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 MB102036

TITLE OF STUDY: Pharmacokinetic Drug Interaction Study of Dapagliflozin and Valsartan or Simvastatin in Healthy Subjects

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 05-Feb-2009 **CLINICAL PHASE:** 1

Study Completion Date: 24-Mar-2009

OBJECTIVES:

Primary Objectives

- To assess the effect of simvastatin on the pharmacokinetics (PK) of dapagliflozin and to determine the effect of dapagliflozin on the PK of simvastatin, when simvastatin and dapagliflozin were co-administered in healthy subjects.
- To assess the effect of valsartan on the PK of dapagliflozin and to determine the effect of dapagliflozin on the PK of valsartan, when valsartan and dapagliflozin were co-administered in healthy subjects.

Secondary Objectives

- To assess the safety and tolerability of dapagliflozin when administered alone, with valsartan, or with simvastatin in healthy subjects.
- To assess the safety and tolerability of the combination of dapagliflozin with valsartan, and the combination of dapagliflozin with simvastatin in healthy subjects.
- To assess the effect of dapagliflozin on the PK of simvastatin acid (active metabolite of simvastatin), when co-administered in healthy subjects.

METHODOLOGY: This was an open-label, randomized, 5-period, 5-treatment, unbalanced crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days prior to dosing on Day 1 of Period 1. On Day 1 of Period 1, all subjects were randomized to receive the following 5 treatments in 1 of 12 treatment sequences:

Treatment A (SIM): 40 mg simvastatin (single dose)
Treatment B (DAP + SIM): 20 mg dapagliflozin (single dose) + 40 mg simvastatin (single dose)
Treatment C (DAP): 20 mg dapagliflozin (single dose)

Treatment D (VAL): 320 mg valsartan (single dose)
Treatment E (DAP + VAL): 20 mg dapagliflozin (single dose) + 320 mg valsartan (single dose)

Subjects received each treatment once (1 treatment per period) according to the randomization assignment and underwent a 4-day (96-hour) washout (W) before receiving the next scheduled dose.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 24 subjects were planned, randomized, and treated. Of the 24 subjects, 23 completed the study as designed. All available data were included in the PK and safety analyses.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy men, and women (not nursing or pregnant and using an acceptable method of contraception), 18 to 45 years of age with a body mass index (BMI) of 18 to 32 kg/m^2 inclusive, were eligible to enroll in the study.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Treatment B [20 mg dapagliflozin (single dose) + 40 mg simvastatin (single dose)] and Treatment E [20 mg dapagliflozin (single dose) + 320 mg valsartan (single dose)]. All doses were administered orally after a 10-hour fast. The batch numbers for dapagliflozin are provided in Table 1. Valsartan and simvastatin tablets were provided as marketed product by the Investigator at the clinical site.

Table 1: Drug Information

Unit	Formulation	Route	Product ID Number	Product Batch Number	Label Batch Number	Expiry Date
BMS-512148 Tablet	10 mg	Oral	[redacted]	[redacted]	[redacted]	28-Feb-2010

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Treatment A [40 mg simvastatin (single dose)], Treatment C [20 mg dapagliflozin (single dose)], and Treatment D [320 mg valsartan (single dose)]. All doses were administered orally after a 10-hour fast. The batch numbers for dapagliflozin are provided in Table 1. Valsartan and simvastatin tablets were provided as marketed product by the Investigator at the clinical site.

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, electrocardiograms (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 [Cmax, Tmax, AUC(0-T), AUC(INF), and T-HALF were derived from plasma concentration versus time profiles for dapagliflozin, simvastatin, simvastatin acid, and valsartan.

STATISTICAL CONSIDERATIONS:

Sample Size: The sample size was not based on statistical power considerations. However, data from 22 subjects would have provided at least 90% confidence that the estimated ratios of the geometric means for simvastatin Cmax and AUC(INF), respectively, with (Treatment B) or without dapagliflozin (Treatment A), would have been within 17% and 24% of the true population ratios. These calculations assumed that Cmax and AUC(INF) of simvastatin were log-normally distributed and that the intra-subject standard deviations of log(Cmax) and log(AUC(INF)) were no greater than 0.31 and 0.43, respectively.

Data from 18 subjects would have provided at least 90% confidence that the estimated ratios of the geometric means for valsartan Cmax and AUC(INF), respectively, with (Treatment E) or without dapagliflozin (Treatment D), would have been within 11% and 12% of the true population ratios. These

calculations assumed that Cmax and AUC(INF) of valsartan were log-normally distributed with intra-subject coefficients of variation (CVs) no greater than 20.6% and 19.6%, respectively

Data from 18 subjects would have provided at least 90% confidence that the estimated ratios of the geometric means for dapagliflozin Cmax and AUC(INF), respectively, with (Treatment B) or without simvastatin (Treatment C), would have been within 10% and 6% of the true population ratios. Similarly, data from 18 subjects would have provided at least 90% confidence that the estimated ratios of the geometric means for dapagliflozin Cmax and AUC(INF), respectively, with (Treatment E) or without valsartan (Treatment C), would have been within 10% and 6% of the true population ratios. These calculations assumed that Cmax and AUC(INF) of dapagliflozin were log-normally distributed and that the intra-subject standard deviations of log(Cmax) and log(AUC(INF)) were no greater than 0.17 and 0.10, respectively.

To allow for dropouts, 24 subjects were dosed on Day 1 of Period 1.

Statistical Analyses:

Pharmacokinetics: To assess the effect of co-administration of simvastatin or valsartan on the PK of dapagliflozin, point estimates and 90% confidence intervals (CIs) were calculated for the Treatment B to Treatment C ratios and for the Treatment E to Treatment C ratios of geometric means for Cmax and AUC(INF) of dapagliflozin. These estimates were constructed from the results of fitting general linear models for log transformed data with treatments as fixed effects and measurements within each subject as repeated measurements. Point estimates of the differences and their 90% CIs in the log scale were exponentiated to obtain estimates and CIs for ratios of geometric means in the original scale. No adjustments were made for multiplicity.

To assess the effect of co-administration of dapagliflozin on the PK of each of simvastatin, simvastatin acid, and valsartan, point estimates and 90% CIs were calculated for the Treatment B to Treatment A ratios of geometric means for Cmax and AUC(INF) of simvastatin and simvastatin acid, and for the Treatment E to Treatment D ratios of geometric means for Cmax and AUC(INF) of valsartan. These estimates were constructed from the results of fitting general linear models for log transformed data with treatments and periods as fixed effects and measurements within each subject as repeated measurements. Point estimates of the differences and their 90% CIs in the log scale were exponentiated to obtain estimates and CIs for ratios of geometric means in the original scale. No adjustments were made for multiplicity.

Summary statistics were tabulated for all PK parameters by treatment for each analyte.

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. ECG results were listed and summarized by visit. Any significant physical examination findings and clinical laboratory results were listed. ECG readings were evaluated by the Investigator and abnormalities were listed.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Subject disposition information is provided in Table 2.

Table 2: Subject Disposition

	All Treated	Treatment[a] A	B	C	D	E	Not Treated[b]
No. of Subjects Enrolled	24	24	24	24	24	24	67
No. of Subjects Not Treated							
Difficult venipuncture	NA	NA	NA	NA	NA	NA	2
Non-compliance	NA	NA	NA	NA	NA	NA	3
Study full	NA	NA	NA	NA	NA	NA	6
No longer met study criteria	NA	NA	NA	NA	NA	NA	1
Withdrew consent	NA	NA	NA	NA	NA	NA	9
Screen failure	NA	NA	NA	NA	NA	NA	46
No. of Subjects Treated	24	24	24	23[c]	23[d]	24	NA
No of Subject excluded from analysis	0	0	0	0	0	0	NA
No. of Subjects Discontinued from Treatment	1	0	0	1	1	0	NA
Adverse Event	1	0	0	1	1	0	NA

[a] All subjects were scheduled to receive all treatments in this crossover study.

[b] Subjects were enrolled in the study but not randomized to treatment.

[c] One subject discontinued due to unrelated AEs prior to completing the study.

NA = Not applicable

Baseline demographic characteristics and physical measurements are provided in Table 3.

Table 3: Demographic Characteristics and Physical Measurements

Characteristics	All Treated Subjects (n = 24)	Subjects Not Treated (n=67)
Age, years		
Mean (SD)	32 (7)	34 (8)
Range	21-43	19-45
Gender, n (%)		
Male	23 (96)	56 (84)
Female	1 (4)	11 (16)
Race, n (%)		
White	7 (29)	13 (19)
Black/African American	15 (63)	49 (73)
Other	2 (8)	2 (3)
Height, cm		
Mean (SD)	178.0 (7.1)	NA
Range	165.1-182.9	
Weight, kg		
Mean (SD)	84.7 (9.9)	NA
Range	64.0-99.8	
Body Mass Index, kg/m^2		
Mean (SD)	26.8 (3.2)	NA
Range	19.6-31.6	

NA = Not available

Safety Results:

Administration of single doses of dapagliflozin alone or in combination with simvastatin or valsartan was safe and generally well tolerated by the healthy men and women in this study. There were no deaths. One subject was discontinued due to an AE of moderate agitation. The same subject had a serious AE of very severe mental disorder (psychiatric hospitalization) that occurred 24 days after study discontinuation. Both events were considered unrelated to study treatment.

Overall, 12 subjects experienced 34 AEs, the most common of which was headache [3 of 24 (12.5%) of subjects]. Twenty-eight (28) AEs were mild, 5 were moderate, none were severe, and 1 was very severe. Two subjects had marked abnormalities (MA) in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values that were also reported as AEs. These events occurred after Treatment A (40 mg simvastatin) and Treatment B (20 mg dapagliflozin + 40 mg simvastatin) and resolved during subsequent treatment periods.

Fourteen (14) subjects had a total of 48 MAs in clinical laboratory values. In addition to the 2 subjects with AST and ALT values reported as AEs, one subject had a MA in total bilirubin that occurred following Treatments A (40 mg simvastatin) and B (20 mg dapagliflozin + 40 mg simvastatin) and returned to normal limits during subsequent treatment periods. Six (6) subjects had MAs in urine glucose, consistent with the mechanism of action for dapagliflozin. One subject had a serum creatinine value that met the criteria for MA (>1.33 x baseline value) at discharge on Day 20 but was still within normal limits. Other MAs appeared to be transient changes and most had resolved by the end of the study.

There were no clinically significant changes in vital signs measurements, or ECG or physical examination findings.

Pharmacokinetic Results:

Dapagliflozin: Dapagliflozin PK parameters are summarized by treatment in Table 4 and the results of statistical analyses are presented in Table 5. The Cmax and AUC of dapagliflozin were comparable with or without co-administration of simvastatin or valsartan (90% CI within 80% to 125%), except in the case of an 11.9% decrease in dapagliflozin Cmax in the presence of valsartan, where the lower bound of the 90% CI was 79.6%.

Table 4: 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)
C (DAP) (n = 23)	254 (31)	980 (25)	941 (25)	16.13 (7.599)	0.55 (0.50, 2.03)
B (DAP + SIM) (n = 24)	245 (27)	953 (27)	906 (28)	18.61 (9.095)	1.00 (0.50, 2.00)
E (DAP + VAL) (n = 24)	221 (34)	990 (27)	947 (27)	15.89 (7.004)	0.99 (0.48, 2.00)

Treatments: B=20 mg dapagliflozin + 40 mg simvastatin
C=20 mg dapagliflozin
E=20 mg dapagliflozin + 320 mg valsartan

Table 5: Results of Statistical Analyses of Dapagliflozin Pharmacokinetic Parameters

Dapagliflozin Pharmacokinetic Parameter	Adjusted Geometric Means			Ratio of Adjusted Geometric Means Point Estimate (90% CI)	
	Trt C (DAP)	Trt B (DAP + SIM)	Trt E (DAP + VAL)	(Trt B/Trt C)	(Trt E/Trt C)
Cmax (ng/mL)	251	245	221	0.978 (0.887, 1.078)	0.881 (0.796, 0.975)
AUC(INF) (ng·h/mL)	966	953	990	0.986 (0.957, 1.017)	1.024 (1.000, 1.049)
AUC(0-T) (ng·h/mL)	928	906	947	0.977 (0.948, 1.006)	1.020 (0.995, 1.045)

Simvastatin: Simvastatin PK parameters are summarized by treatment in Table 6 and the results of statistical analyses are presented in Table 7. There was no change in the Cmax of simvastatin when administered with dapagliflozin, however, the geometric mean ratios of both AUC(0-T) and AUC(INF) increased by approximately 19% [90 % CI for the ratios of population geometric means with and without dapagliflozin for AUC(0-T) and AUC(0-INF) was (1.009, 1.395) and (1.018, 1.399), respectively].

Table 6: Summary Statistics for Simvastatin Pharmacokinetic Parameters

Treatment	Simvastatin 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 (SIM) (n = 24)	5.14 (52)	26.97 (61)	25.21 (62)	5.59 (3.502)	1.50 (0.48, 8.00)
B (DAP + SIM) (n = 24)	4.81 (43)	32.18 (66)	29.90 (69)	7.84 (5.010)	1.99 (1.00, 6.03)

Treatments: A=40 mg simvastatin
B=20 mg dapagliflozin + 40 mg simvastatin

Table 7: Results of Statistical Analyses of Simvastatin Pharmacokinetic Parameters

Simvastatin Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt B/Trt A)	
	Trt A (SIM)	Trt B (DAP + SIM)	Point Estimate	90% CI
Cmax (ng/mL)	5.14	4.81	0.936	(0.816, 1.073)
AUC(INF) (ng·h/mL)	26.97	32.18	1.193	(1.018, 1.399)
AUC(0-T) (ng·h/mL)	25.21	29.90	1.186	(1.009, 1.395)

Valsartan: Valsartan PK parameters are summarized by treatment in Table 8 and the results of statistical analyses are presented in Table 9. The point estimates for Cmax and AUC of valsartan were within 7% of unity, suggesting that values were comparable with or without co-administration of dapagliflozin, although the 90% CI were not within the 80% to 125% no-effect interval for any of the PK parameter values, probably due to greater than anticipated variability of valsartan PK. In the case of valsartan Cmax, the lower bound of the 90% CI was less than 0.80 and in the case of the AUC values, the upper bound of the 90% CI were greater than 125%.

Table 8: Summary Statistics for Valsartan Pharmacokinetic Parameters

Treatment	Valsartan 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)
D (VAL) (n = 23)	5528 (34)	40136 (31)[a]	38220 (32)	16.79 (18.604)[a]	3.98 (1.00, 5.98)
E (DAP + VAL) (n = 24)	5184 (56)	41721 (47)[b]	40536 (49)	13.47 (9.875)[b]	3.50 (0.50, 4.23)

Treatments: D=320 mg valsartan
E=20 mg dapagliflozin + 320 mg valsartan

[a] n=22. AUC(INF) and T-HALF of valsartan were missing for Subject [redacted], as they could not be characterized appropriately.

[b] n=23. AUC(INF) and T-HALF of valsartan were missing for Subject [redacted], as they could not be characterized appropriately.

Table 9: Results of Statistical Analyses of Valsartan Pharmacokinetic Parameters

Valsartan Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt E/Trt D)	
	Trt D (VAL)	Trt E (DAP + VAL)	Point Estimate	90% CI
Cmax (ng/mL)	5525	5184	0.938	(0.762, 1.156)
AUC(INF) (ng·h/mL)	40004	41830	1.046	(0.850, 1.286)
AUC(0-T) (ng·h/mL)	38238	40536	1.060	(0.865, 1.299)

Simvastatin Acid: Simvastatin acid PK parameters are summarized by treatment in Table 10 and the results of statsitical analyses are presented in Table 11. There was no change in the Cmax of simvastatin acid when simvastatin was administered with dapagliflozin, however, the geometric mean ratios [90 % CI for the ratios of population geometric means with and without dapagliflozin] for AUC(0-T) and AUC(INF) increased by 32% (1.169, 1.494) and 35% (1.178, 1.545), respectively.

Table 10: Summary Statistics for Simvastatin Acid Pharmacokinetic Parameters

Treatment	Simvastatin Acid 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 (SIM) (n = 24)	1.42 (42)	17.73 (47)[a]	16.40 (46)	8.35 (7.995)[a]	6.00 (2.00, 12.00)
B (DAP + SIM) (n = 24)	1.50 (52)	23.72 (45)	21.27 (40)	12.21 (12.017)	6.00 (3.00, 11.97)

Treatments: A=40 mg simvastatin, B=20 mg dapagliflozin + 40 mg simvastatin

[a] n=23. AUC(INF) and T-HALF of simvastatin acid for Treatment A were missing for Subject [redacted] since these parameters could not be reliably characterized.

Table 11: Results of Statistical Analyses on Simvastatin Acid Pharmacokinetic Parameters

Simvastatin Acid Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt B/Trt A)	
	Trt B (DAP + SIM)	Trt A (SIM)	Point Estimate	90% CI
Cmax (ng/mL)	1.50	1.40	1.077	(0.931, 1.247)
AUC(INF) (ng·h/mL)	23.71	18.10	1.311	(1.146, 1.499)
AUC(0-T) (ng·h/mL)	21.27	16.40	1.297	(1.146, 1.468)

CONCLUSIONS:

[redacted]

DATE OF REPORT: 01-Mar-2010