Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Irbesartan		
Name of Active Ingredient: BMS 186295		

SYNOPSIS

Document Type CV131169

TITLE OF STUDY: Irbesartan Versus Placebo in Combination with Standard Cardiovascular Protection ACE-I Therapy with Ramipril for the Treatment of Albuminuria in Hypertensive Subjects at Elevated Cardiovascular Risk

INVESTIGATORS: 72 investigators (randomized subjects)

STUDY CENTERS: 72 study sites (randomized subjects)

PUBLICATIONS: None

STUDY PERIOD: **Error! Unknown document property name.**: 27-Sep-2004

Error! Unknown document property name.: 09-Nov-2005

CLINICAL PHASE: 3B

OBJECTIVES: The primary objective was to compare the change in albumin excretion rate (AER), measured in overnight urine collections, from baseline to Week 20 between groups assigned to ramipril plus irbesartan or to ramipril plus placebo.

The secondary objectives were: 1) to estimate the reduction from baseline in seated systolic blood pressure (SeSBP) and seated diastolic blood pressure (SeDBP) at Week 20 within each of the treatment groups, 2) to compare the change from baseline in SeSBP and SeDBP at Week 20 between treatment groups, and 3) to characterize the safety profiles of each of the 2 treatment groups.

METHODOLOGY: This was a Phase 3B, multicenter, double-blind, randomized, placebo-controlled parallel group study evaluating the efficacy and safety of ramipril plus irbesartan compared to ramipril plus matching placebo in the treatment of albuminuria in hypertensive subjects at cardiovascular risk. The study design comprised a placebo lead-in phase and an active treatment phase. Eligible subjects were currently receiving angiotensin converting enzyme inhibitor (ACE-I) therapy at doses equivalent to 5 mg or more of ramipril for 2 months prior to their screening/enrollment visit. Subjects who met the inclusion criteria were required to discontinue or taper their current ACE-I and other antihypertensive medications and begin taking placebo tablets once daily for 14 days (Period A). Following the completion of the placebo lead-in phase, eligible subjects began taking open-label ramipril 5 mg at Week 0 for 1 week and were then titrated to 10-mg open-label ramipril once daily at Week 1. Subjects remained at the ramipril dose of 10 mg once daily throughout the remaining 18 weeks of the study. At the same visit, (Week 0) subjects were randomized to double-blind irbesartan or matching placebo.

The double-blind irbesartan arm began with 2 weeks of dummy placebo to allow safe titration to the target ramipril dose. Upon completion of ramipril titration to 10 mg, subjects began taking irbesartan 150 mg once daily for 2 weeks and at Week 4 were titrated to irbesartan 300 mg for the remaining 16 weeks of the study. The double-blind placebo arm subjects began receiving placebo at randomization (Week 0) and continued for the entire 20 weeks of the double-blind period.

In this study, the urinary AER was measured in 1 timed overnight collection at the screening/enrollment visit and 2 timed overnight collections at Day 14 (Visit 3, baseline measurement) and the final study visit (Week 20).

NUMBER OF SUBJECTS: A total of 838 subjects were enrolled; 405 were randomized (204 to ramipril plus irbesartan and 201 to ramipril plus placebo) and 433 were not randomized.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female subjects, at elevated CV risk and receiving ACE-I therapy, with albuminuria and a documented history of hypertension.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Irbesartan, 150-mg tablets administered daily for 2 weeks and titrated to 300 mg once daily for 16 weeks during the double-blind phase of the study (Period B). The batch numbers for the irbesartan 150-mg tablets were: 8MME382, 8MAE421, and 8MDM200.

DURATION OF TREATMENT: 22 weeks (2 weeks placebo lead-in and 20 weeks of double-blind treatment)

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo tablets administered orally once daily for 14 days in the lead-in period (Period A) and 14 days during double-blind treatment (Period B), open-label ramipril 5-mg capsules/tablets administered orally once daily for 7 days and then 10-mg tablets/capsules administered orally once daily for 19 weeks (Period B). Subjects with elevated blood pressure despite titration to the highest study drug dose were permitted to receive adjunctive antihypertensive treatment with the exception of ACE-I and angiotensin II receptor blockers (ARBs). The batch numbers for the placebo lead-in were: 3A67550, 8MME381, and 8MME380. The batch numbers for the placebo 150-mg tablets were: 8MME378, 8MAE420, and 3A67533. The batch numbers for the ramipril 5-mg tablets were: 4C92550, 093436, and 093430. The batch numbers for the ramipril 10-mg tablets were: AA2073, 033423, 073422, and L557.

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy outcome measure was defined as the change in AER, measured in overnight urine collections, from baseline to Week 20. Subjects with a baseline AER <20 μg/min were excluded from the primary efficacy analysis. Secondary efficacy measures were the change from baseline in SeSBP and SeDBP at Week 20.

Safety: Safety measurements included the frequency of adverse events (AEs), related AEs, treatment discontinuations due to AEs, serious adverse events (SAEs), and laboratory marked abnormalities.

STATISTICAL METHODS: The change from baseline (end of placebo lead-in phase) in AER at Week 20 was analyzed on the natural log scale using analysis of covariance (ANCOVA) to compare the ramipril plus irbesartan and ramipril plus placebo groups. Since the analysis was in terms of logarithms, change from baseline in either group was expressed as a geometric mean ratio of Week 20 to baseline. A total of approximately 200 subjects randomized to each group provided at least 80% power to detect a 20% reduction in the geometric mean ratio for irbesartan relative to placebo. This planned sample size included allowance for a 10% dropout rate and assumed a standard deviation of 0.73 natural logarithm units for the logarithmically-transformed ratio of post to baseline AER and 2-sided testing at an alpha level of 0.05 for the primary analysis.

EFFICACY RESULTS: The study sample was predominantly male (251/405, 62.0%), white (377/405, 93.1%), diabetic (89.1%), and had a mean age of 65.7 years. Baseline geometric means for AER for subjects included in the primary efficacy analysis were 99.6 µg/min and 103.4 µg/min in the ramipril plus irbesartan and ramipril plus placebo groups, respectively. Adjusted Week 20 to baseline geometric mean ratios were 0.539 for the ramipril plus irbesartan group (a 46% decrease) and 0.584 for the ramipril plus placebo group (a 42% decrease). The ratio of the adjusted mean ratios was 0.922 (P=0.540) with a 95% CI (0.711, 1.195); the irbesartan adjusted geometric mean ratio was 7.8% less than the adjusted mean ratio for placebo. The combination of ramipril plus irbesartan was not established to be more effective in reducing AER than the combination of ramipril plus placebo.

Two sensitivity analyses, for the change in AER from baseline to Week 20, were performed. The first sensitivity analysis included randomized subjects with a baseline AER < 20 µg/min. The second sensitivity analysis was a last observation carried forward (LOCF) analysis that included all randomized subjects except those with AER < 20 µg /min when averaged over the 2 baseline qualifying measurements. The results of these 2 sensitivity analyses were consistent with the primary analysis. For the subgroup analyses that were performed based on baseline AER classification, Type II diabetes classification, or achieved Week 20 BP, AER was reduced in all subgroups but to a similar extent in each treatment group.

Baseline mean seated blood pressures were 163/89 mmHg and similar between groups. The adjusted mean change in SeDBP from baseline to Week 20 was -10.9 mmHg in the ramipril plus irbesartan group and -9.1 mmHg in the ramipril plus placebo group. This represented a difference between treatments of -1.8 mmHg (P=0.019) with a 95% CI (-3.333, -0.294). The adjusted mean change in SeSBP from baseline to Week 20 was -22.8 mmHg in the ramipril plus irbesartan group and -19.9 mmHg in the ramipril plus placebo group. This represented a difference between treatments of -2.9 mmHg (P=0.047) with a 95% CI (-5.825, -0.038).

The percentage of subjects achieving BP control according to JNC VII criteria (SeDBP < 80 mmHg and SeSBP < 130 mmHg) at Weeks 6, 12, and 20 were 10.3, 18.0 and 17.3%, respectively, in the ramipril plus irbesartan group and 10.5, 13.2 and 10.8%, respectively, in the ramipril plus placebo group.

Use of concomitant BP lowering medication increased similarly in both groups from the end of the placebo lead-in to the end of the study. At the end of the placebo lead-in, 98 subjects (98/204, 48.0%) and 113 subjects (113/201, 56.2%) in the ramipril plus irbesartan and ramipril plus placebo groups, respectively, were using anti-hypertensive medication and, at the end of the study, 121 subjects (121/204, 59.3%) and 136 subjects (136/201, 67.7%) in the ramipril plus irbesartan and ramipril plus placebo groups, respectively, were using anti-hypertensive medication. The most commonly used anti-hypertensives other than study medication were beta blockers and calcium channel blockers.

SAFETY RESULTS: The incidence of AEs was similar between the 2 treatment groups. There were 187 treatment-emergent AEs in 87 subjects (87/204, 42.6%) in the ramipril plus irbesartan group and 160 AEs in 85 subjects (85/201, 42.3%) in the ramipril plus placebo group.

The most frequent AEs in the ramipril plus irbesartan group were dizziness (8/204, 3.9%), headache (6/204 subjects, 2.9%), hyperkalemia (6/204 subjects, 2.9%), influenza (6/204, 2.9%), back pain (5/204, 2.5%), upper respiratory tract infection (5/204, 2.5%), nasopharyngitis (5/204, 2.5%), diarrhea (4/204, 2.0%), nausea (4/204, 2.0%), cough (4/204, 2.0%), dyspnea (4/204, 2.0%), hypertension (3/204, 1.5%), myalgia (3/204, 1.5%), edema peripheral (3/204, 1.5%), angina pectoris (3/204, 1.5%), and arthralgia (3/204, 1.5%).

The most frequent AEs in the ramipril plus placebo group were headache (12/201, 6.0%), hyperkalemia (6/201, 3.0%), hypertension (7/201, 3.5%), diarrhea (6/201, 3.0%), influenza (5/201, 2.5%), upper respiratory tract infection (4/201, 2.0%), edema peripheral (4/201, 2.0%), acute myocardial infarction (4/201, 2.0%), asthenia (3/201, 1.5%), angina pectoris (3/201, 1.5%), and cough (3/201, 1.5%).

The incidence of AEs assessed as related to study drug was similar for both treatments: 29 total events in 20 subjects (20/204, 9.8%) for the ramipril plus irbesartan treatment and 20 total events in 18 subjects (18/201, 9.0%) in the ramipril plus placebo treatment. The most frequently reported drug-related AE was hyperkalemia, reported by 5 subjects (5/204, 2.5%) in the ramipril plus irbesartan treatment group and 5 subjects (5/201, 2.5%) in the ramipril plus placebo treatment group.

One death was reported (Subject [redacted] in the ramipril plus placebo treatment group) due to a circulatory collapse that was judged not likely to be related to study drug by the investigator. Twenty-eight (28) subjects experienced at least 1 treatment-emergent SAE; 13 in the ramipril plus irbesartan group and 15 in the ramipril plus placebo group. The majority of the SAEs reported were considered by the investigator as not likely to be related or not related to study drug. One SAE was considered to be possibly related to study drug; Subject [redacted] in the ramipril plus irbesartan group experienced moderate acute renal failure. One SAE was considered probably related to study drug; Subject [redacted] in the ramipril plus irbesartan group experienced moderate urticaria.

A total of 17 subjects (17/405, 4.2%) were discontinued from the study due to AEs; 7 (7/204, 3.4%) in the ramipril plus irbesartan group and 10 (10/201, 5.0%) in the ramipril plus placebo group.

Mean changes from baseline to Week 20 in creatinine and potassium were similar in the ramipril plus irbesartan and ramipril plus placebo groups; 0.04 mg/dL and 0.03 mEq/L in the ramipril plus irbesartan group and 0.02 mg/dL and 0.0 mEq/L in the ramipril plus placebo group, respectively.

The most frequently reported marked laboratory abnormalities were: high serum glucose (8 subjects [8/187, 4.3%] in the ramipril plus irbesartan group and 1 subject [1/180, 0.6%] in the ramipril plus placebo group); high potassium levels (3 subjects [3/195, 1.5%] in the ramipril plus irbesartan group and 5 subjects [5/194, 2.6%] in the ramipril plus placebo group); and high creatinine levels (5 subjects [5/194, 2.6%] in the ramipril plus irbesartan group and 6 subjects [6/194, 3.1%] in the ramipril plus placebo group).

CONCLUSIONS:

- It was not established that the combination of ramipril plus irbesartan more effectively reduces albumin excretion rate than ramipril plus placebo. Results showed that the irbesartan adjusted geometric mean ratio was 7.8% less than the adjusted mean ratio for placebo. The 95% CI for the point estimate was wide indicating that the actual irbesartan adjusted geometric mean ratio was anywhere from 28.9% less than that for placebo to 19.5% greater than that for placebo.
- Mean blood pressures at Week 20 were reduced from baseline by 22.8/10.9 mmHg in the ramipril plus irbesartan group and 19.9/9.1 mmHg in the ramipril plus placebo group, representing a statistically significant but small improvement of ramipril plus irbesartan over ramipril plus placebo. Concomitant blood pressure lowering therapies were used by a majority of subjects and usage increased during the study to a similar extent in both treatment groups.
- The incidence of AEs, treatment-related AEs, SAEs, and discontinuations for AEs was similar between the 2 treatment groups and the majority of AEs reported were mild or moderate in intensity
- The majority of SAEs reported were considered by the investigator as not likely to be related or not related to study drug and only 1 death was reported; this event was judged by the investigator as not likely to be related to study drug
- Irbesartan, initiated at 150 mg and increased after 2 weeks to 300 mg, was safe and well tolerated when added to ramipril 10 mg

DATE OF REPORT: 10-Apr-2006