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

Clinical Study Report MB102008

TITLE OF STUDY: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-Group, Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-512148 as Monotherapy in Subjects With Type 2 Diabetes Mellitus Who Are Treatment Naive And Have Inadequate Glycemic Control on Diet and Exercise.

STUDY CENTERS: A total of [redacted] sites in United States, Puerto Rico, Canada, and Mexico.

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 14-Dec-2005

Date last subject completed: 27-Feb-2007

CLINICAL PHASE: 2b

OBJECTIVES: To compare the changes from baseline in hemoglobin A1C (A1C) achieved with each dose of BMS-512148 vs placebo after 12 weeks of double-blind therapy.

METHODOLOGY: Randomized, double-blind, seven-arm, parallel-group, placebo-controlled, multicenter trial.

NUMBER OF SUBJECTS: 440 subjects were enrolled; 389 subjects entered the double-blind period; 355 entered the follow-up period.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects with type 2 diabetes mellitus (T2DM), 18 to 79 years old inclusive, who had inadequate glycemic control defined as A1C $\geq$ 7.0% and $\leq$ 10.0% on diet and exercise alone. Subjects were not to have been treated with any antihyperglycemic agent or to have received treatment for diabetes for less than 30 days total since diagnosis and were to have been treated for $\leq$ 3 consecutive or $\leq$ 7 non-consecutive days in the 30 days prior to screening. Subjects must have had a body mass index $\leq$ 40 kg/m^2 and a fasting C-peptide > 1.0 ng/mL (0.33 nmol/L). Subjects could not have evidence of Chronic Renal Insufficiency (if male, S_{Cr} < 1.5 mg/dL [132.6 μmol/L]; if female, S_{Cr} <1.4 mg/dL [123.8 μmol/L]) and glomerular filtration rate (GFR) as calculated by the Modification in Diet and Renal disease (MDRD) study formula > 60 mL/min/1.73 m^2 or overt proteinuria (urine microalbumin/creatinine [S_{cr}] ratio $\geq$ 300 mg/g).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: BMS-512148 2.5 mg, BMS-512148 5.0 mg, BMS-512148 10.0 mg, BMS-512148 20.0 mg, BMS-512148 50.0 mg, oral, for the 12-week double-blind period. Batch numbers were:

Treatment Group[a]	Batch Numbers
Dapagliflozin 2.5 mg	[redacted]
Dapagliflozin 5 mg	[redacted]
Dapagliflozin 10 mg	[redacted]
Dapagliflozin 20 mg	[redacted]
Dapagliflozin 50 mg	[redacted]
Placebo	[redacted]
Metformin	[redacted]

[a] [redacted] was randomized to dapagliflozin 20 mg but initially received the wrong kit and was treated with 5 mg of dapagliflozin for a short time.

DURATION OF TREATMENT: The duration of treatment was 14 weeks: there was a 2-week lead-in phase followed by a 12-week double-blind treatment period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Matching placebo tablets for BMS-512148 2.5 mg, BMS-512148 5.0 mg, BMS-512148 10.0 mg, BMS-512148 20.0 mg, BMS-512148 50.0 mg, and matching placebo for metformin XR 750 mg/1500 mg, oral, for the 2-week lead-in phase and 12-week double-blind phase; metformin XR 750 mg/1500 mg for the 12-week double-blind phase.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy outcomes were evaluated using glycemic parameters including A1C, fasting plasma glucose (FPG), urine glucose, fructosamine, fasting and postprandial insulin and C-peptide, and post-prandial glucose and derived indices.

Safety: Safety outcomes were assessed by treatment-emergent adverse events, medical history, physical examinations, and laboratory measurements including 24-hour urine collections (urinary volume, electrolytes, and markers of bone metabolism).

STATISTICAL METHODS: The primary efficacy analysis compared the change in A1C from baseline to Week 12, or the last post-baseline measurement prior to Week 12, if no Week 12 assessment was available, for dapagliflozin 2.5-, 5- , 10- , 20- and 50-mg groups vs the placebo group. The analysis of the primary endpoint was based on an analysis of covariance (ANCOVA) model with treatment group as an effect and the baseline value as a covariate. The comparisons between each of the dapagliflozin treatment groups and placebo were performed at the nominal 0.012 level using Dunnett's adjustment so that the familywise type I error was controlled at the 5% significance level.

EFFICACY RESULTS: A statistically significant greater reduction in A1C from baseline to Week 12 was achieved for all dapagliflozin groups compared with placebo ($P < 0.008$ or less). The mean reduction in A1C from baseline at Week 12 was -0.71%, -0.72%, -0.85%, -0.55%, -0.90% for the 2.5-, 5-, 10-, 20-, and 50-mg dapagliflozin treatment groups, respectively, and -0.18% and -0.73% for the placebo and metformin groups, respectively. Although all dapagliflozin doses were effective at lowering A1C, no log-linear dose response relationship was demonstrated within the dose range (P value for trend = 0.4139). A statistically significant larger reduction from baseline at Week 12 in FPG was achieved in 4 dapagliflozin treatment groups compared with the placebo group ($P < 0.005$ or less for the comparisons between the 5-, 10-, 20-, and 50-mg dapagliflozin groups vs the placebo group), while the comparison between dapagliflozin 2.5 mg and placebo did not reach statistical significance because the p-value (0.0312) was greater than the Dunnett

adjusted significance level. The proportion of subjects achieving a therapeutic glycemic response, defined as A1C < 7% at Week 12 (LOCF) regardless of baseline A1C value, was higher in the dapagliflozin treatment groups compared with the placebo group. Statistical significance compared with placebo was achieved in the 50-mg dapagliflozin treatment group ($P < 0.01$). The change from baseline to Week 12 in 24-hour urinary glucose-creatinine ratio was statistically significantly higher in all dapagliflozin treatment groups compared with the placebo group ($P < 0.0001$). A reduction in change from baseline to Week 12 in postprandial glucose AUC was achieved in the dapagliflozin treatment groups compared with the placebo group. Body weight at Week 12 was reduced for all treatment groups; the percent reduction was numerically larger in the dapagliflozin-treated groups (-2.52% to -3.38%) than in the placebo group (-1.15%).

SAFETY RESULTS: In general, dapagliflozin was safe and well tolerated and no dose-relationship for adverse events was apparent. No death or related serious adverse event (SAE) occurred during the study. Five SAEs, considered unrelated to dapagliflozin by the investigator, were reported for 4/279 (1.4%) subjects in 4 dapagliflozin treatment groups. One hundred and seventy-seven subjects (63%) treated with dapagliflozin; 29 subjects (55%) treated with placebo; and 38 subjects (68%) treated with metformin reported at least 1 AE during the double-blind period. Among the 177 (63%) subjects treated with dapagliflozin for whom AEs were reported, AEs of urinary tract infection (UTI) were reported most frequently (21 subjects [7.5%]), followed by nausea (15 subjects [5.4%]), dizziness (14 subjects [5.0%]), and headache (13 subjects [4.7%]). There was no report of confirmed hypoglycemia (symptoms of hypoglycemia with fingerstick glucose ≤ 50 mg/dL). AEs reported during the double-blind period were considered by the investigator to be of mild intensity for 49.5% (138/279) and unrelated for 79.6% of the subjects in the dapagliflozin treatment groups. Among subjects treated with dapagliflozin, 8/279 subjects (2.9 %) were discontinued due to an AE; 1 subject (2.1%) in the 10-mg group was discontinued due to an SAE.

No event of kidney injury was reported. Serum creatinine concentrations were essentially unchanged from baseline in all dapagliflozin, placebo, and metformin treatment groups. An increase in urinary excretion of renal tubular markers n-acetyl glucosamine and alpha 1-microglobulin (NAG and A1M, respectively) was observed in subjects receiving dapagliflozin. No liver function safety signal was identified in conjunction with dapagliflozin treatment. Although marked laboratory abnormalities were reported in individual subjects, overall, no clinically relevant mean changes from baseline to Week 12 in serum sodium, chloride, bicarbonate, or potassium concentrations occurred in any treatment group. Increases of approximately 0.2 mEq/L in mean serum magnesium were seen with dapagliflozin treatment; these resolved during the follow-up period. Decreases of approximately 1 mg/dL in mean serum uric acid were seen with dapagliflozin treatment; these lessened during the follow-up period. Marked abnormalities for hyperphosphatemia were more frequent in the dapagliflozin 20 mg and 50 mg dose arms than placebo; however, this pattern did not hold when the MA criterion was replaced with a more clinically relevant criterion. The mean serum phosphate concentration increased by 0.1 mg/dL more than placebo in the 20-mg and 50-mg dapagliflozin treatment groups at Week 12; this change resolved during the follow-up period. Marked abnormalities for elevated hematocrit were more frequent in the dapagliflozin dose arms than placebo during the double-blind period; this improved in the follow-up period. There were dose-related increases from baseline in mean hematocrit of 1.5% to 2.9% in the dapagliflozin arms during the double-blind period; these lessened during the follow-up period. With respect to laboratory assessment of bone metabolism, serum 1,25-dihydroxy vitamin D and 25-hydroxy vitamin D values were unchanged. Increases in mean change from baseline in parathyroid hormone (PTH) concentrations that did not appear to be dose-related occurred in the dapagliflozin treatment groups. Mean change from baseline in serum osteocalcin concentrations also increased in the dapagliflozin treatment and placebo groups. Mean excretion at Week 12 of deoxypyridinoline (DPD) and C-terminal telopeptide of type I collagen (CTX) increased from baseline in dapagliflozin treatment groups. These increases in excretion of DPD and CTX were for the most part less after discontinuation of dapagliflozin. The clinical importance of the changes noted in serum chemistry parameters is unknown.

CONCLUSIONS: [redacted]

DATE OF REPORT: 06-Feb-2008