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: BMS-512148		

SYNOPSIS

Final Clinical Study Report for Study MB102058

TITLE OF STUDY: Study of the Effect of Dapagliflozin on the Pharmacokinetics of Warfarin and Digoxin in Healthy Subjects

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 11-Jun-2009 **CLINICAL PHASE:** 1

Study Completion Date: 12-Aug-2009

OBJECTIVES:

Primary Objectives:

- To assess the effect of dapagliflozin on the pharmacokinetics (PK) of S-warfarin, when warfarin and dapagliflozin are co-administered in healthy subjects (Cohort 1)
- To assess the effect of dapagliflozin on the PK of digoxin, when digoxin and dapagliflozin are co-administered in healthy subjects (Cohort 2)
- To assess the effect of dapagliflozin on the pharmacodynamics (PD) of warfarin, when warfarin and dapagliflozin are co-administered in healthy subjects (Cohort 1).

Secondary Objectives:

- To assess the effect of dapagliflozin on the PK of R-warfarin, when warfarin and dapagliflozin are co-administered in healthy subjects (Cohort 1)
- To assess the safety and tolerability of the combination of dapagliflozin with warfarin, and the combination of dapagliflozin with digoxin, in healthy subjects.

METHODOLOGY: This was an open-label, randomized, 2-period, 2-treatment, crossover Phase 1 study in 2 cohorts. Healthy subjects were screened within 28 days prior to dosing on Day 1 of Period 1. Eligible subjects were initially admitted to the clinical research facility on Day -1 of Period 1 and remained confined until discharge on Day 23. On Day 1 of Period 1, subjects were randomly assigned to 1 of 4 treatment sequences: A/B, B/A, C/D, or D/C, where sequences A/B and B/A belonged to Cohort 1 and sequences C/D and D/C belonged to Cohort 2. Treatment A consisted of dapagliflozin plus warfarin, Treatment B consisted of warfarin alone, Treatment C consisted of dapagliflozin plus digoxin, and

Treatment D consisted of digoxin alone. Each subject was to receive 2 study treatments (Periods 1 and 2) according to the randomly assigned sequence, and a washout period of 9 days relative to warfarin or digoxin dosing separated the 2 treatments. Serial blood samples for PK analysis were collected up to 216 hours post-dose for all 4 treatments, while blood samples for PD assessments were obtained for up to 216 hours post-dose following Treatments A and B. Subjects were discharged from the study on Day 11 of Period 2, after all safety assessments had been completed.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 30 subjects were planned, enrolled, and randomly assigned to Cohort 1 (n = 14 [7 to A/B sequence, 7 to B/A sequence]) or Cohort 2 (n = 16 [8 to C/D sequence, 8 to D/C sequence]). Each of the 30 subjects received at least 1 dose of study treatment. Twenty-nine (29) subjects completed the study; 1 subject in Cohort 2 (B/A sequence) was discontinued prematurely for personal reasons (coded as Other).

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 and 45 years, with a body mass index (BMI) of 18 to 32 kg/m^2, inclusive, were eligible to participate. Female subjects who were of childbearing potential (WOCBP), nursing, or pregnant were not eligible, and all women had to have a negative pregnancy test within 24 hours prior to dosing with study medication in Period 1. Male subjects who had intercourse with WOCBP must have agreed to practice effective barrier contraception during the period of study participation and for at least 12 weeks following the last dose of study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: On Day 1 of Period 1 and Period 2, single oral dose of dapagliflozin 20 mg (2 x 10 mg tablet) (Treatments A and C). During Periods 1 and 2, once daily (QD) oral doses of dapagliflozin 10 mg (1 x 10-mg tablet) for 7 days (Days 2 to 8 of Treatments A and C), co-administered with a single oral dose of warfarin 25 mg on Day 2 (Treatment A) or single oral dose of digoxin 0.25 mg on Day 2 (Treatment C).

All study medications were administered with 240 mL water under fasting conditions (10 hours prior to dosing until 4 hours after). [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: During Periods 1 and 2, single oral 25-mg tablet of warfarin on Day 2 (Treatment B) and single oral 0.25-mg tablet of digoxin on Day 2 (Treatment D). Warfarin and digoxin tablets were supplied by the investigator.

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event (AE) reports (including serious adverse events [SAEs] and discontinuations due to AEs), vital sign measurements, 12-lead electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. The incidence of AEs were tabulated and reviewed for potential significant and clinical importance.

Pharmacokinetics: Single-dose PK parameters of Cmax, Tmax, T-HALF, AUC(0-T), and AUC(INF) for S- and R-warfarin, and Cmax, Tmax, and AUC(0-T) for digoxin, were derived from plasma concentration versus time data. PK parameters [Cmax, Tmax, AUC(TAU)], and Cmin) for dapagliflozin were also assessed.

Pharmacodynamics: Plasma prothrombin time was measured for treatments with warfarin (Treatments A and B) and converted to International Normalization Ratio (INR). The AUC(INR) and observed peak INR value (INRmax) for Treatments A and B were calculated based on derived INR versus time data.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The sample size was not based on statistical power considerations. However, data from 12 completed subjects in Cohort 1 provided at least 90% confidence that the estimated ratios of the geometric means for S-warfarin Cmax and AUC(INF), respectively, with (Treatment A) or without dapagliflozin (Treatment B) would be within 10% and 11% of the true population ratios. In addition, data from 12 completed subjects in Cohort 1 provided at least 90% confidence that the estimated ratios of the geometric means for INRmax and AUC(INR), respectively, with (Treatment A) or without dapagliflozin (Treatment B), would be within 10% and 5% of the true populations. Data from 14 completed subjects in Cohort 2 provided at least 90% confidence that the estimated ratios of the geometric means for digoxin Cmax and AUC(INF), respectively, with (Treatment C) or without dapagliflozin (Treatment D), would be within 12% and 5% of the true population ratios. To allow for dropouts, 30 subjects (14 subjects for Cohort 1 and 16 subjects for Cohort 2) were dosed on Day 2 of Period 1.

Statistical Analysis:

Pharmacokinetics: To assess the effect of co-administration of dapagliflozin on the PK of each of S-, R-warfarin, and digoxin, point estimates and 90% confidence intervals (CIs) were calculated for the Treatment A to Treatment B ratios of geometric means for Cmax, AUC(INF) and AUC(0-T) of S and R-warfarin, and for the Treatment C to Treatment D ratios of geometric means for Cmax and AUC(0-T) of digoxin based on appropriate general linear model analyses. 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 and preferred term and treatment. Vital sign and clinical laboratory test results were listed and summarized by treatment. Marked abnormalities (MAs) in clinical laboratory results as well as any significant physical examination findings or ECG results were listed.

Pharmacodynamics: To assess the effect of dapagliflozin on the PD of warfarin, point estimates and 90% CIs were calculated for the Treatment A to Treatment B ratios of geometric means for AUC(INR) and INRmax based on appropriate general linear model analyses. In addition, summary statistics were tabulated for both of AUC(INR) and INRmax by treatment.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 114 subjects were screened, of whom 30 male subjects were randomized and treated with study medication and 84 were considered screening failures. One (1) subject discontinued the study prematurely after completing Treatment B (single warfarin 25-mg dose) and receiving 3 days of the Treatment A regimen (single loading dose of dapagliflozin 20 mg [Day 1], 2 doses of dapagliflozin 10 mg [Days 2 and 3] and 1 dose of warfarin 25 mg [Day 2]).

Table 1: Subject Disposition, Demographic and Baseline Characteristics

Parameter	Cohort 1 (N=14)	Cohort 2 (N=16)	Total (N=30)
No. (%) completed study	13 (92.9)	16 (100)	29 (96.7)
Age (years), mean (SD)	30 (8)	27 (8)	28 (8)
Gender, Male, n (%)	14 (100)	16 (100)	30 (100)
Race			
White, n (%)	11 (79)	8 (50)	19 (63)
Black, n (%)	3 (21)	6 (38)	9 (30)
Other, n (%)	0	2 (13)	2 (7)
BMI (kg/m^2), mean (SD)	25.9 (2.7)	24.3 (3.4)	25.0 (3.2)

Cohort 1: Treatment sequences: A/B and B/A; Cohort 2 = Treatment sequences C/D and D/C.

Pharmacokinetic Results: The co-administration of dapagliflozin with warfarin in healthy subjects did not affect the PK of S- or R-warfarin; similarly, the co-administration of dapagliflozin with digoxin in healthy subjects did not affect the PK of digoxin (Table 2). The geometric means of S- and R-warfarin Cmax AUC(INF), and AUC(0-T) were < 10% higher when warfarin was co-administered with dapagliflozin (Treatment A) compared with warfarin administered alone (Treatment B). The geometric means of digoxin Cmax and AUC(0-T) were ≤ 1% different when digoxin was co-administered with dapagliflozin (Treatment C) compared with digoxin administered alone (Treatment D). The 90% CIs for the ratio of S-warfarin, R-warfarin, and digoxin Cmax and AUC, with and without dapagliflozin, were within the usual no-effect range of 0.80 to 1.25.

Using the 20 mg loading dose paradigm, trough (Cmin) dapagliflozin concentrations following 10 mg daily doses were at steady state following the second day of once daily dosing.

Table 2: Results of Statistical Analyses on S- and R-Warfarin and Digoxin Pharmacokinetic Parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means	
	S-Warfarin			
	Trt A	Trt B	Point Estimate : Trt A/Trt B	90%CI
Cmax (ng/mL)	1575	1530	1.030	(0.994, 1.124)
AUC(INF) (ng·h/mL)	55617	52088	1.068	(1.002, 1.138)
AUC(0-T) (ng·h/mL)	54001	50326	1.073	(1.009, 1.141)
	R-Warfarin			
	Trt A	Trt B	Point Estimate : Trt A/Trt B	90%CI
Cmax (ng/mL)	1520	1438	1.057	(0.977, 1.145)
AUC(INF) (ng·h/mL)	77242	71585	1.079	(1.030, 1.130)
AUC(0-T) (ng·h/mL)	73195	68006	1.076	(1.032, 1.122)
	Digoxin			
	Trt C	Trt D	Point Estimate : Trt C/Trt D	90%CI
Cmax (ng/mL)	0.838	0.846	0.990	(0.843, 1.162)
AUC(0-T) (ng·h/mL)	9.496	9.479	1.002	(0.860, 1.167)

TRT A = Dapagliflozin 20 mg +Dapagliflozin 10 mg QD + Warfarin 25 mg, TRT B = Warfarin 25 mg,
TRT C = Dapagliflozin 20 mg +Dapagliflozin 10 mg QD + Digoxin 0.25 mg, TRT D = Digoxin 0.25 mg

Safety Results: Co-administration of dapagliflozin (20-mg loading dose on Day 1, 10-mg on Days 2 to 8) and warfarin (25 mg on Day 2) or digoxin (0.25 mg on Day 2) was safe and generally well tolerated by the healthy subjects in this study (Table 3). Vital signs, clinical laboratory tests (hematology, clinical chemistry), ECGs, and physical examinations did not show clinically meaningful changes or trends following study drug administration. Glucosuria was present in 10 subjects following treatment with dapagliflozin (Treatments A or C) and was consistent with the pharmacologic action of this drug.

Table 3: Safety Overview (All Treated Subjects)

Number (%) Subjects With:	Trt A (N=14)	Trt B (N=14)	Trt C (N=16)	Trt D (N=16)	Trt A + C (N=30)
Death	0	0	0	0	0
SAE	0	0	0	0	0
AEs	1 (7.1)	3 (21.4)	4 (25.0)	3 (18.8)	5 (16.7)
Related AEs	0	1 (7.1)	3 (18.8)	2 (12.5)	3 (10.0)
Severe AEs	0	0	0	0	0
Discontinued due to AEs	0	0	0	0	0

TRT A = Dapagliflozin 20 mg + Dapagliflozin 10 mg QD + Warfarin 25 mg, TRT B = Warfarin 25 mg,
TRT C = Dapagliflozin 20 mg + Dapagliflozin 10 mg QD + Digoxin 0.25 mg, TRT D = Digoxin 0.25 mg.

Pharmacodynamic Results: The geometric means for INRmax and AUC(INR) increased by < 1% when warfarin 25 mg was co-administered with dapagliflozin compared to the geometric mean values for warfarin 25 mg given alone. The 90% CIs for the ratios of the geometric means, with and without dapagliflozin were (0.967, 1.043) for INRmax and (0.989, 1.025) for AUC(INR), and were contained within the usual no-effect range of 0.80 to 1.25.

CONCLUSIONS:

[redacted]

DATE OF REPORT: 30-Jun-2010