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 MB102059

TITLE OF STUDY: Study of the Absolute Oral Bioavailability of Dapagliflozin in Healthy Subjects

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 07-Jul-2009 **CLINICAL PHASE:** 1
Study Completion Date: 24-Aug-2009

OBJECTIVES:

Primary Objective: To assess the absolute oral bioavailability (BA) of dapagliflozin oral dose form in healthy subjects.

Secondary Objective: To assess the safety and tolerability of dapagliflozin following single oral and intravenous (IV) administration to healthy subjects.

METHODOLOGY:

This was an open-label study in 7 healthy male subjects, who were required to be between 18-45 years of age to participate in the study. Subjects underwent screening evaluations to determine eligibility within 21 days prior to administration of study medication. Subjects who met all the inclusion criteria on Day -1 were admitted to the clinical facility. Study medication was administered in the morning of Day 1 under fasting conditions. Subjects received a 10 mg oral dose of dapagliflozin first followed on hour later by an 80 μg dose of [^{14}C]-dapagliflozin infused intravenously over a 1 minute period. The IV dose was administered into one arm and the other arm was used for pharmacokinetic (PK) sampling and clinical laboratory blood draws. PK samples were collected at selected time points up to 49 hours post oral dose. Subjects were closely monitored for adverse events (AEs) throughout the study. Safety was assessed by monitoring vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests. Subjects were discharged on Day 3 of the study.

NUMBER OF SUBJECTS (Planned and Analyzed): Seven (7) subjects were planned, enrolled and completed the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male subjects (18-45 years of age) with a body mass index (BMI) between 18 and 32 kg/m^2, who were healthy as determined 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: Each subject received a 10 mg oral dose of dapagliflozin first followed one hour later by an 80 μg dose of [^{14}C]-dapagliflozin infused intravenously over a 1 minute period. Dapagliflozin was provided by Bristol-Myers Squibb (BMS) as follows:

- 10-mg film coated tablets (Phase 3 tablet) - [redacted]
- 0.25 mg/mL solution for IV injection - [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable.

CRITERIA FOR EVALUATION:

Pharmacokinetics: Single-dose pharmacokinetic parameters (Cmax, Tmax, AUC(INF), AUC(0-T), T-HALF, CL [IV route only], V_{ss} [IV route only] and F [oral route only]) were derived from plasma concentration versus time data.

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

STATISTICAL CONSIDERATIONS:

Sample Size Determination: Although the sample size was not based on statistical power considerations, data from 6 subjects would provide at least 90% confidence that the estimated geometric mean of the absolute BA of dapagliflozin (F) would be within 10% of the true value.

To allow for dropouts, 7 subjects were dosed on Day 1.

Statistical Analysis:

Pharmacokinetics: To assess absolute BA of dapagliflozin from an oral dose form in healthy subjects, point estimates and 90% confidence interval (CI) for the geometric mean of dapagliflozin F was calculated with Student's t distribution.

A priori, the variable F was log-transformed. The point estimate and 90% CI for F on the log scale was exponentiated to obtain the point estimate and 90% CI for the geometric mean of F on the original scale.

Summary statistics were provided by route of administration for all of the pharmacokinetic parameters of dapagliflozin. Geometric means and coefficients of variation were reported for Cmax, AUC(INF), AUC(0-T), CL and F. Medians, minima, and maxima were reported for Tmax. Means and standard deviations were reported for T-HALF and Vss.

Safety: All recorded AEs were listed and tabulated by system organ class, preferred term and group. Vital signs and clinical laboratory test results were listed and summarized by group and study day. 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:

A total of 7 subjects were administered study drug and completed the study. All subjects were Caucasian males with a mean age of 26 years and a mean BMI of 24.3 kg/m^2 at screening. (Tables 1 and 2)

Table 1: Demographic Characteristics Summary

	All Subjects N=7
Age (yrs)	
N	7
Mean	26
Standard Deviation	11
Median	21
Min-Max	18-45
Q1-Q3	19-38
Age Category n(%)	
< 65 years	7(100)
>= 65 years	0
Not Reported	0
Gender n(%)	
Male	7(100)
Female	0
Not Reported	0
Race n(%)	
Caucasian	7(100)
Black	0
Asian	0
Other	0
Not Reported	0
Ethnicity n(%)	
Hispanic/Latino	0
Not Hispanic/Latino	7(100)
Not Reported	0

Table 2: Physical Measurements Summary

	All Subjects N=7
Weight (kg)	
N	7
Mean	82.1
Standard Deviation	10.9
Median	79.4
Min-Max	71.7-101.9
Q1-Q3	73.6-89.5
Height (cm)	
N	7
Mean	184.1
Standard Deviation	5.5
Median	183.4
Min-Max	179.3-195.1
Q1-Q3	179.4-186.3
BMI (kg/m2)	
N	7
Mean	24.3
Standard Deviation	3.8
Median	22.9
Min-Max	19.4-29.9
Q1-Q3	21.9-27.8

Safety Results:

Administration of a single 80-µg IV dose of [^{14}C]-dapagliflozin and a 10-mg oral dose of dapagliflozin, was safe and generally well-tolerated by the healthy subjects in this study.

There were no deaths, serious AEs (SAEs) or AEs that led to discontinuation (Table 3). Six (6) AEs occurred in 3 subjects, of which 1 AE of epistaxis was considered related to the study medication. The AE began on Day 1 of the study, was considered mild in intensity and resolved without treatment. Six (6) laboratory marked abnormalities (MAs) occurred in 6 subjects, all MAs were elevation of urine glucose. This finding is consistent with the pharmacologic activity of dapagliflozin as an inhibitor of urinary glucose reabsorption. None of the MAs in this study were considered AEs. There were no clinically-important ECG findings, vital sign measurements or physical examination findings.

Table 3: Adverse Event Summary

	Number (%) of Subjects
Adverse event(s)	3 (42.9)
Death	0
Serious adverse event	0
Discontinuation due to adverse event	0

Pharmacokinetic Results:

PK parameters for dapagliflozin are summarized in Table 4.

Table 4: Summary Statistics for Dapagliflozin Pharmacokinetic Parameters

Trt	Dapagliflozin Pharmacokinetic Parameters							
	AUC(INF) (ng.h/mL) Geom. Mean (C.V.%)	AUC(0-T) (ng.h/mL) Geom. Mean (C.V.%)	Cmax (ng/mL) Geom. Mean (C.V.%)	T-HALF (h) Mean (s.d.)	Tmax (h) Median (Min, Max)	CL (mL/min) Geom. Mean (C.V.%)	Vss (L) Mean (s.d.)	F (%) Geom. Mean (C.V.%)
A (n=7)	628 (17)	598 (17)	143 (29)	13.7 (3.44)	1.03 (0.50, 1.50)	NA	NA	77.8 (9)
B (n=7)	6.78 (22)	6.43 (23)	10.2 (49)	12.2 (5.25)	0.03 (0.03, 0.08)	207 (23)	118 (31.6)	NA

Trt: A = dapagliflozin 10 mg po dose
B = [^{14}C]-dapagliflozin 80µg iv dose
Note: NA = not applicable

Details of the statistical analyses on F values for dapagliflozin are summarized in Table 5.

Table 5: Statistical Analyses for Dapagliflozin Absolute Oral Bioavailability

	Geometric Mean	
	Point Estimate	**90% CI**
F (%)	77.8	(73.2, 82.8)

CONCLUSIONS:

[redacted]

DATE OF REPORT: 29-Oct-2010