## 2. SYNOPSIS

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| **Name of Sponsor/Company**:<br><br>Bristol-Myers Squibb | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume**: | **(For National Authority Use Only)** |
| **Name of Finished Product**:<br><br>Dapagliflozin tablets | | |
| **Name of Active Ingredient**:<br><br>10-mg dapagliflozin | **Page**: | |

**Title of study**: Effect of Rifampin on the Pharmacokinetics of Dapagliflozin in Healthy Subjects

**Investigator**: [redacted]

**Study site**: [redacted]

**Publication (reference)**: None

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| **Studied period (years)**: 07 April 2010 to 20 April 2010 | **Phase of development**: 1 |

**Objectives**: The primary objective was to assess the effects of rifampin on the pharmacokinetics of dapagliflozin.

Secondary objectives were:

- To assess the safety and tolerability of dapagliflozin and rifampin administered alone and in combination.
- To characterize the pharmacokinetics of BMS-801576 (M15, hereafter referred to as dapagliflozin 3-O-glucuronide), the pharmacologically inactive metabolite of dapagliflozin, with and without 600 mg once-daily (QD) rifampin.
- To assess the effect of dapagliflozin plus rifampin combination on glucose excretion compared with dapagliflozin alone.

**Methodology**: This was an open-label, nonrandomized, single-sequence study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days before Day 1. On Day 1, subjects were admitted to the clinical facility and confined for 13 days. A total of 14 subjects who met all of the inclusion and none of the exclusion criteria received the following treatments sequentially under fasted conditions:

- Treatment A: dapagliflozin 10 mg (1 × 10-mg tablet) as a single oral dose on Day 1.
- Treatment B: rifampin 600 mg (2 × 300-mg capsules) QD on Days 4 through 8.

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- Treatment C: dapagliflozin 10 mg (1 × 10-mg tablet) as a single oral dose administered concomitantly with rifampin 600 mg (2 × 300-mg capsules) QD on Day 9. Rifampin 600 mg (2 × 300-mg capsules) QD was administered on Days 10 and 11.

There was a 3-day washout period between Treatment A and Treatment B.

Blood and urine samples were collected for pharmacokinetic (PK) analysis of dapagliflozin and metabolite dapagliflozin 3-O-glucuronide (M15) up to 60 hours after dosing on Days 1 and 9. Urine samples were collected for 24-hour glucose and creatinine excretion up to 24 hours after dosing on Days 1 and 9. Subjects were closely monitored for adverse events (AEs) throughout the study, and clinical laboratory evaluations, vital sign measurements, physical examinations, and 12-lead electrocardiograms (ECG) were performed at selected times throughout the study. Subjects were discharged from the clinical facility on Day 12 after the evaluations were completed.

**Number of subjects (planned and analyzed)**: A total of 14 subjects were planned and completed the study. All 14 subjects were included in the PK, PD, and safety analyses.

**Diagnosis and main criteria for inclusion**: Healthy male and female subjects as determined by medical history, clinical laboratory tests, 12-lead ECG, and physical examination were eligible to participate in the study. Subjects were 18 to 45 years of age, inclusive, with a body mass index of 18 to 32 $kg/m^2$, inclusive. Female subjects were documented as postmenopausal or surgically sterile; females of childbearing potential were excluded from study participation. All women had a negative serum or urine pregnancy test within 24 hours before dosing.

**Test product, dose and mode of administration, lot number**: Dapagliflozin 10-mg tablet, single dose administered orally, [redacted]

**Duration of treatment**: The duration of treatment for each subject was approximately 11 days with a 3-day washout between treatment with dapagliflozin (Day 1) and treatment with rifampin (Days 4-8). The duration of participation for each subject, including Screening, was approximately 33 days.

**Reference therapy, dose and mode of administration, lot number**: Rifampin 300-mg capsules, QD (2 × 300-mg capsules) administered orally, [redacted]

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**Criteria for evaluation**:

Pharmacokinetics and Pharmacodynamics: Blood samples for the determination of plasma concentrations of dapagliflozin and its metabolite dapagliflozin 3-O-glucuronide were collected before dosing and at 0.5, 0.75, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, and 60 hours after dosing on Days 1 and 9. On Days 1 and 9, urine samples were collected at the following intervals after dosing: 0 to 24, 24 to 48, and 48 to 60 hours. On Days 1 and 9, urine was also collected from 0 to 24 hours to determine the amount of glucose and creatinine excreted. The following PK parameters were calculated:

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| $AUC_{0-t}$ | area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration |
| $AUC_{0-inf}$ | area under the plasma concentration versus time curve from time 0 extrapolated to infinity |
| $C_{max}$ | maximum observed plasma concentration |
| $T_{max}$ | time to achieve maximum plasma concentration |
| $t_{1/2}$ | terminal half-life |
| CLT/F | apparent total body clearance (only for dapagliflozin) |
| $Ae_{0-60}$ | cumulative amount excreted in urine from 0 to 60 hours |
| %UR | percent urine excretion |
| $CL_r$ | renal clearance |
| AUCratio (M/P) | dapagliflozin 3-O-glucuronide-to-dapagliflozin ratio for $AUC_{0-t}$ and $AUC_{0-inf}$ |

Safety: Safety assessments included AEs, clinical laboratory test results, vital sign measurements, physical examination findings, and 12-lead ECG results.

**Statistical methods**:

Sample Size Determination: The sample size for this study was not based on statistical power considerations. However, data from 12 subjects provided at least 90% confidence that the point estimates for the Treatment C (with rifampin) to Treatment A (without rifampin) ratios of the geometric means for $C_{max}$ and $AUC_{0-inf}$ of dapagliflozin were within 15% and 7% of

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the true ratios of population geometric means for $C_{max}$ and $AUC_{0\text{-}inf}$, respectively. These calculations assumed that $C_{max}$ and $AUC_{0\text{-}inf}$ of dapagliflozin were log-normally distributed and that the intrasubject SDs of $\log(C_{max})$ and $\log(AUC_{0\text{-}inf})$ were no greater than 0.205 and 0.100, respectively, as reported in previous BMS studies.

Pharmacokinetics and Pharmacodynamics: To assess the effect of concomitant administration of rifampin on the pharmacokinetics of dapagliflozin, point estimates and 90% confidence intervals (CIs) were calculated for the Treatment C to Treatment A ratios of geometric means for $C_{max}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ of dapagliflozin. These estimates were constructed from the results of fitting the general linear mixed models for log-transformed data with treatment as a fixed effect and measurements within each subject as repeated measurements. Point estimates of the differences and their 90% CIs on the log scale were exponentiated to obtain estimates and CIs for ratios of geometric means in the original scale.

To assess the effect of dapagliflozin plus rifampin combination on glucose excretion compared with dapagliflozin alone, summary statistics were tabulated by treatment for the total amount of glucose excreted in urine over 24 hours after dosing (absolute and corrected for creatinine).

Safety: Subject disposition, demographics, and baseline characteristics were presented in data listings and summarized. All AE data were presented in data listings and summarized by system organ class, preferred term, and treatment. Vital sign measurements, clinical laboratory test results, and ECG findings were presented in data listings and summarized. Abnormal clinical laboratory results, marked abnormal vital sign measurements, and abnormal physical examination findings were listed.

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**SUMMARY – CONCLUSIONS**

Pharmacokinetics:

The following table summarizes the statistical analysis results of the effect of rifampin on dapagliflozin pharmacokinetics.

| Parameter (unit) | Treatment[a] | N | Geometric LS Mean | Ratio (%) of Geometric LS Means and 90% CI of the Ratio (C/A) |
|---|---|---|---|---|
| $AUC_{0-t}$ (ng·h/mL) | A | 14 | 528 | 77.59 (72.84, 82.64) |
| | C | 14 | 410 | |
| $AUC_{0-inf}$ (ng·h/mL) | A | 14 | 554 | 78.00 (73.13, 83.19) |
| | C | 14 | 432 | |
| $C_{max}$ (ng/mL) | A | 14 | 147 | 93.09 (77.94, 111.18) |
| | C | 14 | 136 | |

Abbreviations: CI, confidence interval; LS, least squares.
Note: A general linear mixed effects model on the natural logarithms of $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ was performed with treatments as fixed effects and measurements within subjects as repeated measurements.
[a] Treatment A dapagliflozin 10 mg single dose.
Treatment C dapagliflozin 10 mg single dose + rifampin 600 mg once daily.

The 90% CIs were not entirely contained within the 80% to 125% limits for $C_{max}$ and AUCs indicating that rifampin decreased the exposures of dapagliflozin when dapagliflozin was administered with rifampin following repeat administration of rifampin for 5 days. In the presence of rifampin, total exposure ($AUC_{0-inf}$) of dapagliflozin decreased by 22% compared with dapagliflozin alone. In the presence of rifampin, peak exposure ($C_{max}$) of dapagliflozin was 7% lower than dapagliflozin alone.

Median time to reach $C_{max}$ ($T_{max}$) for dapagliflozin occurred at 0.75 and 0.88 hours in the presence and absence of rifampin, respectively. Mean terminal half-life ($t_{1/2}$) of dapagliflozin was 11 to 13 hours with or without rifampin. Apparent total clearance (CLT/F) was slightly higher in the presence of rifampin than for dapagliflozin alone (geometric mean of 385 mL/min versus 301 mL/min).

Less than 2% of administered dapagliflozin was excreted unchanged in urine for both treatments. Renal clearance ($CL_r$) of dapagliflozin was unchanged in the presence of rifampin

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with a mean value of 4 mL/min for both treatments.

The geometric mean $C_{max}$ of dapagliflozin 3-O-glucuronide was 164 ng/mL when dapagliflozin was administered with rifampin compared with 160 ng/mL when dapagliflozin was administered alone. The geometric mean $AUC_{0\text{-}inf}$ of dapagliflozin 3-O-glucuronide was 557 ng·h/mL when dapagliflozin was administered with rifampin (12% decrease) compared with 635 ng·h/mL when dapagliflozin was administered alone.

Median $T_{max}$ for dapagliflozin 3-O-glucuronide occurred at 1.50 hours and was unchanged in the presence of rifampin. In the presence and absence of rifampin, mean $t_{1/2}$ was comparable with an arithmetic mean value of approximately 3 hours.

Approximately 69% of administered dapagliflozin was excreted as dapagliflozin 3-O-glucuronide in urine when dapagliflozin was administered alone compared with approximately 50% when administered with rifampin. There was a 10% decrease in 24-hour glucose excretion in urine when dapagliflozin was administered with rifampin (45395 mg versus 50567 mg with and without rifampin, respectively).

The dapagliflozin 3-O-glucuronide-to-dapagliflozin $AUC_{0\text{-}inf}$ ratio was slightly higher in the presence of rifampin with an arithmetic mean value of 0.91 compared with 0.80 in the absence of rifampin.

There was a 10% decrease in 24-hour glucose excretion in urine when dapagliflozin was administered with rifampin.

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Safety:

Subject disposition is summarized in the following table:

| **No. of subjects (%)** | **Overall (N=27)** |
|---|---|
| Enrolled | 27 |
| Screening failure[a] | 13 (48.1) |
| Dosed[a] | 14 (51.9) |
| Safety population[b] | 14 (100.0) |
| Pharmacokinetic population[b] | 14 (100.0) |
| Pharmacodynamic population[b] | 14 (100.0) |
| Completed[b] | 14 (100.0) |

Note: Enrolled subjects included all subjects who signed the informed consent form.

The safety population included all subjects who received any study drug (dapagliflozin or rifampin). The pharmacokinetic population included all subjects who received dapagliflozin and had adequate pharmacokinetic profiles. The pharmacodynamic population included all subjects who received dapagliflozin and had complete urine collection.

[a] Percentages were based on the overall number of enrolled subjects.

[b] Percentages were based on the overall number of dosed subjects.

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Subject demographics and baseline characteristics are summarized in the following table:

| | **Overall (N=14)** |
|---|---|
| Age (years) | |
| Mean (SD) | 31.8 (6.41) |
| Median | 31.0 |
| Minimum, Maximum | 25, 45 |
| Sex, No. (%) | |
| Male | 13 (92.9) |
| Female | 1 (7.1) |
| Race, No. (%) | |
| White | 12 (85.7) |
| Black or African American | 2 (14.3) |
| Ethnicity, No. (%) | |
| Hispanic or Latino | 5 (35.7) |
| Not Hispanic or Latino | 9 (64.3) |
| Height (cm) | |
| Mean (SD) | 173.76 (8.801) |
| Median | 173.65 |
| Minimum, Maximum | 154.7, 188.3 |
| Weight (kg) | |
| Mean (SD) | 78.21 (13.588) |
| Median | 78.75 |
| Minimum, Maximum | 60.6, 102.1 |
| Body mass index ($kg/m^2$) | |
| Mean (SD) | 25.84 (3.523) |
| Median | 26.60 |
| Minimum, Maximum | 20.6, 30.3 |

Note: Percentages were calculated based on the overall number of subjects in the safety population.

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Overall AEs are summarized in the following table:

| | **Treatment[a]** | | | |
|---|---|---|---|---|
| **No. of subjects (%)** | **Single Dose 10-mg Dapagliflozin (N=14)** | **600-mg Rifampin QD (N=14)** | **Single Dose 10-mg Dapagliflozin + 600-mg Rifampin QD (N=14)** | **Overall (N=14)** |
| Total number of AEs | 11 | 4 | 1 | 16 |
| Number of subjects with at least 1 AE | 7 (50.0) | 4 (28.6) | 1 (7.1) | 10 (71.4) |

Abbreviations: AE, adverse event, QD, once daily.
Note: At each level of subject summarization, a subject was counted once if he or she reported 1 or more events. Adverse events were summarized by treatment at onset of the event and were coded using the Medical Dictionary for Regulatory Activities Version 12.1. Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.
[a] Dapagliflozin was administered as a single 10 mg dose and rifampin was administered at 600 mg QD.

There were no deaths, SAEs, or AEs that led to study drug discontinuation. Overall, 10 subjects (71.4%) reported 16 AEs during the study, all of which resolved spontaneously by the end of the study. Fifty percent of subjects reported 11 AEs after receiving dapagliflozin alone, all of which were deemed not related to study medication. Four AEs were reported after rifampin alone, and 1 AE was reported after administration of dapagliflozin with rifampin. The only AEs reported by more than 1 subject were nasopharyngitis (4 subjects; 28.6%) and chromaturia (3 subjects, 21.4%). Nasopharyngitis was reported by 3 subjects (21.4%) after receiving dapagliflozin alone and 1 subject (7.1%) after receiving rifampin alone and was deemed not related to study medication. Chromaturia was reported by 3 subjects (21.4%) after receiving rifampin alone and was the only AE reported that was considered related to study drug. All AEs were mild in intensity with the exception of influenza-like illness of moderate intensity reported by 1 subject. No treatment-related trends were observed in clinical laboratory results, vital sign measurements, physical examination findings, or 12-lead ECG results.

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**CONCLUSIONS:**

[redacted]

**Date of report:** 27 October 2010 (Version 5.0)