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 MB102007

TITLE OF STUDY: The Pharmacodynamics, Pharmacokinetics, and Safety of Dapagliflozin in Type 2 Diabetic Subjects with Mild, Moderate, and Severe Renal Impairment

INVESTIGATORS/STUDY CENTERS: Site 1: [redacted]
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Site 4: [redacted]
Site 5: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 27-Mar-2006 **CLINICAL PHASE:** 1
Study Completion Date: 01-Oct-2008

OBJECTIVES:

Primary Objectives:

- To assess the effect of a single oral dose of dapagliflozin on renal glucose clearance in subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment compared to type 2 diabetic and healthy subjects with normal renal function.
- To assess the effects of various degrees of renal impairment on the single dose pharmacokinetics (PK) of dapagliflozin in diabetic subjects with mild, moderate or severe renal impairment compared to diabetic and healthy subjects with normal renal function.

Secondary Objectives:

- To assess the acute effects of multiple oral doses of dapagliflozin on renal glucose clearance in subjects with T2DM with mild, moderate or severe renal impairment compared to type 2 diabetic and healthy subjects with normal renal function.
- To assess the effects of various degrees of renal impairment on the single and multiple-dose pharmacokinetics of dapagliflozin and BMS-801576, a major inactive glucuronide metabolite of dapagliflozin, in diabetic subjects with mild, moderate or severe renal impairment compared to diabetic and healthy subjects with normal renal function.

- To assess the effects of single and multiple oral doses of dapagliflozin on total amount of glucose excreted in urine over 24 hours in subjects with type 2 diabetes mellitus with mild, moderate and severe renal impairment compared to type 2 diabetic and healthy subjects with normal renal function.
- To assess the acute effects of single and multiple oral doses of dapagliflozin on the following safety serum/urine parameters: sodium, potassium, magnesium, phosphorus, calcium, and total protein (urine only).
- To explore the relationships between exposure measures and PD endpoints such as glucosuria.
- To estimate the protein binding of dapagliflozin in subjects with type 2 diabetes mellitus with mild, moderate or severe renal impairment compared to type 2 diabetic and healthy subjects with normal renal function.
- To assess the safety and tolerability of single and multiple oral doses of dapagliflozin in subjects with type 2 diabetes mellitus with mild, moderate and severe renal impairment.

METHODOLOGY: This was an open-label, parallel, single-dose (Phase A) and subsequent multiple-dose (Phase B) study. At least thirty-six (36) subjects were to be recruited into five groups according to diabetic status and degree of renal function (8 subjects in groups A-D, 4 subjects in Group E, with intent to continue inclusion of at least 4 subjects in Groups B-E in the multiple dose phase of the study):

A: Healthy subjects with normal renal function (creatinine clearance (CLcr) > 80 mL/min)

B: Subjects with type 2 diabetes mellitus (T2DM) and normal renal function (creatinine clearance (CLcr) > 80 mL/min)

C: Subjects with T2DM and mild renal impairment ($50 < CLcr \leq 80$ mL/min)

D: Subjects with T2DM and moderate renal impairment ($30 \leq CLcr \leq 50$ mL/min)

E: Subjects with T2DM and severe renal impairment (CLcr < 30 mL/min) (not receiving dialysis)

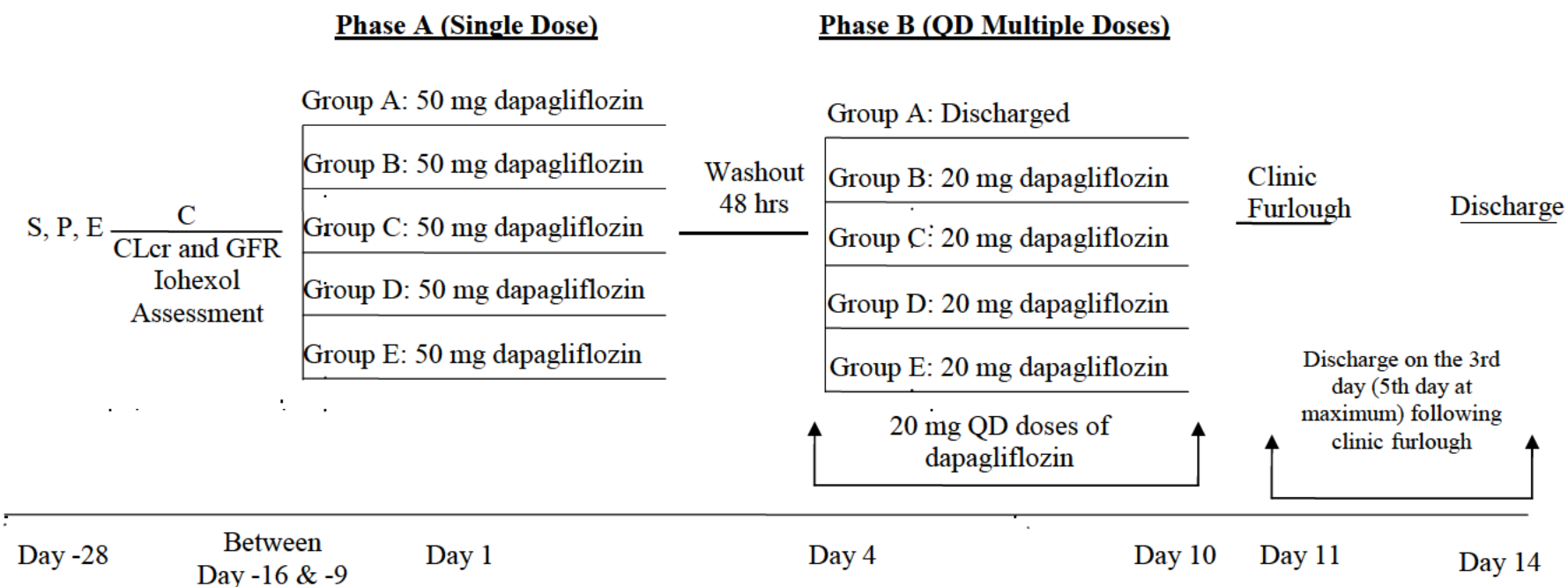
Subjects were preclassified at screening based on estimated creatinine clearance determined by Cockcroft-Gault (C-G) calculation. The Modified Diet in Renal Disease (MDRD) calculation of glomerular filtration rate (GFR) was also performed at screening for the purposes of comparison with other estimates of renal function. Subjects who met inclusion criteria reported to the study site between Day -16 and -9 for a visit lasting approximately 24 hours. A pre-dose serum creatinine sample was collected and compared to screening for an assessment of stability of the subject's renal disease. Subjects with a serum creatinine varying by more than 20% from the screening value were discontinued prior to the administration of iohexol (applicable to subjects with a serum creatinine ≥ 1 mg/dL).

All subjects were readmitted to the clinical facility on the evening of Day -2 where a sample for serum creatinine was collected. Subjects with a serum creatinine value > 20% higher than pre-iohexol administration at the Day -16 to Day -9 visit, were discontinued from the study (applicable to subjects with a serum creatinine ≥ 1 mg/dL) and followed until the serum creatinine returned to pre-iohexol levels. Baseline assessments on Day -1 included the collection of all urine over a 24 hour period for measurement of glucose, creatinine, urinary electrolytes and total protein. Urine collection began at 0 hour (immediately prior to clock time of anticipated dose on Day 1) and was collected in intervals. Blood samples were collected for measurement of serum glucose and creatinine.

On the morning of Day 1, subjects received a single oral dose of 50 mg of dapagliflozin. All urine was collected over a 24 hour period for measurement of glucose, creatinine, and total protein. Blood samples were collected for PK for dapagliflozin and BMS-801576 (a major glucuronide metabolite of dapagliflozin that it is pharmacologically inactive) and for measurement of serum glucose and creatinine. In addition, the

plasma protein binding of dapagliflozin was evaluated in all subjects at a specified time point on Day 1. Subjects in Group A only participated in Phase A of the study and were discharged from the clinical facility in the morning of Day 4 after the completion of PK sample collection and safety evaluations. On the morning of Day 4, subjects in Groups B, C, D, and E started Phase B of the study and received oral doses of 20 mg of dapagliflozin once daily for 7 days, until Day 10. All urine was collected over a 24 hour period on Days 4 and 10 for the measurement of glucose, creatinine, and total protein. Urine collection began at 0 hour and was collected in intervals. On Days 4 and 10, blood samples were collected for measurement of PK and for serum glucose and creatinine.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations were performed at selected times. Blood and urine samples were collected for PK analyses at various times throughout the study. Subjects were closely monitored for adverse events throughout the study. Subjects were furloughed from the clinical facility in the morning of Day 11 after the completion of PK sample collection and safety evaluations. Subjects returned to the clinical facility for a discharge evaluation on Day 14 (3rd day following clinic furlough, but, if necessary, could return no later than on the 5th day following clinic furlough).



S = Screening	Group A: Healthy Subjects with Normal Renal Function (CLcr > 80 mL/min)
P = Pre-classification	Group B: Diabetic Subjects with Normal Renal Function (CLcr > 80 mL/min)
E = Enrollment	Group C: Diabetic Subjects with Mild Renal Impairment (50 mL/min <CLcr ≤ 80 mL/min)
C = Classification	Group D: Diabetic Subjects with Moderate Renal Impairment (30 mL/min ≤ CLcr ≤ 50 mL/min)
D = Discharge	Group E: Diabetic Subjects with Severe Renal Impairment (CLcr < 30 mL/min) (and not receiving dialysis)

NUMBER OF SUBJECTS (Planned and Analyzed): At least 36 subjects were planned; 40 subjects were enrolled and 38 completed Phase A; 18 subjects were enrolled and 16 completed Phase B; 4 subjects discontinued.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects aged 18 to 79 years old inclusive. Eligible subjects with renal impairment could have had clinical, electrocardiogram (ECG) and laboratory findings consistent with their degree of renal dysfunction, as determined by their screening evaluations and medical history. Subjects with normal renal function were to be in good health as determined by no clinically significant deviation from normal in medical history, physical examination, ECGs, and clinical laboratory determinations. For eligible subjects on insulin, the insulin dose should have been stable for at least 1 month prior to enrollment. All women must have had a negative pregnancy test at screening, predose iohexol at the visit occurring between Day -16 and Day -9, and on Day -1 prior to start of study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: 50 mg of dapagliflozin administered as a single oral dose and 20 mg (2 x 10 mg tablet) dapagliflozin administered orally once daily for 7 days (Table 1).

Table 1: Drug Information

Unit	Formulation	Route	Product ID Number	Product Batch Number	Label Batch Number	Expiry Date
BMS-512148 Tablet	50 mg	Oral	[redacted]	[redacted]	[redacted]	[redacted]
BMS-512148 Tablet	10 mg	Oral	[redacted]	[redacted]	[redacted]	[redacted]
BMS-512148 Tablet	10 mg	Oral	[redacted]	[redacted]	[redacted]	[redacted]

Iohexol was supplied by the study sites and lot numbers are listed in Table 2.

Table 2: Iohexol Lot Numbers

Site	Product	Concentration	Amount Administered[a]	Lot Number(s)
1	Iohexol	300 mgI/mL	5 mL	[redacted]
2	Iohexol	300 mgI/mL	5 mL	[redacted]
4	Iohexol	300 mgI/mL	5 mL	[redacted]
5	Iohexol	300 mgI/mL	5 mL	[redacted]

[a] Infused intravenously at constant rate over 15 minutes

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 event (AE) reports and the results of physical examinations, electrocardiograms (ECGs), and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetics: The following PK parameters were derived on Day 1, following 50 mg dapagliflozin were Cmax, Tmax, AUC(0-T), CLT/F (dapagliflozin only), AUC(INF), T-HALF, %UR, CLR, metabolite:parent ratio (MR) [of dapagliflozin and BMS-801576]. Protein binding (% bound) for dapagliflozin was determined.

The following PK parameters were derived, following 20 mg dapagliflozin on Day 4 and Day 10 Cmax, Tmax, AUC(TAU), CLT/F (dapagliflozin only), %UR, CLR, MR [of dapagliflozin and BMS-801576].

Glomerular filtration rate (GFR) was estimated using total body clearance (CLT) of iohexol.

Pharmacodynamics: Pharmacodynamic parameters were renal glucose clearance (0-6 hr) and total cumulative glucose excretion in urine, on Day 1, Day 4 and Day 10.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: If the expected AUC(INF) (unbound or bound) of dapagliflozin for a subject with CLcr = 20 mL/min (severely impaired) was 15% higher than for a subject with CLcr = 90 mL/min (normal), then a total sample size of 36 subjects (8 in each of the normal, mildly impaired, and moderately impaired renal function diabetic groups, 4 in the severely impaired renal function diabetic group and 8 in the healthy group) would provide at least 81% power to reject the null hypothesis of no association between dapagliflozin exposure (unbound or bound) and CLcr in favor of the one-sided alternative that dapagliflozin AUC(INF) increases log-linearly with decreasing CLcr. The 15% higher AUC of the severely impaired renal function subject compared to the normal renal function subject corresponded to a slope of -0.002 for the linear regression of log(AUC) on CLcr (two points [severely impaired and normal] could decide the estimated slope of the linear regression of log(AUC) on CLcr). This calculation assumed that dapagliflozin AUC was log-normally distributed with a 15.76% coefficient of variation, as derived from the data reported in Study MB102001 following a single dose of 50 mg dapagliflozin, and that CLcr values were distributed with a standard deviation of 35.35, as reported in a similar study, AI463011.

Statistical Analysis:

Safety: All recorded adverse events were listed and tabulated by system organ class, preferred term, diabetic status and renal function group. Vital signs and clinical laboratory test results were listed and summarized. Any significant physical examination findings, ECG results, and clinical laboratory results were listed. ECG recordings were evaluated by the investigator and abnormalities, if present, were listed. The effect of dapagliflozin on the amount of protein in urine was assessed by tabulation of summary statistics for the total amount excreted in urine over 24 hours. The effect of dapagliflozin on safety markers in serum (sodium, potassium, magnesium, phosphorus and calcium concentrations) were assessed by tabulation of summary statistics for the serum concentration values**.**

Pharmacokinetics:

One of the primary objectives of this study was to assess the impact of renal function on the PK of dapagliflozin after single dose administration of 50 mg (Phase A). The secondary objective of this study was to assess the effect of renal function on the PK of dapagliflozin and BMS-801576 following a single oral dose of 50 mg dapagliflozin (Phase A) and the PK of dapagliflozin and BMS-801576 in a multiple dose phase after first dose and seventh repeated dosing of 20 mg dapagliflozin (Phase B), linear regression analyses of log(AUC) on iohexol clearance were performed. Point estimates and 95% C.I.s were calculated for the slopes. Model based point estimates and 90% confidence intervals of the ratios of dapagliflozin AUC(INF) geometric means (impaired vs. normal) were computed separately for each of the three renal

impairment groups (C, D, and E). In Phase A, the regression analysis was done to compare impaired vs. normal by pooling the data for normal healthy and subjects with T2DM and normal renal function.

Similar analyses were conducted to relate dapagliflozin Cmax to iohexol clearance, BMS-801576 AUC(INF) and Cmax to iohexol clearance. Similar analyses were conducted for the multiple dose phases (Phase B).

Using the relationship CLT/F = Dose/AUC(INF), the association between dapagliflozin AUC(INF) and iohexol clearance was re-expressed as a relationship between dapagliflozin CLT/F and iohexol clearance.

For Day 1 in Phase A and Day 4 and Day 10 in Phase B, summary statistics for each of the PK parameters were tabulated by diabetic status and renal function group using the estimated CLcr values based on C-G formula. Geometric means and coefficients of variation were provided for Cmax, AUC(0-T), AUC(INF), AUC(TAU), MR, CLT/F and CLR. Medians, minima, and maxima were provided for Tmax. Means and standard deviations were provided for T-HALF and %UR.

Pharmacodynamics To assess the effect of renal function on the renal glucose clearance after single dose administration of 50 mg dapagliflozin (Phase A) and in a multiple dose phase after the first dose and the seventh day of repeated dosing of 20 mg dapagliflozin (Phase B), the association between (fasting) renal glucose clearance and urinary CLcr during the 0 to 6 hour post-dose interval was assessed by linear regression of glucose clearance on urinary CLcr.

In addition, the total amount of glucose excreted in urine over 24 hours (a secondary objective) during Day 1 (Phase A), Day 4 and Day 10 (Phase B) was summarized by study day and group. Fasting serum glucose concentrations were also summarized by time point, study day and group.

To assess the exposure-response relationships of glucosuria and exposure measures, in both Phase A and Phase B of this study, the relationship between the amount of urinary glucose excretion over 24-hour and dapagliflozin AUC(INF) on Day 1 or AUC(TAU) on Day 4 and Day 10 were explored graphically. Similar analyses were performed to assess the relationship between 6-hour (over the 0 to 6 hour after dosing) renal glucose clearance and dapagliflozin AUC on Day 1, Day 4 and Day 10.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Subject disposition information is provided in Table 3.

Table 3: Subject Disposition

	Group A Healthy Subjects with Normal renal function	Group B Subjects with T2DM and normal renal function	Group C Subjects with T2DM and mild renal impairment	Group D Subjects with T2DM and moderate renal impairment	Group E Subjects with T2DM and severe renal impairment	Not Dosed (Not Enrolled)
No of Subjects Enrolled	8	12	8	8	4	90[c]
No. of Subjects Not Treated (if applicable; screen failures)	0	0	0	0	0	90
No. of Subjects Treated Phase A	8	12	8	8	4	0
No. of Subjects Completed Phase A	8	11[a]	8	8	3[b]	0
No. of Subjects Treated Phase B	N/A	4	4	7[d`]	3	0
No. of Subjects Completed Phase B	N/A	4	4	5	3	0
No. of Subjects Discontinued	0	1	0	2	1[a]	90
Withdrew Consent	0	1	0	1	0	10
AE	0	0	0	1	1	0
No longer met study criteria	0	0	0	0	0	65
Other[e]	0	0	0	0	0	15

[a] Subject [redacted] withdrew consent on Day 2 after receiving a single dose of 50 mg dapagliflozin

[b] Subject [redacted] discontinued due to an AE after receiving a single dose of 50 mg dapagliflozin

[c] There were 5 additional subjects who were screen failures in which CRF data was not included in the database.

[d] Subject [redacted] was enrolled and completed Phase A of the study prior to the revision to the protocol that added Phase B.

[e] The category of 'Other' included: administrative reasons by sponsor, met exclusion criteria, sufficient number of subjects enrolled for a treatment group.

Baseline demographic characteristics and physical measurements are provided in Table 4.

Table 4: Demographic Characteristics and Physical Measurements for Treated Subjects

Characteristic	Group A Healthy Subjects with Normal renal function n=8	Group B Subjects with T2DM and normal renal function n=12	Group C Subjects with T2DM and mild renal impairment n=8	Group D Subjects with T2DM and moderate renal impairment n=8	Group E Subjects with T2DM and severe renal impairment n=4	All Dosed Subjects (n=40)
Age, years						
Mean (SD)	43 (15)	55 (9)	66 (7)	72 (5)	66 (6)	59 (14)
Range	25-63	42-67	55-75	62-76	59-73	25-76
Gender, n (%)						
Male	5 (63)	8 (67)	3 (38)	4 (50)	4 (100)	24 (60)
Female	3 (38)	4 (33)	5 (63)	4 (50)	0	16 (40)
Race, n (%)						
White	6 (75)	10 (83)	8 (100)	7 (88)	4 (100)	35 (88)
Black/African American	2 (25)	1 (8)	0	1 (13)	0	4 (10)
Native Hawaiian/Other Pacific Islander	0	1 (8)	0	0	0	1 (3)
Height, cm						
Mean (SD)	167.3 (8.3)	170.9 (9.3)	159.0 (10.2)	165.6 (10.6)	169.9 (4.0)	166.7 (9.8)
Range	153.0-177.8	153.0-181.6	148.0-176.0	147.3-179.0	166.0-174.0	147.3-181.6
Weight, kg						
Mean (SD)	77.9 (9.9)	97.2 (18.4)	73.9 (12.1)	77.4 (17.7)	78.4 (4.1)	82.8 (17.0)
Range	62.2-96.0	69.1-140.4	58.8-90.6	51.8-101.2	72.3-80.9	51.8-140.4
Body Mass Index, kg/m^2						
Mean (SD)	27.8 (2.7)	33.2 (5.1)	29.3 (4.0)	27.9 (4.4)	27.2 (1.1)	29.7 (4.6)
Range	22.7-31.2	24.4-44.4	21.1-34.3	20.2-32.7	26.2-28.7	20.2-44.4

Safety Results:

Administration of single doses of 50 mg dapagliflozin followed by multiple doses of 20 mg dapagliflozin was safe and well-tolerated in diabetic and healthy subjects with normal renal function, and in subjects with T2DM and mild, moderate or severe renal impairment. There were no deaths, SAEs or severe AEs. Overall, 14 (35%) subjects had 26 mild to moderate AEs during this study. There was no apparent trend in frequency of AEs in relation to renal function. Two (2) subjects discontinued from study therapy: 1 subject due to an AE of dizziness after treatment with multiple doses of 20 mg dapagliflozin and 1 subject with worsening gastroesophageal reflux disease (GERD) that began on Day -1 following the iohexol treatment period. The most common AE was headache in which 4 AEs were reported in 3 (7.5%) subjects treated. One subject with T2DM and severe renal impairment had elevated predose serum creatinine values (2.8-3.3-mg/dL; normal range 0.6-1.40 mg/dL) which was further elevated at discharge (3.6 mg/dL) and was reported as an AE that was possibly related to study drug. Overall, 36 subjects had 71 laboratory MAs. The most frequent MA was high urine glucose in 25 (64.1%) of all subjects. Since the mechanism of action for dapagliflozin is to inhibit urinary glucose reuptake, this finding is consistent with the expected pharmacologic activity of dapagliflozin. There were no marked differences in the serum electrolytes, including sodium, before and after treatment with dapagliflozin. Total urinary protein values were highly variable across different study days and did not appear to have meaningful changes associated with administration of dapagliflozin. There was no significant change in vital signs or ECG parameters.

Pharmacokinetic Results:

Dapagliflozin PK Results:

Summary statistics for dapagliflozin PK parameters for Day 1 following 50 mg dapagliflozin are shown in Table 5.

Table 5: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters (Phase A, Single Dose of 50 mg Dapagliflozin)

Diabetic Status, Renal Function Group	Dapagliflozin Pharmacokinetic Parameters							
	Cmax (ng/mL) Geom. Mean (CV%)	**Tmax (h) Median (Min, Max)**	**AUC(INF) (ng·h/mL) Geom. Mean (CV%)**	**AUC(0-T) (ng·h/mL) Geom. Mean (CV%)**	**T-HALF (h) Mean (SD)**	**CLT/F (mL/min) Geom. Mean (CV%)**	**CLR (mL/min) Geom. Mean (CV%)**	**%UR (%) Mean (SD)**
Healthy Normal (n = 8)	710 (31)	1.17 (0.50, 2.00)	2880 (27)	2821 (27)	12.7 (6.95)	289 (26)	3.52 (34)	1.2 (0.45)
Diabetic Normal (n = 12)	647 (37)	1.25 (0.50, 2.00)	2504 (30)	2439 (30)	11.9 (5.72)	333 (26)	3.43 (47)	1.0 (0.44)
Diabetic Mild (n=8)	902 (35)	1.25 (0.50, 2.00)	4018 (26)	3832 (26)	18.4 (8.15)	207 (25)	2.85 (55)	1.4 (0.96)
Diabetic Moderate (n=8)	897 (41)	1.00 (0.50, 2.98)	5182 (38)	4847 (35)	17.9 (3.39)	161 (26)	2.06 (81)	1.6 (1.30)
Diabetic Severe (n = 4)	772 (11)	1.17 (0.75, 1.50)	4884 (10)[a]	4385 (12)	15.0 (4.15)[a]	171 (10)[a]	0.84 (46)	0.5 (0.23)

[a] n=3; Subject [redacted] was excluded from summary statistics due to an incomplete PK profile

Regression analyses of dapagliflozin and BMS-801576 PK parameters vs. iohexol clearance were used to determine the effect of renal function on these PK parameters.

Compared to healthy subjects and subjects with T2DM and normal renal function (mean iohexol clearance is 100 mL/min), the geometric means of dapagliflozin Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM with mild renal impairment (mean iohexol clearance is 65 mL/min) were 14%, 28% and 25% higher, respectively.

Compared to healthy subjects and subjects with T2DM and normal renal function (mean iohexol clearance is 100 mL/min), the geometric means of dapagliflozin Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM with moderate renal impairment (mean iohexol clearance is 40 mL/min) were 26%, 52% and 46% higher, respectively.

Compared to healthy subjects and subjects with T2DM and normal renal function (mean iohexol clearance is 100 mL/min), the geometric means of dapagliflozin Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM with severe renal impairment (mean iohexol clearance is 25 mL/min) were 36%, 75% and 65% higher, respectively.

Summary statistics of dapagliflozin PK parameters for Day 4 and Day 10 following 20 mg QD dapagliflozin are shown in Table 6.

Table 6: **Summary Statistics for Dapagliflozin Pharmacokinetic Parameters (Phase B, 20 mg Dapagliflozin Once-Daily)**

Diabetic Status, Renal Function Group	Study Day	Dapagliflozin Pharmacokinetic Parameters				
		Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)
Diabetic Normal	Day 4 (n=4)	249 (21)	1.00 (0.50, 1.50)	864 (11)	5.22 (38)	1.4 (0.51)
	Day 10 (n=4)	310 (22)	1.00 (0.50, 1.00)	853 (8)	6.51 (34)	1.7 (0.52)
Diabetic Mild	Day 4 (n=4)	410 (23)	1.00 (1.00, 6.00)	1428 (38)	2.37 (54)	1.1 (0.38)
	Day 10 (n=4)	358 (25)	1.00 (1.00, 1.50)	1443 (21)	2.52 (51)	1.2 (0.54)
Diabetic Moderate	Day 4 (n=6)	466 (21)	1.00 (0.50, 1.00)	1807 (31)	2.54 (71)	2.0 (2.15)
	Day 10 (n=5[a])	512 (23)	1.00 (0.50, 1.50)	2467 (37)	2.06 (77)	1.8 (1.11)
Diabetic Severe	Day 4 (n=3)	330 (6)	1.00 (0.50, 2.00)	1920 (26)	1.42 (30)	0.9 (0.43)
	Day 10 (n=3)	338 (16)	1.00 (0.50, 1.00)	2207 (27)	1.13 (19)	0.8 (0.31)

[a] n=5 All PK parameters for Subject [redacted] were missing because the subject discontinued from the study on Day 8.

Compared to subjects with T2DM and normal renal function, the geometric means of dapagliflozin Cmax and AUC(TAU) on Day 10 for subjects with T2DM with mild renal impairment were 4% and 32% higher, respectively.

Geometric means of dapagliflozin Cmax and AUC(TAU) on Day 10 were 6% and 60% higher, respectively, for moderately impaired subjects with T2DM compared to subjects with T2DM and normal renal function.

For subjects with T2DM and severe renal impairment, compared to subjects with T2DM and normal renal function, geometric means of Cmax and AUC(TAU) were 9% and 87% higher, respectively.

BMS-801576 Pharmacokinetic Results:

BMS-801576 PK parameters on Day 1 following 50 mg dapagliflozin are summarized by group in Table 7.

Table 7: Summary Statistics for BMS-801576 Pharmacokinetic Parameters (Phase A, Single Dose of 50 mg Dapagliflozin)

Diabetic Status, Renal Function Group	BMS-801576 Pharmacokinetic Parameters							
	Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	T-HALF (h) Mean (SD)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)	MR (ng·h/mL) Geom. Mean (CV%)
Healthy, Normal (n = 8)	960 (33)	2.00 (1.00, 3.00)	4634 (30)	4565 (30)	12.1 (5.99)	151 (54)	63.1 (24.72)	1.12 (45)
Diabetic Normal (n = 12)	1391 (29)	2.00 (1.00, 3.00)	6616 (32)	6500 (33)	11.2 (3.71)	76 (67)	51.5 (30.50)	1.85 (36)
Diabetic Mild (n=8)	1641 (26)	2.00 (1.00, 3.00)	9830 (24)	9413 (23)	17.5 (8.17)	75 (33)	64.3 (24.75)	1.71 (27)
Diabetic Moderate (n=8)	2037 (31)	1.75 (1.00, 3.00)	16831 (36)	15943 (35)	16.0 (2.68)	43 (62)	62.6 (25.22)	2.27 (40)
Diabetic Severe (n = 4)	1986 (22)	2.00 (1.83, 4.00)	22409 (31)[a]	19045 (36)	12.9 (2.43)[a]	11 (23)	18.5 (7.78)	2.64 (49)

[a] n= Subject [redacted] was excluded from summary statistics due to an incomplete PK profile.

Compared to healthy subjects and subjects with T2DM and normal renal function, the geometric means of BMS-801576 Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM and mild renal impairment were 20%, 50% and 47% higher, respectively.

Compared to healthy subjects and subjects with T2DM and normal renal function, the geometric means of BMS-801576 Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM and moderate renal impairment were 36%, 101% and 93% higher, respectively.

Compared to healthy subjects and subjects with T2DM and normal renal function, geometric means of BMS-801576 Cmax, AUC(INF) and AUC(0-T) for subjects with T2DM and severe renal impairment, were 51%, 154% and 140% higher, respectively.

Summary statistics for BMS-801576 PK parameters for Day 4 and Day 10 following 20 mg dapagliflozin are shown in Table 8.

Table 8: Summary Statistics for BMS-801576 Pharmacokinetic Parameters (Phase B, 20 mg Dapagliflozin Once-Daily)

Diabetic Status, Renal Function Group	Study Day	BMS-801576 Pharmacokinetic Parameters					
		Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)	MR Geom. Mean (CV%)
Diabetic Normal	Day 4 (n=4)	644 (21)	1.75 (1.00, 2.00)	2818 (40)	139 (48)	79.9 (15.41)	2.28 (31)
	Day 10 (n=4)	637 (26)	1.50 (1.00, 1.50)	2769 (36)	93 (66)	60.5 (33.26)	2.27 (34)
Diabetic Mild	Day 4 (n=4)	791 (31)	1.75 (1.50, 6.00)	4164 (22)	79 (31)	68.7 (20.94)	2.04 (28)
	Day 10 (n=4)	843 (18)	1.50 (1.50, 2.00)	4278 (25)	72 (49)	68.0 (27.60)	2.07 (9)
Diabetic Moderate	Day 4 (n=6)	911 (38)	1.50 (1.00, 2.00)	6502 (39)	37 (52)	50.1 (15.68)	2.5 (37)
	Day 10 (n=5[a])	1088 (24)	1.50 (1.00, 2.00)	8442 (40)	37 (48)	66.0 (20.57)	2.39 (41)
Diabetic Severe	Day 4 (n=3)	770 (21)	2.00 (1.50, 4.00)	7947 (46)	15 (39)	27.7 (15.97)	2.89 (22)
	Day 10 (n=3)	965 (18)	2.00 (1.50, 4.00)	10549 (31)	10 (28)	23.2 (9.79)	3.34 (41)

[a]: n=5 All PK parameters for Subject [redacted] were missing because the subject discontinued from the study on Day 8.

Compared to subjects with T2DM and normal renal function, the geometric means of BMS-801576 Cmax and AUC(TAU) at Day 10 for subjects with T2DM and mild renal impairment were 20% and 54% higher, respectively.

Compared to subjects with T2DM and normal renal function, the geometric means of BMS-801576 Cmax and AUC(TAU) at Day 10 for subjects with T2DM and moderately impaired were 37% and 110% higher, respectively.

Compared to subjects with T2DM and normal renal function, the geometric means of BMS-801576 Cmax and AUC(TAU) at Day 10 for subjects with T2DM and severe impaired were 52% and 169% higher, respectively.

Protein Binding

The mean plasma protein binding of dapagliflozin for the subjects in this study was between 92.3 to 94.6%. The results indicate that the plasma protein binding of dapagliflozin was similar between subjects with normal and impaired renal function and between healthy subjects and subjects with T2DM**.**

Iohexol and Other Methods of Measuring GFR

There were generally good correlations between iohexol total body clearance (considered an accurate measure of GFR) and C-G CLcr (correlation coefficient, r=0.86) and between iohexol total body clearance and 24-hr urinary CLcr (correlation coefficient, r=0.76), indicating that C-G CLcr and 24-hr urinary CLcr are appropriate methods for estimating renal function (GFR) and that the subjects in this study were generally appropriately categorized with respect to their renal function by C-G CLr. . Similarly, there was a good relationship between MDRD and iohexol total body clearance. Overall, these analyses indicate that subjects enrolled in this study were categorized appropriately by all methods of estimating GFR.

Pharmacodynamic Results:

Table 9 summarizes the renal glucose clearance results.

Table 9: Effects of Various Degrees of Renal Impairment on 6-Hr Renal Glucose Clearance

Regression Function	6-Hr Urinary CLcr (mL/min)	Predicted Mean[a]	Difference of Predicted Means		
			Comparison	Difference	95% CI
Day 1					
RGC = 0.0666+ 0.3375· Urinary CLcr	100[b]	33.82			
	65	22.01	65 vs 100	-11.81	(-13.48, -10.15)
	40	13.57	40 vs 100	-20.25	(-23.11, -17.40)
	20	6.82	20 vs 100	-27.00	(-30.81, -23.20)
Day 4					
RGC = 2.6874+ 0.2390· Urinary CLcr	100[c]	26.59			
	65	18.22	65 vs 100	-8.37	(-11.98, -4.75)
	40	12.25	40 vs 100	-14.34	(-20.54, -8.15)
	20	7.47	20 vs 100	-19.12	(-27.38, -10.86)
Day 10					
RGC = 0.1345+ 0.4037· Urinary CLcr	100[c]	40.51			
	65	26.38	65 vs. 100	-14.13	(-17.83, -10.43)
	40	16.28	40 vs 100	-24.22	(-30.57, -17.87)
	20	8.21	20 vs 100	-32.30	(-40.77, -23.83)

[a] Predicted mean is based on the linear regressions of 6-hr renal glucose clearance on 6-hr urinary CLcr for Day 1, Day 4 and Day 10.

[b] Healthy subjects and subjects with T2DM and normal function

[c] Subjects with T2DM and normal renal function

Compared to healthy subjects and subjects with T2DM and normal renal function, the mean 6-hr renal glucose clearance on Day 1 decreased 11.81 mL/min, 20.25 mL/min and 27.00 mL/min for subjects with mild, moderate and severe renal impairment, respectively. After 7 day administration of dapagliflozin, compared to subjects with T2DM and normal renal function, the mean 6-hr renal glucose clearance of Day 10 decreased 14.13 mL/min, 24.22 mL/min and 32.30 mL/min for mild, moderate and severely impaired group, respectively.

CONCLUSIONS:

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