Name of Sponsor/Company: Bristol-Myers K.K.	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Not known		
Name of Active Ingredient: Dapagliflozin (r-INN)		

SYNOPSIS

Clinical Study Report for Study MB102025

TITLE OF STUDY: A Placebo-Controlled, Ascending Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Dapagliflozin in Type 2 Diabetic Japanese Subjects

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted], Osaka, JAPAN

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 06-Nov-2007 **CLINICAL PHASE:** 1

Study Completion Date: 10-May-2008

OBJECTIVES:

Primary Objective:

To assess the safety and tolerability of multiple oral doses of dapagliflozin administered in Type 2 diabetic Japanese subjects following a 14-day dosing.

Secondary Objectives:

To assess the pharmacokinetics of dapagliflozin and its major metabolite, BMS-801576, in Type 2 diabetic Japanese subjects following a 14-day dosing;

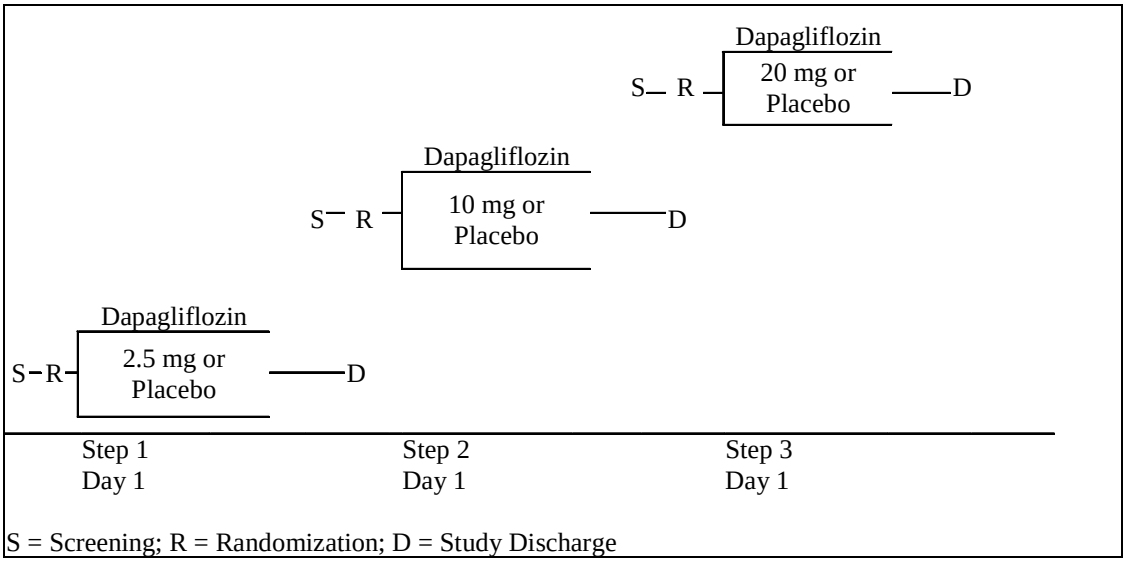
To assess the pharmacodynamic effect of multiple doses of dapagliflozin on fasting and post-prandial serum glucose, serum insulin, serum C-peptide, urinary glucose and calcium excretion;

To assess the effect of multiple doses of dapagliflozin on the following urine safety markers: calcium, magnesium, sodium, potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, deoxypyridinoline (D-pyr) cross-links, C-telopetide (CTX), N-aceyl-β-D-glucosaminidase (NAG), and β2-microglobulin (β2-MG);

To assess the effect of multiple doses of dapagliflozin on the percent inhibition of renal glucose resorption; and

To assess the effect of multiple doses of dapagliflozin and its major metabolite, BMS-801576, on the QTc interval.

METHODOLOGY:



This was a randomized, placebo-controlled, double-blind, sequential, ascending, multiple-dose study. In each of 3 sequential dose steps (2.5 mg, 10 mg or 20 mg dapagliflozin or placebo), 12 subjects were assigned to receive either multiple oral doses of dapagliflozin (n=9) or placebo (n=3).

Subjects were admitted to the study site on Day -3 and randomized on Day 1. Subjects received either dapagliflozin or placebo on Day 1 and continued to receive the same dose once-daily up to Day 14. Subjects were released from the study site on Day 2. They visited the study site on Day 7 for designated examinations, and were admitted again on Day 12 and released on Day 15. Final visit for study discharge took place on Day 21.

Study drug administration for the next dose level was only initiated after safety data through the follow-up evaluation on Day 15 for at least 9 subjects of the current dose level were reviewed by the Principal Investigator and the Sponsor, and evaluated to be safe and tolerable. Then the succeeding group of 12 subjects received the next dose of dapagliflozin (n=9) or placebo (n=3). There was no intra-subject dose escalation.

NUMBER OF SUBJECTS (Planned and Analyzed):

Planned: Twelve (12) for each dose step: dapagliflozin (n=9) and placebo (n=3), total of 36 subjects

Treated: Twelve (12) for each dose step: dapagliflozin (n=9) and placebo (n=3), total of 36 subjects

Analyzed: Thirty-six (36) for safety and pharmacodynamic analyses, 27 for pharmacokinetic analysis

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

1. Signed written informed consent

   a) Signed written informed consent

2. Target population

   b) Established diagnosis of Type 2 diabetes mellitus (T2DM)

   c) Body Mass Index (BMI) < 32 kg/m^2, weight ≥ 50 kg for male and ≥ 40 kg for female subjects
   BMI=weight (kg)/[height (m)]^2

   d) Fasting glucose ≤ 240 mg/dL

   e) HbA1c within the range of 6.0% to 10.0%, inclusive

   f) Serum creatinine ≤ 1.5 mg/dL for male and ≤ 1.4 mg/dL for female subjects

   g) Urine protein ≤ 2+ on dipstick at routine clinical laboratory tests

   h) ALT ≤ 1.5 × upper limit of normal (ULN) and serum bilirubin ≤ 2 × ULN

   i) Subjects are not treated with oral hypoglycemic drug, or
   Subjects who are treated with oral hypoglycemic drug can discontinue the treatment at least 2 weeks during the screening period and throughout the study, as permitted by the physician in charge

3. Age and sex

   j) Males and females, aged between 20 and 70 years, inclusive

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Product	Potency and Description	Batch Number
Dapagliflozin 2.5 mg tablet	Green, diamond-shaped, film-coated tablet containing 2.5 mg dapagliflozin	[redacted]
Dapagliflozin 10 mg tablet	Green, diamond-shaped, film-coated tablet containing 10 mg dapagliflozin	[redacted]
Placebo matching 2.5 mg tablet	Green, diamond-shaped, film-coated tablet	[redacted]
Placebo matching 10 mg tablet	Green, diamond-shaped, film-coated tablet	[redacted]

Subjects received multiple oral doses of one tablet of dapagliflozin 2.5 mg or matching placebo in Step 1, one tablet of dapagliflozin 10 mg or matching placebo in Step 2, or 2 tablets of dapagliflozin 10 mg or matching placebo in Step 3, with 150 mL of water once daily around 9AM for 14 days.

CRITERIA FOR EVALUATION:

Safety: Primary safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, 12-lead ECGs, physical examinations, and clinical laboratory tests. The effect on QTc intervals was also assessed. The incidences of AEs were reviewed for potential significance and clinical importance. The following urine safety markers were assessed: calcium, magnesium, sodium,

potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, D-pyr cross-links, CTX, NAG, and β2-MG.

Pharmacokinetics: Multiple-dose pharmacokinetic parameters (Cmax, Tmax, AUC(TAU), T-HALF, %UR, AI and CLR) of dapagliflozin and its major metabolite BMS-801576, were derived from plasma concentration-time data and urinary excretion data, and summarized by dose. The molar AUC(TAU) ratio (MR) of BMS-801576 to dapagliflozin was also calculated.

Pharmacodynamics: Fasting and post-prandial serum glucose, serum insulin, serum C-peptide, urinary glucose excretion, and the percent inhibition of renal glucose resorption were assessed.

STATISTICAL CONSIDERATIONS:

Safety: All recorded AEs were summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) and treatment. Summary statistics were provided for vital signs and clinical laboratory test results. ECG parameters and their changes from baseline were summarized by treatment. For each urine safety marker, summary statistics were provided for the total amount excreted in urine over 24 hours (absolute and corrected for creatinine), and for the changes from baseline, by treatment and study day. For each serum marker, summary statistics were provided for the serum concentrations and for the changes from baseline, by treatment and study day.

Pharmacokinetics: Summary statistics were provided for the pharmacokinetic parameters for dapagliflozin and BMS-801576 by dose and study day. To assess the dependency on dose, scatter plots of Cmax and AUC(TAU) were provided versus doses by subject, study day and dose.

Pharmacodynamics: Summary statistics were provided for the total amount of glucose excreted in urine over 24 hours (absolute and corrected for creatinine), and for the changes from baseline, by treatment and study day. The means for the total amount of glucose excreted in urine over 24 hours (absolute and corrected for creatinine) were plotted versus study day by treatment. Summary statistics were also provided for the rate of glucose excretion over each collection interval, by treatment and study day. The means for the rate of glucose excretion over each collection interval were plotted versus midpoint of each collection interval, by treatment and study day.

Serum glucose and serum insulin AUC values over 4 hours following Oral Glucose Tolerance Test (OGTT) were summarized by treatment and study day.

Summary statistics were provided for the total amount of calcium excreted in urine over 24 hours (absolute and corrected for creatinine), and for the changes from baseline, by treatment and study day. The means for the changes from baseline in the total amount of calcium excreted in urine over 24 hours (absolute and corrected for creatinine) were plotted versus study day by treatment.

Summary statistics were provided for the percent inhibition of renal glucose resorption over each collection interval, by treatment and study day. The means for the percent inhibition of renal glucose resorption over each collection interval were plotted versus study day by treatment.

SUMMARY OF RESULTS:

Demographics, and Other Subject Baseline Characteristics:

Subject disposition is summarized in Table 5.1 and in Appendix 2.1B. Within each dose step, 12 subjects were randomized to receive either dapagliflozin (9 subjects) or placebo (3 subjects). No subjects discontinued the study prematurely and all 36 subjects completed the study.

Safety Results:

Seven (7) of 9 subjects (77.8%) experienced 10 AEs following the dose of dapagliflozin 2.5 mg, 3 of 9 subjects (33.3%) experienced 3 AEs following the dose of 10 mg, 4 of 9 subjects (44.4%) experienced 6 AEs following the dose of 20 mg, and 2 of 9 subjects (22.2%) experienced 3 AEs following the dose of placebo.

Out of 22 AEs reported, 8 events were considered to be adverse reactions of dapagliflozin. These were "Protein urine present" observed in 2 subjects each receiving 2.5 mg and 20 mg, "Thirst" and "Pollakiuria" in one subject each receiving 2.5 mg, "Nocturia" and "Blood alkaline phosphatase increased" in one subject each receiving 10 mg. None of the subjects experienced prolonged QTc or any other abnormalities related to 12-lead ECG.

The linear regression of QTc changes from baseline on dapagliflozin and BMS-801576 plasma concentrations suggests that dapagliflozin and BMS-801576 have no concentration-related effect on QTc changes from baseline.

There were no serious AEs or AEs leading to discontinuation.

Pharmacokinetic Results:

When dapagliflozin doses increased in a ratio of 1:4:8 (2.5, 10, and 20 mg), dapagliflozin Cmax increased in the ratios of 1:4:7 on Day 1 and 1:4:6 on Day 14 while dapagliflozin AUC(TAU) increased in the ratio of 1:5:8 on Day 1 and Day 14.

For BMS-801576 (glucuronide conjugate of dapagliflozin), Cmax and AUC(TAU) increased equal to the ratio of dapagliflozin dose increase (1:4:8) on both Day 1 and Day 14 except for the Cmax on Day 14 which increased in a ratio of 1:3:7.

Accumulation Index was around 1.2 to 1.3 for dapagliflozin and 1.1 for BMS-801576.

Less than 2% of the administered dose was recovered as dapagliflozin intact in the urine. Urinary clearance of dapagliflozin was approximately 4.3 mL/min, ranged from 3.8 to 5.1 mL/min for three dose groups.

More than 80% of the administered dose was recovered in the urine as the glucuronide of dapagliflozin, BMS-801576. Urinary clearance of BMS-801576 was greater than 130 mL/min for all dose groups.

Pharmacodynamic Results:

Dapagliflozin increased the amount of glucose excreted in urine. The rate of urinary glucose excretion was faster following dapagliflozin doses compared to placebo, and faster following 10 mg and 20 mg doses compared to 2.5 mg, whereas it was comparable between 10 mg and 20 mg.

Dapagliflozin increased the renal glucose clearance and percent inhibition of renal glucose resorption. Renal glucose clearance and percent inhibition of renal glucose were higher at 10 mg and 20 mg doses compared to 2.5 mg, whereas they were comparable between 10 mg and 20 mg.

Total amount of calcium excreted in urine slightly increased following all doses of dapagliflozin but no apparent dose-related changes were observed among the dapagliflozin doses.

Dapagliflozin decreased the AUC(0-4h) values of serum glucose and differences between Day -2 and Day 13 were statistical significant for dapagliflozin 10 mg and 20 mg dose groups. Dapagliflozin also decreased the AUC(0-4h) values of serum insulin and differences between Day -2 and Day 13 were statistical significant for all dapagliflozin dose groups.

CONCLUSIONS:

DATE OF REPORT: 28-Apr-2009 (Ver.1.0)