BMS-477118

Indication: Type 2 Diabetes Mellitus

Protocol No.: CV181008

Phase: 2

Study Initiation Date: 12-May-2003

Study Completion Date: 24-May-2004

Report Date: 20-Jul-2005

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF BMS-477118 AS MONOTHERAPY IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS WHO HAVE INADEQUATE GLYCEMIC CONTROL

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This study was conducted in accordance with Good Clinical Practice.

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SYNOPSIS

Clinical Study Report CV181008

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial to Evaluate the Safety and Efficacy of BMS-477118 as Monotherapy in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control

INVESTIGATORS: 154 investigators

STUDY CENTERS: 152 sites in the United States

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 12 May 2003
               Date last subject completed: 24 May 2004

CLINICAL PHASE: 2

OBJECTIVES:
The primary objective was to evaluate the positive efficacy trend among doses of BMS-477118 in subjects with type 2 diabetes mellitus by assessing the change from baseline in HbA$_1c$ following 12 weeks of double-blind treatment.

Other objectives were to evaluate the effect of BMS-477118 versus placebo on fasting HbA$_1c$, fructosamine, and lipid parameters; on fasting and postprandial glucose, insulin, C-peptide, and glucagon; and the effect on body weight, waist circumference, BMI, and vital signs.

METHODOLOGY: This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled trial of the antihyperglycemic activity of BMS-477118 in drug naïve subjects with type 2 diabetes who had inadequate glycemic control (defined as a screening HbA$_1c$ $\geq$ 6.8% and $\leq$ 9.7%) with diet and exercise. Following a 2-week dietary and placebo lead-in phase, subjects were randomized to once daily BMS-477118 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg, or placebo. An amendment to the protocol added 2 new dose arms, BMS-477118 100 mg and placebo. Subjects who completed the double-blind treatment period or who met pre-specified hyperglycemic rescue or discontinuation criteria continued into the 4-week follow-up treatment period. In the follow-up period, subjects were reassigned to either placebo, metformin or placebo plus metformin.

NUMBER OF SUBJECTS/PATIENTS: 457 subjects were enrolled in the study. Of these, 423 subjects were randomized; 338 subjects were randomized through the original protocol (0-40 mg cohort) and 85 subjects were randomized via Amendment 4 (0,100 mg cohort).
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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Men and women (non-nursing, non-pregnant) ≥ 21 and ≤ 70 years of age, with type 2 diabetes mellitus who were drug-naive and had a screening HbA1c ≥ 6.8% and ≤ 9.7% and C-peptide > 0.5 ng/mL.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
BMS-477118 gray, opaque, two-piece, hard gelatin capsules for oral administration once daily. Doses and batch numbers: 2.5 mg (2M51656), 5 mg (2M51831), 20 mg (N01191, 3A61720, 3C76496, 3J73684).

DURATION OF TREATMENT: 12 Weeks double-blind treatment for the 0-40 mg cohort and 6 weeks double-blind treatment for the 0, 100 mg cohort. The study also included a 2 week dietary and placebo lead-in phase and a 4 week follow-up period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Matching placebo capsules for BMS-477118 for oral administration (2H54279) once daily during the double-blind period. Metformin 500 mg (8MCM173) for oral administration during the follow-up period.

CRITERIA FOR EVALUATION:
Efficacy: The primary efficacy endpoint was to demonstrate a log linear trend in HbA1c reduction across the treatment groups at Week 12.

Other efficacy variables were related to changes in fasting HbA1c, fructosamine, lipid parameters; fasting and postprandial glucose, insulin, C-peptide and glucagon; and changes in body weight, waist circumference, BMI and vital signs.

Exploratory efficacy and pharmacodynamic variables that were assessed but not included in the protocol were plasma DPP-IV activity and GLP-1 concentration.

Safety: Safety outcome measures were evaluated by assessing adverse events and marked abnormalities in laboratory tests throughout the study.

STATISTICAL METHODS: The primary analysis was a test for log linear trend with respect to changes in HbA1c across the 5 BMS-477118 doses (2.5, 5, 10 20, and 40 mg) with placebo included in the model as a “zero dose”. The test was carried out using an orthogonal linear contrast (with coefficients 0, -2, -1, 0, 1, 2) within the framework of an analysis of covariance (ANCOVA) model, with randomization group as main effect and baseline value as covariate, using a significance level of \( \alpha = 0.05 \).

STUDY POPULATION: Drug naïve patients with type 2 diabetes mellitus who had inadequate glycemic control with diet and exercise. In the 0-40 mg cohort, a total of 338 subjects received at least one dose of double-blind treatment (271 subjects received active treatment and 67 subjects received placebo). These subjects comprised the population used in the primary analysis. In the 0, 100 mg cohort, 44 subjects received BMS-477118 100 mg and 41 subjects received placebo. The overall demographic and baseline characteristics profiles were similar in both cohorts.

EFFICACY RESULTS: The primary objective of this study was to evaluate the positive efficacy trend among doses of BMS-477118 in subjects with type 2 diabetes mellitus by assessing the change from baseline in HbA1c following 12 weeks of double-blind treatment. Similar reductions in HbA1c were seen in all active treatment groups, and the test for log linear trend across the treatment groups did not demonstrate a statistically significant dose-response relationship after 12 weeks of treatment.

The results of this phase 2 proof of concept study demonstrate that daily doses of 2.5, 5, 10, 20, 40 mg BMS-477118 for 12 weeks or 100 mg for 6 weeks effectively reduces: 
• HBA1c and fructosamine
• Fasting serum glucose
• Postprandial serum glucose AUC

No consistent discernible effects were observed on fasting insulin, glucagon, C-peptide, the insulinogenic index, the Matsuda index, or the insulin resistance index. Increases in postprandial insulin AUC and decreases in postprandial glucagon excursion was observed and the estimate of beta-cell function, using a homeostatic model assessment (HOMA), indicated improved beta-cell function following treatment with BMS-477118. A clear dose-response relationship was not observed for any of these efficacy variables.

Compared with baseline, DPP-IV activity was inhibited in all active treatment groups at the end of double-blind treatment, with larger reductions in DPP-IV at higher doses of BMS-477118. There was a greater change from baseline in GLP-1 concentration at 15 minutes after a MTT at the end of double-blind treatment in the active treatment groups compared with the placebo group.

Efficacy results for the 0-40 mg cohort are summarized in the following table.

### Efficacy Measures at the End of Double-Blind Treatment: 0–40 mg Cohort

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>BMS-477118</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Adjusted mean Δ HbA1c(%)</td>
<td>-0.27</td>
<td>-0.72</td>
</tr>
<tr>
<td>Placebo-subtracted adjusted mean Δ HbA1c (%)</td>
<td>-0.45</td>
<td>-0.63</td>
</tr>
<tr>
<td>Percent of subjects with glycemic response a (HbA1c &lt; 7%)</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Adjusted mean Δ fructosamine (µmol/L)</td>
<td>-9</td>
<td>-21</td>
</tr>
<tr>
<td>Adjusted mean Δ fasting serum glucose (mg/dL)</td>
<td>3</td>
<td>-11</td>
</tr>
<tr>
<td>Adjusted mean Δ serum glucose total AUC (0-60) (mg.min/dL)</td>
<td>174</td>
<td>-1121</td>
</tr>
<tr>
<td>Mean serum glucose concentration postprandial at 60 min (mg/dL)</td>
<td>212.3</td>
<td>186.9</td>
</tr>
<tr>
<td>Mean excursion serum glucose concentration postprandial at 60 min (mg/dL)</td>
<td>57.2</td>
<td>49.3</td>
</tr>
<tr>
<td>Adjusted mean Δ fasting insulin (µU/mL)</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Adjusted mean Δ insulin total AUC (0-60) (µU.min/mL)</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>Adjusted mean Δ fasting glucagon (pg/mL)</td>
<td>-7.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Adjusted mean Δ postprandial glucagon excursion at 30 min (pg/mL)</td>
<td>4.5</td>
<td>-6.0</td>
</tr>
<tr>
<td>Δ β cell function (HOMA, %β)</td>
<td>-1</td>
<td>24</td>
</tr>
<tr>
<td>Δ DPP-IV activity 60 min before MTT (IU)</td>
<td>-1.04</td>
<td>-7.17</td>
</tr>
<tr>
<td>Δ DPP-IV activity 60 min after MTT (IU)</td>
<td>-1.03</td>
<td>-11.22</td>
</tr>
<tr>
<td>GLP-1 concentration, fasting (pmol/L)</td>
<td>4.15</td>
<td>4.79</td>
</tr>
<tr>
<td>GLP-1 concentration 15min after MTT (pmol/L)</td>
<td>9.84</td>
<td>12.89</td>
</tr>
<tr>
<td>GLP-1 concentration 60 min after MTT (pmol/L)</td>
<td>5.52</td>
<td>9.18</td>
</tr>
</tbody>
</table>

a For subjects with baseline HbA1c ≥ 7.0%
Δ = change from baseline
Similar results were observed in the 0,100 mg cohort.

SAFETY RESULTS:

Adverse Events:

Adverse Events: In the 0-40 mg cohort, the proportion of subjects with AEs was similar across all the treatment arms and did not appear to be dose related. In the 0,100 mg cohort, AEs were reported in 66% of subjects in the BM477118 100-mg arm and in 59% of subjects in the placebo arm.

Headache was the most frequently occurring AE during double-blind treatment in both cohorts. In the 0-40 mg cohort, headache was reported in 33 of the 271 (12.2%) subjects randomized to any BMS-477118 treatment arm versus 6 subjects (9.0%) in the placebo treatment arm. Headache did not appear to be dose related. In the 0, 100 mg cohort, headache was reported more frequently in the BMS-477118 treatment group (11.4%) versus placebo (4.9%).

Other than headache, there was no apparent increase in neurological or psychiatric AEs in either cohort. The rate of gastrointestinal AEs was comparable across the active and placebo treatment groups in both cohorts.

There were no confirmed cases of hypoglycemia at the 2.5-, 5-, 10-, 20-, or 40-mg doses. Only 2 cases of confirmed hypoglycemia (defined as symptoms of hypoglycemia in the setting of a fingerstick glucose of ≤50 mg/dL) were reported in the 100 mg dose group.

Serious Adverse Events: No deaths were reported during the study. No SAEs were reported in the 0, 100 mg cohort. In the 0-40 mg cohort, 6 subjects had SAEs. Of these, 3 subjects in the BMS-477118 treatment arms (1 subject in the 2.5 mg arm had pneumonia, 1 subject in the 10 mg arm had appendicitis, and 1 subject in the 20 mg arm had gastroenteritis) and 1 in the placebo arm (umbilical hernia) had SAEs during the double-blind treatment period. In one subject with gastroenteritis, the investigator categorized the SAE as possibly related to the study drug. Two subjects had SAEs during the follow-up period; SAEs were not attributed to the study drug in either subject.

Discontinuations Due to AEs: There were no discontinuations due to AEs in the 0,100 mg cohort or during the follow-up treatment period. A total of 6 subjects in the 0-40 mg cohort (5 subjects in the active treatment arms and 1 subject in the placebo arm) discontinued double-blind therapy due to AEs. Adverse events that led to discontinuation are listed in the following table.
### Listing of Adverse Events that Caused Discontinuation of Study Drug

<table>
<thead>
<tr>
<th>Study Drug/ Dose</th>
<th>Preferred Term</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS 5 mg</td>
<td>ALT increased myalgia, asthenia, weight decreased, hypotonia</td>
<td>All AEs were of mild to moderate intensity and resolved from 7 to 56 days after onset; classified as possibly related to study drug.</td>
</tr>
<tr>
<td>BMS 10 mg</td>
<td>rectal hemorrhage</td>
<td>Mild intensity and resolved in 7 days after onset. Classified as possibly related to study drug.</td>
</tr>
<tr>
<td>BMS 20 mg</td>
<td>Headache</td>
<td>Moderate intensity and resolved 2 days after onset. Classified as possibly related to study drug.</td>
</tr>
<tr>
<td>BMS 40 mg</td>
<td>Alopecia</td>
<td>Mild intensity. Did not resolve. Classified as possibly related to study drug.</td>
</tr>
<tr>
<td>BMS 40 mg</td>
<td>abdominal pain, feces discolored, headache, facial edema</td>
<td>All AEs of mild to moderate intensity and resolved from 3 to 16 days after onset. Abdominal pain and feces discolored classified as not likely related to the study drug; headache and facial edema were possibly related to study drug.</td>
</tr>
<tr>
<td>Placebo</td>
<td>diarrhea, nausea, asthenia, myalgia, confused state</td>
<td>All AEs of mild intensity and resolved from 4 to 5 days after onset. Classified as possibly related to study drug.</td>
</tr>
</tbody>
</table>

### Laboratory Evaluation

**Laboratory Evaluation**: Included in the laboratory analysis were evaluation of laboratory abnormalities and mean changes from baseline in selected laboratory analytes.

**Laboratory Abnormalities**: Laboratory abnormalities were evaluated based on predefined marked abnormality (MA) criteria. Laboratory abnormalities that met MA criteria were infrequent during double-blind treatment in both cohorts, and in most cases, returned to within normal range or to baseline values during the double-blind or follow-up periods. In the 0-40 mg cohort, 6 subjects experienced decreases in absolute lymphocytes (< 750 cells/µL) in the BMS-477118 5-mg (1 subject), 10-mg (2 subjects), 20-mg (2 subjects), and 40-mg (1 subject) treatment arms. Absolute lymphocytes counts returned to within normal levels during the double-blind treatment period in 5 subjects and during the follow-up period in 1 subject. There were no subjects who had absolute lymphocyte MAs in the 0, 100-mg cohort.

Four subjects in the 0-40 mg cohort (1 subject each in the BMS-477118 2.5, 5, 20, 40-mg arms) had MA values of elevated creatine kinase (> 5 X ULN). In 3 subjects, creatine kinase returned to within normal levels or baseline levels while receiving double-blind treatment. One subject in the 2.5-mg arm had a single creatine kinase MA at the end of double-blind treatment; the creatine kinase MA resolved during the follow-up period but remained above the upper limit of normal. In the 0,100 mg cohort, creatine kinase MA values were seen in 1 subject in the 100 mg group and in 1 subject in the placebo group. Creatine kinase returned to within normal levels during double-blind treatment in both subjects.

**Mean Changes from Baseline**: There were no consistent or meaningful changes from baseline in laboratory parameters across the treatment arms in both cohorts. While mean absolute lymphocyte counts remained within normal limits across the treatment arms in both cohorts, a reduction from baseline in absolute lymphocyte count was apparent at doses ≥ 20 mg in the BMS-477118 treatment arms. This effect was reversible upon discontinuation of study drug. In the 0-40 mg cohort, mean changes from baseline at Week 12 ranged from -0.38 X 10³ cells/µL in the 40-mg arm to no change in the 2.5 mg arm, and no change in
the placebo arm. In the 0.100 mg cohort, mean changes from baseline at Week 6 were -0.28 X 10^3 cells/µL in the 100 mg arm versus -0.01 X 10^3 cells/µL in the placebo arm.

**Other Safety Parameter:** There was no evidence of a drug effect on QTcF interval, blood pressure, BMI, body weight, or waist circumference.

**CONCLUSIONS:** The results of this phase 2 proof of concept study demonstrate that daily doses of 2.5, 5, 10, 20, and 40 mg BMS-477118 for 12 weeks or 100 mg BMS-477118 for 6 weeks are effective in reducing HbA1c, fasting serum glucose, as well as postprandial serum glucose AUC and glucagon. The effect was similar at all doses studied; therefore, the primary endpoint, to show a log linear dose response within the dose range tested, was not met. The safety and tolerability profile was comparable to that of placebo at doses of BMS-477118 below 20 mg.

**DATE OF REPORT:** 20-Jul-2005