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		

SYNOPSIS

Final Clinical Study Report for Study MB102037

TITLE OF STUDY: Pharmacokinetic Drug Interaction Study of Dapagliflozin and Glimepiride or Sitagliptin in Healthy Subjects

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 26-Mar-2009 **CLINICAL PHASE:** 1
Study Completion Date: 19-May-2009

OBJECTIVES:

The primary objectives of this study were:

- To assess the effect of glimepiride on the pharmacokinetics (PK) of dapagliflozin and the effect of dapagliflozin on the PK of glimepiride, when co-administered in healthy subjects (Phase A)
- To assess the effect of sitagliptin on the PK of dapagliflozin and the effect of dapagliflozin on the PK of sitagliptin, when co-administered in healthy subjects (Phase B)

The secondary objectives of this study were:

- To assess the safety and tolerability of dapagliflozin, glimepiride, and sitagliptin when administered alone in healthy subjects
- To assess the safety and tolerability of the combination of dapagliflozin with glimepiride, and the combination of dapagliflozin with sitagliptin in healthy subjects

METHODOLOGY:

This was an open-label, randomized, 5-period, 5-treatment, unbalanced crossover study in healthy subjects.

On Day 1 of Period 1, all subjects were randomized to receive the following 5 treatments in 1 of 12 treatment sequences: Treatment A, B, or C during the first 3 periods (Phase A), followed by Treatment D or E in Periods 4 and 5 (Phase B).

Phase A
Treatment A: 20 mg dapagliflozin (single dose)
Treatment B: 4 mg glimepiride (single dose)

Treatment C: 20 mg dapagliflozin (single dose) + 4 mg glimepiride (single dose)

Phase B
Treatment D: 100 mg sitagliptin (single dose)
Treatment E: 20 mg dapagliflozin (single dose) + 100 mg sitagliptin (single dose)

Subjects received each treatment once (1 treatment per period) according to the randomization assignment then underwent a 4-day (96-hour) washout before receiving the next scheduled dose. All study treatments were administered following a fast of at least 10 hours.

In each period, subjects were maintained in a fasted state (except for glucose solution administered per protocol) for 4 hours postdose, and serial blood samples were collected for up to 72 hours postdose for PK assessments.

Study medications were administered with 240 mL of 20% glucose solution in water (unflavored). Thereafter, each subject was administered 60 mL of a 20% glucose solution in water every 15 minutes for 4 hours postdose in order to reduce the risk of possible hypoglycemia. Within 4 hours postdose, if a subject reported symptoms (e.g., dizziness, sweating, palpitation, fatigue) and hypoglycemia was confirmed by fingerstick glucose level, additional glucose solution was given. A commercial glucose solution was used up to 4 hours postdose to avoid administration of treatments that could potentially affect PK. After 4 hours postdose, if a subject reported symptoms (e.g., dizziness, sweating, palpitation, fatigue) and hypoglycemia was confirmed by fingerstick glucose level, standard care for hypoglycemia (i.e., orange juice or another treatment deemed appropriate by the study site) was administered.

Subjects were confined to the clinical facility for the duration of the study.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations were performed at selected times throughout the study. Subjects were closely monitored for adverse events throughout the study. Less than 500 mL of blood was drawn from each subject during the study.

The approximate duration of the study for each subject, including the screening period and washout periods, was 41 days.

NUMBER OF SUBJECTS (Planned and Analyzed): Eighteen (18) subjects were planned for analysis; 18 subjects were treated; and the data from all 18 treated subjects were analyzed.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male or female subjects, aged 18 to 45 years, with a body mass index (BMI) of 18 to 32 kg/m^2, and determined to be healthy by medical history, physical examination, 12-lead ECG, and clinical laboratory evaluations, were eligible to participate in the study.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: A single oral dose of dapagliflozin 20 mg (2 x 10 mg) co-administered with glimepiride 4 mg (Treatment C) or a single oral dose of dapagliflozin 20 mg (2 x 10 mg) co-administered with sitagliptin 100 mg (Treatment E). Product information for dapagliflozin is provided in Table 1.

Table 1: Dapagliflozin Product Information

Treatment	Formulation	Route	Product ID Number	Product Batch Number	Label Batch Number
Dapagliflozin (BMS-512148) 10 mg	Tablet	Oral	[redacted]	[redacted]	[redacted]

Dapagliflozin was packaged and supplied to the study site by BMS. Glimepiride and sitagliptin were provided by the investigator.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: A single oral dose of dapagliflozin 20 mg (2 x 10 mg) (Treatment A) (see Table 1 for batch numbers); a single oral dose of glimepiride 4 mg (Treatment B); and a single oral dose of sitagliptin 100 mg (Treatment D).

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event reports and the results of physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory data.

Pharmacokinetics: Single-dose PK parameters (maximum observed plasma concentration [Cmax], time of maximum observed plasma concentration [Tmax], area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration [AUC(0-T)], area under the plasma concentration-time curve from time zero extrapolated to infinite time [AUC(INF)], and plasma half-life [T-HALF]) of dapagliflozin, glimepiride, and sitagliptin were derived from plasma concentration versus time data.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The sample size was not based on statistical power considerations. However, data from 15 subjects would provide at least 90% confidence that the estimated ratios of the geometric means for glimepiride Cmax and AUC(INF), respectively, with (Treatment C) or without dapagliflozin (Treatment B), would be within 15% and 11% of the true population ratios and the estimated ratios of the geometric means for dapagliflozin Cmax and AUC(INF), respectively, with (Treatment C) or without glimepiride (Treatment A), would be within 11% and 6% of the true population ratios. Data from 13 subjects would provide at least 90% confidence that the estimated ratios of the geometric means for sitagliptin Cmax and AUC(INF), respectively, with (Treatment E) or without dapagliflozin (Treatment D), would be within 9% and 3% of the true population ratios and the estimated ratios of the geometric means for dapagliflozin Cmax and AUC(INF), respectively, with (Treatment E) or without sitagliptin (Treatment A), would be within 12% and 7% of the true population ratios.

Statistical Analysis: Frequency distributions of gender and race were tabulated. Summary statistics for age, body weight, height, and BMI were tabulated.

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 recordings were evaluated by the investigator and abnormalities were listed.

To assess the effect of co-administration of glimepiride or sitagliptin on the PK of dapagliflozin, point estimates and 90% confidence intervals were calculated for the Treatment C to Treatment A ratios and for the Treatment E to Treatment A ratios of geometric means for Cmax and AUC(INF) of dapagliflozin. These estimates were constructed from the results of fitting general linear models for logtransformed data with treatments as fixed effects and measurements within each subject as repeated measurements. Point

estimates of the differences and their 90% confidence intervals in the log scale were exponentiated to obtain estimates and confidence intervals 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 glimepiride and sitagliptin, point estimates and 90% confidence intervals were calculated for the Treatment C to Treatment B ratios of geometric means for Cmax, AUC(INF), and AUC(0-T) of glimepiride, and for the Treatment E to Treatment D ratios of geometric means for Cmax, AUC(INF), and AUC(0-T) of sitagliptin. 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% confidence intervals in the log scale were exponentiated to obtain estimates and confidence intervals for ratios of geometric means in the original scale. No adjustments were made for multiplicity.

Summary statistics were tabulated for Cmax, Tmax, AUC(INF), AUC(0-T), and T-HALF by treatment, for each analyte. Geometric means and coefficients of variation were presented for Cmax, AUC(INF), and AUC(0-T). Medians and ranges were presented for Tmax. Means and standard deviations were presented for T-HALF.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

The disposition of treated subjects is summarized in Table 2. Of the 18 subjects who received study medication, all completed the study as planned.

Table 2: Subject Disposition

No. of subjects enrolled	64
No. of subjects treated	18
No of subjects excluded from analysis	0
No. of subjects discontinued	0
No. of subjects completing the study	18

Demographic characteristics and baseline physical measurements for treated subjects are summarized in Table 3. Subjects were predominantly male (67%) and all subjects were white. The median age was 30 years and mean body mass index was 26.7 kg/m^2.

Table 3: Demographic Characteristics and Physical Measurements

Characteristics	Randomized Subjects N = 18
Age (years)	
Mean (SD)	33 (7)
Median	30
Range	25 - 42
Gender, n (%)	
Male	12 (67)
Female	6 (33)
Race, n (%)	
White	18 (100)
Ethnicity, n (%)	
Hispanic/Latino	6 (33)
Not Hispanic/Latino	12 (67)
Weight (kg)	
Mean (SD)	77.3 (14.9)
Range	52.8 - 103.5
Height (cm)	
Mean (SD)	169.8 (8.9)
Range	154.0 - 182.0
Body Mass Index (kg/m^2)	
Mean (SD)	26.7 (3.7)
Range	19.2 - 31.2

SD = standard deviation

Safety Results:

There were no deaths, serious adverse events, or treatment discontinuations due to adverse events. A total of 22 treatment-emergent adverse events (i.e., adverse events that began or worsened after randomization) were reported for 9 subjects (50%) during the study. The frequency of adverse events, as well as the proportion of subjects with adverse events, was similar across treatments. Overall, the most frequently reported adverse events were nausea (6 subjects; 33.3%) and headache (3 subjects; 16.7%). All adverse events resolved prior to study completion. Table 4 shows a summary of adverse events.

Table 4: Adverse Event Summary

	Number (%) of Subjects						
	TRT A N = 18	**TRT B N = 18**	**TRT C N = 18**	**TRT D N = 18**	**TRT E N = 18**	**Any BMS N = 18**	**All Subjects N = 18**
Adverse event(s)	2 (11.1)	4 (22.2)	5 (27.8)	3 (16.7)	4 (22.2)	8 (44.4)	9 (50.0)
Death	0	0	0	0	0	0	0
Serious adverse event	0	0	0	0	0	0	0
Discontinuation due to adverse event	0	0	0	0	0	0	0

TRT A = dapagliflozin 20 mg, TRT B = glimepiride 4 mg, TRT C = dapagliflozin 20 mg + glimepiride 4 mg, TRT D = sitagliptin 100 mg, TRT E = dapagliflozin 20 mg + sitagliptin 100 mg

There were no clinically relevant mean changes over time in any hematology, serum chemistry, or urinalysis parameter. Overall, 9 subjects had a total of 13 laboratory marked abnormalities during the study: 2 subjects had a decreased hematocrit; 1 subject had an increased creatinine level and a high urine glucose value; and 6 other subjects had a total of 9 high urine glucose values (high urine glucose values are consistent with the pharmacodynamic effect of dapagliflozin). There were no laboratory marked abnormalities for alanine aminotransferase, aspartate aminotransferase, or total bilirubin.

There were no clinically relevant mean changes in electrocardiogram heart rate or conduction intervals during the study, and no clinically relevant changes in vital signs or physical findings over time.

Pharmacokinetic Results:

Summary statistics for dapagliflozin PK parameters and results of statistical analyses are presented in Table 5 and Table 6, respectively.

Table 5: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters

Treatment	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)**
A (n = 18)	151 (23)	1.50 (1.00, 4.00)	1139 (27)	1101 (28)	14.3 (10.07)
C (n = 18)	152 (28)	1.50 (1.00, 6.00)	1126 (26)	1095 (27)	12.4 (3.42)
E (n = 17)	143 (29)	1.68 (1.00, 6.00)	1184 (20)	1135 (21)	15.9 (7.10)

CV = coefficient of variation

Treatments: A = dapagliflozin 20 mg
C = dapagliflozin 20 mg + glimepiride 4 mg
E = dapagliflozin 20 mg + sitagliptin 100 mg

Table 6: Results of Statistical Analyses on Dapagliflozin Pharmacokinetic Parameters

Dapagliflozin Pharmacokinetic Parameter	Adjusted Geometric Means			Ratio of Adjusted Geometric Means Point Estimate (90% CI)	
	Trt A	**Trt C**	**Trt E**	**(Trt C / Trt A)**	**(Trt E / Trt A)**
Cmax (ng/mL)	151	152	145	1.006 (0.921, 1.097)	0.958 (0.875, 1.049)
AUC (INF) (ng·h/mL)	1139	1126	1232	0.989 (0.958, 1.020)	1.081 (1.031, 1.133)
AUC(0-T) (ng·h/mL)	1101	1095	1184	0.995 (0.969, 1.021)	1.075 (1.026, 1.126)

CI = confidence interval; Trt = treatment

Treatments: A = dapagliflozin 20 mg
C = dapagliflozin 20 mg + glimepiride 4 mg
E = dapagliflozin 20 mg + sitagliptin 100 mg

Co-administration with single-dose glimepiride (4 mg) in healthy subjects did not affect the PK of dapagliflozin (20 mg) since the 90% confidence intervals for the ratio of dapagliflozin Cmax, AUC(0-T), and AUC(INF), with and without glimepiride, were within the usual 0.80 to 1.25 no-effect interval, even though a no-effect interval was not predefined. Co-administration with single-dose dapagliflozin in healthy subjects did not affect the glimepiride Cmax since the 90% confidence interval for the ratio, with and without dapagliflozin, was within the usual 0.80 to 1.25 no-effect interval, even though a no-effect interval was not predefined. However, the glimepiride AUC(0-T) and AUC(INF) were increased by approximately 13% when co-administered with dapagliflozin and the upper 90% confidence boundary for the ratio, with and without dapagliflozin, extended slightly above the usual 0.80 to 1.25 no-effect interval. Summary

statistics for glimepiride PK parameters and results of statistical analyses are presented in Table 7 and Table 8, respectively.

Table 7: Summary Statistics for Glimepiride Pharmacokinetic Parameters

	Glimepiride Pharmacokinetic Parameters				
Treatment	**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)**
B (n = 18)	145 (51)	8.00 (1.50, 8.03)	994 (44)	970 (45)	5.1 (2.06)
C (n = 18)	151 (33)	8.00 (1.50, 12.00)	1125 (39)	1094 (39)	6.0 (3.25)

CV = coefficient of variation

Treatments: B = glimepiride 4 mg
C = dapagliflozin 20 mg + glimepiride 4 mg

Table 8: Results of Statistical Analyses on Glimepiride Pharmacokinetic Parameters

Glimepiride Pharmacokinetic Parameter	**Adjusted Geometric Means**		**Ratio of Adjusted Geometric Means (Trt C / Trt B)**	
	Trt B	**Trt C**	**Point Estimate**	**90% CI**
Cmax (ng/mL)	145	151	1.043	(0.905, 1.201)
AUC(INF) (ng·h/mL)	994	1125	1.132	(0.996, 1.287)
AUC(0-T) (ng·h/mL)	970	1094	1.128	(0.989, 1.286)

CI = confidence interval; Trt = treatment

Treatments: B = glimepiride 4 mg
C = dapagliflozin 20 mg + glimepiride 4 mg

Co-administration of single-dose dapagliflozin (20 mg) and sitagliptin (100 mg) in healthy subjects did not affect the PK of either drug since the 90% confidence intervals for the ratio of Cmax, AUC(0-T), and AUC(INF), with and without the other drug, were within the usual 0.80 to 1.25 no-effect interval for both dapagliflozin and sitagliptin, even though a no-effect interval was not predefined. Summary statistics for sitagliptin PK parameters and results of statistical analyses are presented in Table 9 and Table 10, respectively.

Table 9: Summary Statistics for Sitagliptin Pharmacokinetic Parameters

	Sitagliptin Pharmacokinetic Parameters				
Treatment	**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)**
D (n = 18)	288 (42)	3.00 (0.50, 5.80)	3388 (14)	3335 (14)	14.2 (2.01)
E (n = 17)	254 (19)	4.00 (1.50, 8.00)	3412 (13)	3352 (13)	14.4 (2.01)

CV = coefficient of variation
Treatments: D = sitagliptin 100 mg
E = dapagliflozin 20 mg + sitagliptin 100 mg

Table 10: Results of Statistical Analyses on Sitagliptin Pharmacokinetic Parameters

Sitagliptin Pharmacokinetic Parameter	**Adjusted Geometric Means**		**Ratio of Adjusted Geometric Means (Trt E / Trt D)**	
	Trt D	**Trt E**	**Point Estimate**	**90% CI**
Cmax (ng/mL)	288	255	0.887	(0.807, 0.974)
AUC(INF) (ng·h/mL)	3388	3429	1.012	(0.985, 1.040)
AUC(0-T) (ng·h/mL)	3335	3369	1.010	(0.983, 1.038)

CI = confidence interval; Trt = treatment
Treatments: D = sitagliptin 100 mg
E = dapagliflozin 20 mg + sitagliptin 100 mg

CONCLUSIONS:

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

DATE OF REPORT: 17-Mar-2010