SYNOPSIS

Final Synoptic Clinical Study Report for Study MB102016

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

PURPOSE: The purpose of this study was to evaluate the pharmacokinetic (PK) interaction between dapagliflozin and glimepiride when co-administered to healthy subjects. It was anticipated that the PK of dapagliflozin and glimepiride co-administered would not be substantially different compared to each agent administered alone. Bristol-Myers Squibb terminated the study prior to its completion because of dosing errors and frequent subject discontinuations for mild hepatic transaminase elevations.

METHODOLOGY: This was a Phase 1, open-label, randomized, 3-period, 3-treatment, crossover study balanced for carryover effects in healthy subjects. On Day 1 of Period 1, each subject was randomized to 1 of the 6 possible treatment sequences. The 3 treatments in this study were:

- Treatment A: dapagliflozin 20 mg
- Treatment B: glimepiride 4 mg
- Treatment C: dapagliflozin 20 mg + glimepiride 4 mg

All study treatments were administered following an overnight fast of at least 10 hours. Treatments were administered with 240 mL of a 20% glucose solution in water.

NUMBER OF SUBJECTS: For statistical purposes, 18 subjects were planned for analysis. Overall, 33 subjects were screened and enrolled. Eleven (11) subjects were randomized.

DISPOSITION, DEMOGRAPHICS, AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Table 1 summarizes subject disposition.

Table 1: Subject Disposition

	Number of Subjects
Enrolled	33
Treated	11
Completed	3
Randomized Subjects Who Discontinued	8
Adverse event	6
Poor/Non-compliance[a]	2

[a] Dosing error (both subjects received dapagliflozin 10 mg instead of 20 mg)

Table 2 shows baseline and demographic characteristics of the 11 randomized subjects.

Table 2: Baseline and Demographic Characteristics

	Randomized Subjects N = 11
Age (yrs)	
Mean (SD)	31 (6)
Median	31
Range	22 - 39
Gender, n (%)	
Male	9 (82)
Female	2 (18)
Race, n (%)	
White	11 (100)
Body Mass Index (kg/m^2)	
Mean (SD)	24.9 (4.3)
Median	25.1
Range	18.3 - 31.7

SD = standard deviation

SUMMARY OF SAFETY RESULTS: An adverse event (AE) summary is shown in Table 3. There were no deaths or serious adverse events (SAEs) reported in this study. Six (6) treated subjects were discontinued from the study: 3 due to isolated elevations of alanine aminotransferase (ALT) and 3 due to elevations of both ALT and aspartate aminotransferase (AST). All AEs of hepatic transaminase elevations were mild in intensity, and all resolved except for 1 subject who was lost to follow-up. All elevations for ALT were < 3.2x the upper limit of normal (ULN), and all elevations for AST were < 1.5xULN.

Overall, a total of 24 treatment-emergent AEs were reported in 8 of the 11 subjects (72.7%) during treatment with dapagliflozin or the combination of dapagliflozin and glimepiride. The treatment-emergent AEs reported in the greatest proportion of subjects during treatment with dapagliflozin or the combination of dapagliflozin and glimepiride were increased ALT (6 subjects, 54.5%), dyspepsia (3 subjects, 27.3%), and contact dermatitis (3 subjects, 27.3%). During treatment with glimepiride alone, 3 subjects (60.0%) had a total of 5 treatment-emergent AEs, none of which occurred in more than a single subject. All AEs were of mild or moderate intensity.

Table 3: Adverse Event Summary

	Number (%) of Subjects				
	TRT A N = 8	**TRT B N = 5**	**TRT C N = 7**	**Any Dapagliflozin N = 11**	**All Subjects N = 11**
Adverse Event(s)	6 (75.0)	3 (60.0)	4 (57.1)	8 (72.7)	9 (81.8)
Death	0	0	0	0	0
Serious Adverse Event(s)	0	0	0	0	0
Discontinuation Due to Adverse Event(s)	4 (50.0)	0	2 (28.6)	6 (54.5)	6 (54.5)

TRT A = dapagliflozin 20 mg; TRT B = glimepiride 4 mg; TRT C = dapagliflozin 20 mg + glimepiride 4 mg

Marked laboratory abnormalities were reported for ALT (7 subjects, 63.6%), AST (4 subjects, 36.4%), urine glucose (3 subjects, 27.3%), and absolute eosinophils (1 subject, 9.1%) during treatment with dapagliflozin or the combination of dapagliflozin and glimepiride, and a marked laboratory abnormality of blood in the urine was reported for 1 subject (20.0%) during treatment with glimepiride alone. Except for 1 subject who was lost to follow-up, all subjects were followed until their abnormal laboratory levels normalized. The subject lost to follow-up showed improvement in the abnormal laboratory value at the last evaluation.

There was no evidence that dapagliflozin had any clinically relevant effects on electrocardiogram parameters, systolic and diastolic blood pressures, heart rate, respiration, or body temperature.

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