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

SYNOPSIS

Final Clinical Study Report for Study MB102065

TITLE OF STUDY: Bioavailability Study of Two Prototype Fixed Dose Combination (FDC) Formulations of 10 mg Dapagliflozin and 1000 mg Metformin Extended Release (XR) Tablet Relative to Dapagliflozin 10 mg Tablet and Glucophage® XR 2 x 500 mg Tablets Coadministered to Healthy Subjects in a Fasted State

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 16-Nov-2009 **CLINICAL PHASE:** 1

Study Completion Date: 25-Jan-2010

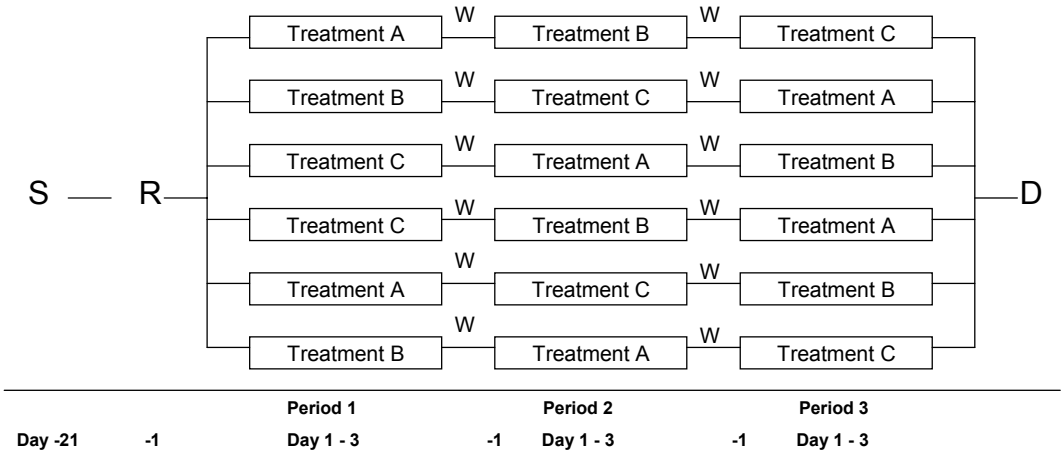
OBJECTIVES:

Primary Objective: The primary objective of this study was to assess the relative bioavailability (BA) of dapagliflozin and metformin from the 2 FDC formulations, comprised of 10 mg dapagliflozin and 1000 mg metformin XR, relative to coadministration of a dapagliflozin 10 mg tablet and 2 x 500 mg Glucophage XR tablets, in healthy subjects in a fasted state.

Secondary Objective: The secondary objective of this study was to assess the safety and tolerability of dapagliflozin 10 mg and metformin 1000 mg coadministered to healthy subjects in a fasted state.

METHODOLOGY: This was an open-label, randomized, 3-period, 3-treatment, crossover study. Fifteen (15) subjects were randomized to receive Treatment A, B, or C during Period 1. The alternate treatments were administered during Periods 2 and 3. Blood samples were collected for pharmacokinetic (PK) analysis for dapagliflozin and metformin up to 48 hours postdose. The washout between the 2 consecutive doses was at least 7 days. See Figure 1 for treatments and treatment sequences.

Figure 1: Treatment Schematic



Treatment A: FDC tablet of dapagliflozin 10 mg and metformin XR 1000 mg (FDC1), fasted

Treatment B: FDC tablet of dapagliflozin 10 mg and reduced mass (RM) metformin XR 1000 mg (FDC2), fasted

Treatment C: Coadministration of a dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets, fasted

S = Screening; R = Randomization; D = Study Discharge; W = Washout at least 7 Days between doses (≥ 4 days between periods)

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 44 subjects were enrolled (signed the informed consent) in this study. Fifteen (15) subjects were randomized and administered study drug, of which 13 subjects completed the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy subjects with a body mass index (BMI) of 18 to 32 kg/m^2, aged 18 to 45 years as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations were eligible to participate in the study. Women of childbearing potential (WOCBP) could not be nursing or pregnant and had to be willing to use an acceptable method of contraception for at least 1 month before study drug administration. All women were to have a negative pregnancy test within approximately 24 hours prior to study drug administration in Period 1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Each subject received (orally) a single dose of one of the 2 prototype formulations of FDC tablet (FDC1 or FDC2) during one of the three periods of the study, in a fasted state. Subjects received the investigational products according to a randomization schedule. Each subject underwent a washout of at least 7 days following the previous dose before receiving the next scheduled treatment.

Table 1 presents the test product information.

Table 1: Test Product Information

Formulation	Unit	Route	Product Identification No.	Batch Product No.	Batch Label No.
FDC1 tablet: Dapagliflozin/Metformin XR	10 mg/ 1000 mg	Oral	[redacted]	[redacted]	[redacted]
FDC2 tablet: Dapagliflozin/RM Metformin XR	10 mg/ 1000 mg	Oral	[redacted]	[redacted]	[redacted]

RM = reduced mass

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Each subject received a single dose of dapagliflozin 10 mg tablet coadministered with Glucophage XR 2 x 500 mg tablets, during one of the three periods of the study. Subjects received the investigational products according to a randomization schedule. Each subject underwent a washout of at least 7 days following the previous dose before receiving the next scheduled treatment. Table 2 presents the reference therapy information.

Table 2: Reference Therapy Information

Formulation	Unit	Route	Product Identification No.	Batch Product No.	Batch Label No.
Dapagliflozin tablet	10 mg	Oral	[redacted]	[redacted]	[redacted]
Glucophage XR tablet	500 mg	Oral	N/A	[redacted]	[redacted]

XR = extended release

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance.

Pharmacokinetics: Single-dose PK parameters of dapagliflozin and metformin were derived from their respective plasma concentration versus time data. The PK parameters assessed included:

Cmax	maximum observed plasma concentration
Tmax	time of maximum observed plasma concentration
AUC(0-T)	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to infinite time
T-HALF	plasma terminal half-life

STATISTICAL CONSIDERATIONS:

Sample Size Determination: Although the sample size was not based on statistical power considerations, 12 completed subjects provided at least 90% confidence that the ratios of geometric means of dapagliflozin Cmax and AUC(INF) between test (FDC1 and FDC2) and reference (dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets) formulations would be within 15% and 7% of the true population

values, respectively. Similarly, 12 completed subjects provided at least 90% confidence that the ratios of geometric means of metformin Cmax and AUC(INF) between test (FDC1 and FDC2) and reference (dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets) formulations would be within 10% and 9% of the true population values, respectively. In order to avoid the impact of subject dropouts, 15 subjects were dosed on Day 1 of Period 1.

Statistical Analysis:

Safety: All recorded AEs were listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results were listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results were listed. Electrocardiogram readings were evaluated by the Investigator and abnormalities, if present, were listed.

Pharmacokinetics: To assess the BA of dapagliflozin from the 2 prototype FDC formulations of 10 mg dapagliflozin and 1000 mg metformin XR tablet (Treatment A and Treatment B) relative to 10 mg dapagliflozin tablet and 2 x 500 mg Glucophage XR tablets co-administered (Treatment C) to healthy subjects in a fasted state, the general linear mixed model analysis was performed on log(Cmax), log[AUC(INF)], and log[AUC(0-T)] of dapagliflozin, respectively. Point estimates and 90% confidence intervals (CIs) were calculated based on the model for the Treatment A to Treatment C ratios and Treatment B to Treatment C ratios of geometric means for Cmax, AUC(INF) and AUC(0-T) of dapagliflozin. Similar analysis was performed to assess the BA of metformin from the 2 prototype FDC formulations (Treatment A and Treatment B) relative to the reference formulation (Treatment C). No adjustments were made for multiplicity and no comparison was planned between Treatment A and Treatment B.

SUMMARY OF RESULTS:

Disposition:

Table 3 summarizes the subject disposition.

Table 3: Subject Disposition

	Dosed	Not Dosed	All Subjects
No. of Subjects Enrolled	15	29	44
No. of Subjects Discontinued			
Adverse Event	1	0	1
Back-up/Not used	0	1	1
Repeat Screening ECG in Error	0	1	1
Excluded due to PI discretion	1	0	1
No longer met study criteria	0	18	18
Withdrew consent	0	9	9
No. of Subjects Completing Study	13	0	13

PI = Principal Investigator

Populations Analyzed:

Safety Data Set: Fifteen (15) subjects who were enrolled and received at least 1 dose of study drug were included in the safety data set.

PK Data Set: Actual blood sample collection times were used for PK data analysis and nominal blood sample collection times were used for generation of mean plasma concentration-time tables and plots. Of the 15 subjects randomized and who received at least 1 dose, 13 subjects completed the study. All available

data, including data from completed treatments from subjects who did not complete the study, were included in the PK data set, summary statistics, and statistical analyses of dapagliflozin and metformin.

Baseline Physical Measurements/Demographic Characteristics:

Table 4 summarizes the baseline physical measurements and demographic characteristics.

Table 4: Baseline Physical Measurements and Demographic Characteristics

Characteristic	All Subjects (N = 15)
Age (yrs)	
Mean (SD)	31 (8)
Range	21 – 43
Gender, n (%)	
Male	5 (33)
Female	10 (67)
Race, n (%)	
White	10 (67)
Black/African American	5 (33)
Weight (kg)	
Mean (SD)	71 (13.8)
Range	50.9 – 104.9
Height (cm)	
Mean (SD)	166.7 (9.7)
Range	145.0 – 181.0
Body Mass Index (kg/m^2)	
Mean (SD)	25.5 (4.1)
Range	19.5 – 32.0

Abbreviations: kg = kilogram, m = meter, n = number, SD = standard deviation, yrs = years

Safety Results: There were no deaths or serious adverse events (SAEs). Two (2) subjects were discontinued from the study following study drug administration: 1 due to an adverse event (elevated creatine kinase [CK]), after receiving Treatment C and 1 at the discretion of the Investigator for trace amounts of RBCs in the urine in a female subject that were not likely due to menses, after receiving Treatment A. Safety findings are summarized in Table 5.

Table 5: Safety Results

Adverse Events	Number (%) of Subjects			
	TRT A (N=14)	TRT B (N=14)	TRT C (N=14)	All Subjects (N=15)
Subjects with at least 1 AE	2 (14.3)	3 (21.4)	6 (42.9)	9 (60.0)
Death	0	0	0	0
SAE	0	0	0	0
Discontinuation due to AEs	0	0	1 (7.1)	1 (7.1)

Abbreviations: AE = adverse event, SAE = serious adverse event, TRT = Treatment

Treatments:

A: FDC tablet of dapagliflozin 10 mg and metformin XR 1000 mg (FDC1), fasted

B: FDC tablet of dapagliflozin 10 mg and RM metformin XR 1000 mg (FDC2), fasted

C: Coadministration of a dapagliflozin 10 mg tablet and Glucophage XR 2 x 500 mg tablets, fasted

Nine (9) subjects reported 13 AEs among which 10 AEs from 7 subjects were mild in intensity and 3 AEs from 2 subjects were moderate in intensity. Of the 13 AEs reported, 5 were considered by the Investigator to be related to study drug. The most frequently reported AEs were: headache (3 subjects, 20%), nausea (2 subjects, 13.3%), and contusion (2 subjects, 13.3%). All AEs resolved by either the time of study discharge or subject follow-up.

Seventeen (17) clinical laboratory results for 10 subjects met BMS-defined marked abnormality (MA) criteria; 1 of the values meeting MA criteria (elevated CK) was reported as an AE by the Investigator and resulted in discontinuation from the study. One (1) subject had an ECG abnormality (sinus bradycardia) prestudy. This ECG abnormality was not considered an AE and did not result in the discontinuation of the subject from the study.

Pharmacokinetic Results: Individual dapagliflozin PK parameters are summarized by treatment in Table 6.

Table 6: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters

Treatment	Dapagliflozin Pharmacokinetic Parameters				
	Cmax (ng/mL) Geom. Mean (CV%)	**AUC(INF) (ng·h/mL) Geom. Mean (CV%)**	**AUC(0-T) (ng·h/mL) Geom. Mean (CV%)**	**T-HALF (h) Mean (SD)**	**Tmax (h) Median (Min, Max)**
A (N = 14)	142 (24)	543 (42)	518 (41)	12.4 (4.94)	0.50 (0.50, 2.00)
B (N = 14)	142 (25)	580 (38)	552 (38)	11.4 (5.20)	1.00 (0.50, 4.00)
C (N = 14)	140 (29)	576 (42)	550 (41)	11.6 (3.29)	1.00 (0.50, 1.03)

Abbreviations: Geom. = Geometric

Treatments: A = FDC1 (dapagliflozin 10 mg/metformin XR 1000 mg)
B = FDC2 (dapagliflozin 10 mg/RM metformin XR 1000 mg)
C = Coadministration of 10 mg dapagliflozin and 2 x 500 mg Glucophage XR tablets

Details of the statistical analyses of Cmax, AUC(INF), and AUC(0-T) of dapagliflozin are summarized in Table 7.

Table 7: Results of Statistical Analyses of Dapagliflozin Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Parameter	Adjusted Geometric Means			Ratio of Adjusted Geometric Means Point Estimate (90% CI)	
	TRT A	TRT B	TRT C	(TRT A/TRT C)	(TRT B/TRT C)
Cmax (ng/mL)	134	143	139	0.962 (0.852, 1.086)	1.023 (0.919, 1.138)
AUC(INF) (ng h/mL)	530	574	567	0.933 (0.877, 0.994)	1.011 (0.950, 1.076)
AUC(0-T) (ng·h/mL)	505	547	543	0.931 (0.876, 0.989)	1.007 (0.949, 1.069)

Treatments: A = FDC1 (dapagliflozin 10 mg/metformin XR 1000 mg)
B = FDC2 (dapagliflozin 10 mg/RM metformin XR 1000 mg)
C = Coadministration of 10 mg dapagliflozin and 2 x 500 mg Glucophage XR tablets

Note: The adjusted geometric means presented here are geometric means obtained from general linear mixed models after accounting for all other effects in the model. They can be different from the geometric means reported in Table 6.

The geometric means for Cmax, AUC(INF) and AUC(0-T) of dapagliflozin were 4%, 7% and 7% lower, respectively, after administration of FDC1 dapagliflozin 10 mg/metformin XR 1000 mg relative to those following co-administration of dapagliflozin 10 mg and Glucophage XR (2 x 500 mg tablets). Although a bioequivalence (BE) interval was not predefined, the 90% CIs for the ratios of population geometric means were within the usual (0.80, 1.25) BE interval for Cmax, AUC(INF), and AUC(0-T) of dapagliflozin.

The geometric means for Cmax, AUC(INF) and AUC(0-T) of dapagliflozin were 2%, 1% and 1% higher after administration of FDC2 dapagliflozin 10 mg/reduced mass metformin XR 1000 mg relative to those following co-administration of dapagliflozin 10 mg and Glucophage XR (2 x 500 mg tablets). Although a BE interval was not predefined, the 90% CIs for the ratios of population geometric means were within the usual (0.80, 1.25) BE interval for Cmax, AUC(INF), and AUC(0-T) of dapagliflozin.

Individual metformin PK parameters are summarized by treatments in Table 8.

Table 8: Summary Statistics for Metformin Pharmacokinetic Parameters

Treatment	Metformin Pharmacokinetic Parameters				
	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng h/mL) Geom. Mean (CV%)	AUC(0-T) (ng h/mL) Geom. Mean (CV%)	T-HALF (h) Mean (SD)	Tmax (h) Median (Min, Max)
A (N = 14)	980 (38)	7242 (31)[a]	6891 (31)	12.1 (4.54)[a]	3.93 (2.00, 4.08)
B (N = 14)	962 (47)	7320 (33)[a]	7255 (35)	11.3 (10.35)[a]	4.00 (1.00, 6.07)
C (N = 14)	805 (29)	6493 (21)	6091 (23)	14.5 (5.67)	3.01 (2.00, 4.08)

[a] N = 13 (Subject [redacted] and Subject [redacted] were excluded because the terminal phase of their metformin concentration-time profiles were not adequately characterized for these PK parameters)

Treatments: A = FDC1 (dapagliflozin 10 mg/metformin XR 1000 mg)
B = FDC2 (dapagliflozin 10 mg/RM metformin XR 1000 mg)
C = Coadministration of 10 mg dapagliflozin and 2 x 500 mg Glucophage XR tablets

Details of the statistical analyses of Cmax, AUC(INF), and AUC(0-T) of metformin are summarized in Table 9.

Table 9: Results of Statistical Analyses of Metformin Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Parameter	Adjusted Geometric Means			Ratio of Adjusted Geometric Means Point Estimate (90% CI)	
	TRT A	TRT B	TRT C	(TRT A/TRT C)	(TRT B/TRT C)
Cmax (ng/mL)	982	942	806	1.218 (0.973, 1.525)	1.169 (0.986, 1.386)
AUC(INF) (ng·h/mL)	7440	7338	6476	1.149 (0.994, 1.328)	1.133 (1.002, 1.281)
AUC(0-T) (ng·h/mL)	7040	7109	6066	1.161 (1.001, 1.346)	1.172 (1.020, 1.346)

Treatments: A = FDC1 (dapagliflozin 10 mg/metformin XR 1000 mg)
B = FDC2 (dapagliflozin 10 mg/RM metformin XR 1000 mg)
C = Coadministration of 10 mg dapagliflozin and 2 x 500 mg Glucophage XR tablets

Note: The adjusted geometric means here are geometric means obtained from general linear mixed models after accounting for all other effects in the model. They can be different from the geometric means reported in Table 8.

The geometric means for Cmax, AUC(INF), and AUC(0-T) of metformin were 22%, 15%, and 16% higher, respectively, after administration of FDC1 dapagliflozin 10 mg/metformin XR 1000 mg relative to those following co-administration of dapagliflozin 10 mg and Glucophage XR (2 x 500 mg tablets). The 90% CIs for the ratios of population geometric means extended above the usual (0.80, 1.25) BE interval for

Cmax, AUC(INF), and AUC(0-T) of metformin, with higher values observed for FDC1 dapagliflozin 10 mg/metformin XR 1000 mg compared to FDC2.

The geometric means for Cmax, AUC(INF), and AUC(0-T) of metformin were 17%, 13%, and 17% higher, respectively, after administration of FDC2 dapagliflozin 10 mg/reduced mass metformin XR 1000 mg relative to the observed values following co-administration of dapagliflozin 10 mg and Glucophage XR (2 x 500 mg tablets). The 90% CIs for the ratios of population geometric means extended above the usual (0.80, 1.25) BE interval for Cmax, AUC(INF), and AUC(0-T) of metformin, with higher values observed for FDC2 dapagliflozin 10 mg/reduced mass metformin XR 1000 mg.

CONCLUSIONS:

[redacted]

DATE OF REPORT: 31-Oct-2010