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: Dapagliflozin (BMS-512148)		

SYNOPSIS

Final Clinical Study Report for MB102026

TITLE OF STUDY: Pharmacokinetic Drug Interaction Study with Dapagliflozin and Metformin in Healthy Subjects

INVESTIGATOR/STUDY CENTER: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 16-Nov-2007 **CLINICAL PHASE:** 1
Study Completion Date: 22-Feb-2008

OBJECTIVES:

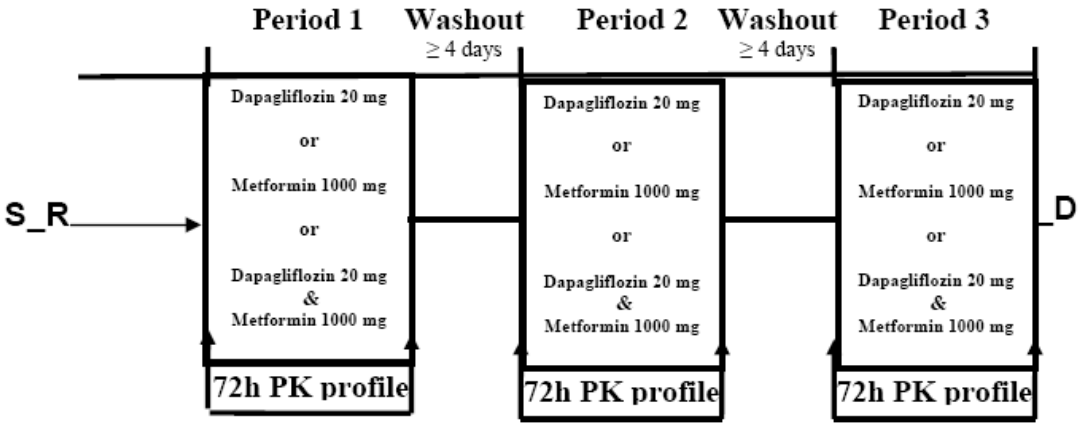
Primary Objectives:

- To determine the effect of metformin on the PK of dapagliflozin, when coadministered in healthy subjects
- To determine the effect of dapagliflozin on the PK of metformin, when coadministered in healthy subjects.

Secondary Objective:

- To assess the safety and tolerability of dapagliflozin when administered alone or with metformin.

METHODOLOGY: This was an open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects. There was at least a 4-day washout between the consecutive periods. All study treatments were administered with 240 mL of 20% glucose solution following a 10-hour fast. Pharmacokinetic (PK) samples were obtained for 72 hours after dosing. The study duration was approximately ≥33 days. Subjects were screened 21 days prior to dosing on Day 1 of Period 1. On Day 1 of Period 1, subjects were randomized to receive Treatment A (single oral dose of 20 mg dapagliflozin), Treatment B (single oral dose of 1000 mg metformin, immediate-release formulation), or Treatment C (coadministration of single oral doses of 20 mg dapagliflozin and 1000 mg metformin) in 1 of 6 treatment sequences.



D = Discharge; S = Screening; R = Randomization

NUMBER OF SUBJECTS (Planned and Analyzed):

There were 18 subjects planned. A total of 74 subjects were enrolled in the study; 18 were randomized and treated with study drugs; 56 discontinued prior to study drug administration. Of the 18 treated subjects, 17 completed the study and 1 subject discontinued due to an adverse event (AE).

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

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:
Treatment C: an oral dose of 20 mg dapagliflozin and an oral dose of 1000 mg metformin (immediate-release formulation).

Table 1: Investigational Product Information

Unit	Formulation	Route	Product ID Number	Product Batch Number	Label Batch Number	Expiry Date
BMS-512148 Tablet	20 mg	Oral	[redacted]	[redacted]	[redacted]	[redacted]

Metformin (1000 mg; [redacted]) was supplied by the Investigator.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Treatment A: a single oral dose of 20 mg dapagliflozin alone. Treatment B: a single oral dose of 1000 mg metformin alone. Batch number information is provided in Table 1, above.

CRITERIA FOR EVALUATION:

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

Pharmacokinetics: Single-dose pharmacokinetic parameters [Cmax, Tmax, AUC(0-T), AUC(INF), and $T_{1/2}$] were derived from plasma concentration versus time profiles for dapagliflozin and metformin.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: Lack of an effect of metformin on the PK of dapagliflozin would be concluded if the 90% confidence intervals for the Treatment C to Treatment A ratios of population geometric means were contained within 80% and 125% for both Cmax (maximum observed concentration) and AUC(INF) (area under the concentration-time curve from time zero extrapolated to infinite time) of dapagliflozin. If coadministration of metformin had no effect on the PK of dapagliflozin, then data from 18 subjects would provide at least 89% and at least 99% power with respect to Cmax and AUC(INF) of dapagliflozin, respectively, to conclude that metformin had no effect on the PK of dapagliflozin.

Lack of an effect of dapagliflozin on the PK of metformin would be concluded if the 90% confidence intervals for the Treatment C to Treatment B ratios of population geometric means were contained within 80% and 125% for both Cmax and AUC(INF) of metformin. If coadministration of dapagliflozin had no effect on the PK of metformin, then data from 18 subjects would provide at least 99% and at least 99% power with respect to Cmax and AUC(INF) of metformin, respectively, to conclude that dapagliflozin had no effect on the PK of metformin.

A total of 18 subjects were enrolled and randomized in this study with no replacement. With no more than 4 dropouts, at least 76% power for dapagliflozin Cmax and at least 99% power for dapagliflozin AUC(INF) could be achieved to conclude that metformin had no effect on the PK of dapagliflozin and at least 98% and 99% power for metformin Cmax and metformin AUC(INF), respectively, to conclude that dapagliflozin had no effect on the PK of metformin.

Statistical Analysis:

Pharmacokinetics: To assess the effect of coadministration of metformin and dapagliflozin on the PK of dapagliflozin and metformin, analyses of variance were performed on both Cmax and AUC(INF) of each analyte. In the analysis of variance, sequence, period and treatment were considered as fixed effects and subject within sequence as a random effect. A priori, the variables Cmax and AUC(INF) were log-transformed. Point estimates and 90% confidence intervals for treatment differences on the log scale were exponentiated to obtain point estimates and 90% confidence intervals for the ratios of geometric means on the original scale of measurement. Lack of an effect of metformin on the PK of dapagliflozin would be concluded if the 90% confidence interval for the Treatment C to Treatment A ratios of population geometric means were contained within 80% and 125% for both Cmax and AUC(INF) of dapagliflozin. Similarly, lack of an effect of dapagliflozin on the PK of metformin would be concluded if the 90% confidence interval for the Treatment C to Treatment B ratios of population geometric means were contained within 80% and 125% for both Cmax and AUC(INF) of metformin.

Summary statistics were tabulated for Cmax, AUC(INF), AUC(0-T) (area under the concentration-time curve from time zero to the time of the last quantifiable concentration), Tmax (time of maximum observed concentration), and $T_{1/2}$ (half-life) by treatment, for each analyte.

Safety: All recorded adverse events 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. ECG results were listed and summarized by visit (at screening and at study discharge). Any significant physical examination findings, clinical laboratory results, or ECG results were listed.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: A total of 74 subjects were enrolled for the study. Of the 74 subjects, 18 were randomized and treated with study drugs; 56 subjects discontinued prior to study drug administration. Of the 18 randomized subjects, 17 completed the study. One (1) subject discontinued from the study due to an AE. Most subjects (83%) were male; the mean age was 33 years (range 22 to 45 years). The majority of subjects (67%) were black; 33% of subjects were white. The mean BMI was 26.1 kg/m^2 (range 19.6 to 31.6 kg/m^2).

Pharmacokinetic Results: Individual dapagliflozin pharmacokinetic parameters are summarized in the following table. The 90% confidence intervals for the ratios of population geometric means for dapagliflozin Cmax, AUC(0-T) and AUC(INF) following administration of dapagliflozin 20 mg, with and without 1000 mg metformin, were within the no-effect interval (0.80, 1.25), indicating that metformin did not affect the pharmacokinetics of dapagliflozin.

Table 2: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters

	Treatments	
Dapagliflozin Pharmacokinetic Parameter	**A (n=18)**	**C (n=18)**
Cmax (ng/mL); Geometric Mean (CV %)	134 (31)	125 (22)
Tmax (h); Median (Min, Max)	1.50 (1.00, 3.00)	1.50 (1.00, 2.00)
AUC(INF) (ng•h/mL); Geometric Mean (CV %)	947 (22)	943 (20)
AUC(0-T) (ng•h/mL); Geometric Mean (CV%)	903 (21)	908 (21)
$\mathbf{T_{1/2}}$ (h); Mean (SD)	16.5 (8.85)	14.0 (7.96)

Treatments: A=Dapagliflozin 20 mg single dose; C=Dapagliflozin 20 mg single dose and Metformin 1000 mg single dose

CV = coefficient of variation

Table 3: Results of Statistical Analyses on Dapagliflozin Pharmacokinetic

Dapagliflozin Pharmacokinetic Parameter	**Adjusted Geometric Means**		**Ratio of Adjusted Geometric Means (Trt C / Trt A)**	
	Trt A (n=18)	**Trt C (n=18)**	**Point Estimate**	**90% CI**
Cmax (ng/mL)	134	125	0.93	(0.85, 1.02)
AUC(INF) (ng•h/mL)	947	943	1.00	(0.94, 1.05)
AUC(0-T) (ng•h/mL)	903	908	1.01	(0.95, 1.06)

Treatments: A=Dapagliflozin 20 mg single dose; C=Dapagliflozin 20 mg single dose and Metformin 1000 mg single dose

Individual metformin pharmacokinetic parameters are summarized in the following table. The 90% confidence intervals for the ratios of population geometric means for metformin Cmax, AUC(0-T), and AUC(INF) following administration of metformin 1000 mg, with and without 20 mg dapagliflozin, were within the no-effect interval (0.80, 1.25), indicating that dapagliflozin did not affect the pharmacokinetics of metformin.

Table 4: Summary Statistics for Metformin Pharmacokinetic Parameters

Metformin Pharmacokinetic Parameter	Treatments	
	B (n=17)	C (n=18)
Cmax (ng/mL); Geometric Mean (C.V. %)	1078 (26)	1033 (27)
Tmax (h); Median (Min, Max)	3.00 (1.00, 4.00)	3.00 (1.00, 6.00)
AUC(INF) (ng•h/mL); Geometric Mean (CV %)	8869 (23)	8922 (22)
AUC(0-T) (ng•h/mL); Geometric Mean (CV %)	8716 (21)	8761 (22)
$\mathbf{T_{1/2}}$ (h); Mean (SD)	13.6 (11.52)	15.4 (10.86)

Treatments: B=Metformin 1000 mg single dose; C=Dapagliflozin 20 mg single dose and Metformin 1000 mg single dose

Table 5: Results of Statistical Analyses on Metformin Pharmacokinetic

Metformin Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt C / Trt B)	
	Trt B (n=17)	Trt C (n=18)	Point Estimate	90% CI
Cmax (ng/mL)	1084	1033	0.95	(0.87, 1.05)
AUC(INF) (ng•h/mL)	8910	8922	1.00	(0.93, 1.08)
AUC(0-T) (ng•h/mL)	8753	8761	1.00	(0.94, 1.07)

Treatments: B=Metformin 1000 mg single dose; C=Dapagliflozin 20 mg single dose and Metformin 1000 mg single dose

Safety Results: Administration of single doses of dapagliflozin and/or metformin was safe and well-tolerated by the healthy male and female subjects in this study. There was no death or serious adverse event (SAE). One marked abnormality (MA) of severe elevated creatine phosphokinase (CK) was considered as an AE in 1 subject 9 (Day 8) after administration of a single dose of dapagliflozin 20 mg and metformin 1000 mg on Day 1 and a single dose of dapagliflozin 20 mg on Day 4. As a result of the event the subject discontinued from the study (Day 12). The event of elevated CK was not associated with myalgia or other muscle-related AEs. All AEs but 1 (severe elevated CK) were mild in intensity. The most frequently reported treatment-emergent AE was nausea (n=6; 33.3%). There was no significant change in vital signs or ECG parameters.

Seven subjects had positive urine glucose results (5 subjects on Day 4 postdose and 2 subjects on Day 8 postdose); 5 of these 7 cases resolved during the study period. The positive urine glucose results were not unexpected because the mechanism of action for dapagliflozin includes inhibition of urinary glucose uptake.

CONCLUSIONS:

- [redacted]
- [redacted]
- [redacted]

DATE OF REPORT: 09-Feb-2009