0	0	6
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	28
SUBJECT WITHDREW CONSENT	0	0	0	3
NO. SUBJECTS COMPLETING STUDY	12	12	24	0

TREATMENT GROUP: TRTGRP A = Patients with T2DM, TRTGRP B = Healthy Subjects

Table 2: **Demographic Characteristics Summary**

	TRTGRP A N=12	TRTGRP B N=12	Dosed Subjects N=24
Age (yrs)			
N	12	12	24
Mean	53	41	47
Standard Deviation	9	10	11
Median	55	40	50
Min-Max	37-64	30-57	30-64
Q1-Q3	46-60	32-50	38-57
Age Category n(%)			
< 65 years	12(100)	12(100)	24(100)
>= 65 years	0	0	0
Not Reported	0	0	0
Gender n(%)			
Male	7(58)	7(58)	14(58)
Female	5(42)	5(42)	10(42)
Not Reported	0	0	0
Race n(%)			
White	9(75)	11(92)	20(83)
Black/African American	2(17)	1(8)	3(13)
Asian	1(8)	0	1(4)
Other	0	0	0
Not Reported	0	0	0
Ethnicity n(%)			
Not Hispanic/Latino	7(58)	8(67)	15(63)
Hispanic/Latino	5(42)	4(33)	9(38)
Not Reported	0	0	0

TREATMENT GROUP:TRTGRP A = Patients with T2DM, TRTGRP B = Healthy Subjects

Table 3: Summary Statistics for HbA1C and Fasting Plasma Glucose at Screening

Parameter	T2DM (n=12)		Healthy (n=12)	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max
HbA1C (%)	6.5 (0.60)	5.40-7.20	5.5 (0.27)	5.0-5.9
Fasting Plasma Glucose (mg/dL)	107.7 (28.60)	73.0-164.0	84.6 (5.23)	74.0-93.0

Safety Results:

Administration of 10-mg dapagliflozin for 10 days was safe and generally well-tolerated in the subjects with T2DM and the healthy subjects in this study.

There were no deaths, serious AEs (SAEs), or discontinuations in this study. Overall, there were 21 AEs that occurred in 13 (54.2%) subjects, of which nausea (16.7%) and headache (16.7%) were the most common. There were no unresolved AEs and all of the AEs were considered mild in intensity by the Investigator. The occurrence of AEs was similar across treatment groups (Table 4).

Subject [redacted], a 30-year-old healthy white male, had an AE of hypoglycemia on Day 7 after receiving 10-mg dapagliflozin. The AE occurred following the hyperglycemic clamp, when the glucose and hormone infusions were discontinued, lasted 54 minutes and resolved without treatment. The subject experienced mild sweating and hot flashes associated with a minimum blood glucose measurement of 63 mg/dL. The AE was considered mild in intensity and related to the study drug by the Investigator This subject also had a laboratory MAs of elevated urine glucose at screening and on Day 7.

Overall, there were 21 laboratory marked abnormalities (MAs) that occurred in this study. The most common laboratory MA was elevated urine glucose in 16 (66.7%) subjects. This finding is consistent with the pharmacologic activity of dapagliflozin as an inhibitor of urinary glucose reuptake. One (1) subject had laboratory MAs of increased AST (55 U/L; ULN=40 U/L) and ALT (87 U/L; ULN=40 U/L) on Day 8/Discharge that was not considered clinically significant by the Investigator.

There were no clinically-important ECG findings, vital sign abnormalities, or physical examination findings.

Table 4: Adverse Event Summary

	Number (%) of Subjects		
	T2DM N = 12	**Healthy N = 12**	**All Subjects N = 24**
Adverse event(s)	7 (58.3)	6 (50.0)	13 (54.2)
Death	0	0	0
SAE	0	0	0
Discontinuation due to AEs	0	0	0
Most Frequent AEs			
Nausea	3 (25.0)	1 (8.3)	4 (16.7)
Headache	3 (25.0)	1 (8.3)	4 (16.7)

Pharmacokinetic Results:

After multiple dose administration of dapagliflozin, healthy subjects and subjects with T2DM had similar geometric mean peak (Cmax), systemic exposure (AUC), and Cmin values. Overall there was no apparent difference in dapagliflozin PK between healthy subjects or subjects with T2DM after multiple dose administration of dapagliflozin.

Pharmacokinetic parameters for dapagliflozin are summarized in Table 5.

Table 5: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters on Day 7

Treatment Group	**Cmax (ng/mL) Geo. Mean (CV)**	**Tmax (h) Median (Min, Max)**	**AUC(TAU) (ng·h/mL) Geo. Mean (CV)**	**Cmin (ng/mL) Geo. Mean (CV)**
T2DM (n=12)	53.5 (40)	2.00 (1.33, 4.00)	318 (47)	4.27 (45)
Healthy (n=12)	57.5 (46)	2.67 (1.33, 4.67)	332 (26)	4.40 (41)

GFR as Estimated by Iohexol Renal Clearance:

Details of percent change from baseline in IGFR are summarized in Table 6.

Table 6: Summary Statistics for IGFR and % Change from Baseline

Treatment Group	IGFR (mL/min)		% Change from Baseline (%) Geo. Mean (90% C.I.)
	Baseline Geo. Mean (CV%)	Day 7 Geo. Mean (CV%)	
T2DM (n=12)	122.5 (27)	105.5 (26)	-13.93 (-21.77, -5.30)
Healthy (n=12)	123.6 (28)	106.0 (35)	-14.31 (-21.21, -6.80)

The percent change from baseline in iohexol renal clearance showed a reduction of 14.31% in healthy subjects and a reduction of 13.93% in subjects with T2DM. The results from Table 6 show that baseline IGFR, Day 7 IGFR, and the change in IGFR as a result of dapagliflozin treatment were similar in healthy subject and in subjects with T2DM.

Pharmacodynamic Assessment:

The individual $T_{mG,}$ splay and threshold values were estimated from models using the glucose titration curve. The modeled $T_{mG,}$ splay and threshold for healthy subject [redacted] were excluded in the main analyses because his modeled Tm_G at baseline (997 mg/min) was not consistent with the reported values from Mogensen in which the maximal T_{mG} value is 498 mg/min and the mean T_{mG} value is 352 mg/min for healthy subjects and also much higher than the largest baseline value from other healthy subjects (429.4 mg/min) in this study.

Details of $T_{mG,}$ splay, and threshold at baseline and following treatment with oral dapagliflozin 10 mg for 7 days are summarized in Table 7.

Table 7: Summary Statistics for T_{mG} and Splay (Model Derived)

Treatment Group	Baseline Mean (S.D.)	Day 7 Mean (S.D.)	Change From Baseline Mean (S.D.)
T_{mG} (mg/min)			
T2DM (n=12)	443 (150.5)	184 (55.6)	-260 (116)
Healthy (n=11)	326 (79.0)	154 (36.8)	-173 (70.7)
Splay (mg^2/min^2)			
T2DM (n=12)	28650 (9617.7)	17810 (6223.2)	-10840 (5610.0)
Healthy (n=11)	14248 (5132.0)	9018 (2621.0)	-5230 (3182.6)

Note: Excluding subject [redacted]

Details of the statistical analyses of baseline T_{mG} and baseline splay are presented in Table 8.

Table 8: Results of Statistical Analyses on Baseline T_{mG} and Baseline Splay

PD Parameter	Adj. Geo. Mean		Ratio of Adj. Geo. Means (T2DM / Healthy)	
	T2DM	Healthy	Point Estimate	90% CI
T_{mG} (mg/min)	420	317	1.322	(1.059, 1.650)
Splay (mg^2/min^2)	27328	13598	2.010	(1.608, 2.512)

Note: Excluding subject [redacted]

Overall, these results indicate that the baseline T_{mG} and splay are higher in subjects with T2DM than in healthy subjects.

Details of the statistical analyses of T_{mG} and splay are presented in Table 9. The interactions were not significant, which means that the planned models without treatment group-by-baseline interaction for T_{mG} and splay are appropriate.

Table 9: Results of Statistical Analyses on T_{mG} and Splay

PD Parameter	% Change from Baseline Adj. Geo. Mean (90% CI)		Ratio of Percent Change from Baseline (%) Adj. Geo. Mean (90% CI)	% Difference in Percent Change from Baseline Between T2DM Relative to Healthy (%) Adj. Geo. Means (90% CI)
	T2DM	Healthy	(T2DM / Healthy)	
T_{mG} (mg/min)	-55.7 (-60.1, -50.8)	-55.5 (-60.2, -50.3)	99.6 (84.9, 116.9)	-0.4 (-15.1, 16.9)
Splay (mg^2/min^2)	-33.9 (-40.5, -26.4)	-40.3 (-46.7, -33.1)	110.8 (92.1, 133.3)	10.8 (-7.9, 33.3)

Note: Excluding subject [redacted]

Because subjects with T2DM had higher T_{mG} and splay at baseline, the absolute reduction in T_{mG} and splay after 7 days of oral administration of 10-mg dapagliflozin was greater in subjects with T2DM relative to healthy subjects (Table 7). However, the percent reductions in T_{mG} and splay after 7 days of oral administration of 10-mg dapagliflozin in healthy subjects and subjects with T2DM are equivalent.

Details of threshold at baseline and following treatment with oral dapagliflozin 10 mg for 7 days are summarized in Table 10.

Table 10: Summary Statistics for Threshold (mg/dL) (Model Derived)

Treatment Group	Baseline Mean (S.D.)	Day 7 Mean (S.D.)	Change From Baseline Mean (S.D.)
T2DM (n=12)	196 (63.4)	21 (46.3)	-175 (67.3)
Healthy (n=11)	171 (57.0)	37 (39.5)	-134 (64.6)

Note: Excluding subject [redacted]

The plasma glucose threshold for urinary glucose appearance at baseline is similar although numerically higher in subjects with T2DM (~196 mg/dL) compared to healthy subjects (~171 mg/dL).

CONCLUSIONS:

[redacted]

DATE OF REPORT: 12-Dec-2011