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| Name of Sponsor/Company:<br>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 CV131185

**TITLE OF STUDY:** The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Patients with Moderate Hypertension

**INVESTIGATORS:** 135

**STUDY CENTERS:** 135 study centers in USA, Canada, Germany, France.

**PUBLICATIONS:** None.

**STUDY PERIOD:** Date first subject enrolled: 7-Oct-2004

Date last subject completed: 30-Jun-2005

**CLINICAL PHASE:** 3

**OBJECTIVES:** To compare the change from baseline in (SeSBP) seated systolic blood pressure between the first-line combination arm and each of the two monotherapy arms at Week 8.

**METHODOLOGY:** Multicenter, randomized, double-blind, active-controlled, parallel group. Subjects enrolled into a 21-day single-blind placebo lead-in period (Period A). Those who qualified at the end of Period A were randomized into double-blind Period B in a 3:1:1 ratio to irbesartan/HCTZ, irbesartan, or HCTZ.

**NUMBER OF SUBJECTS/PATIENTS:** 769 subjects were enrolled into the placebo lead-in phase and 538 were randomized into double-blind therapy (Period B): 328 subjects in irbesartan/HCTZ treatment group, 106 subjects in irbesartan monotherapy treatment group, 104 subjects in HCTZ monotherapy treatment group

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Adult male and female subjects with uncontrolled moderate hypertension documented at entry, defined as:

- **Untreated Subjects:** SeSBP ≥160mmHg and <180mmHg, and SeDBP <110 mmHg **or** SeDBP ≥100 mmHg and <110mmHg and SeSBP ≥130mmHg and <180mmHg
- **Subjects Receiving Antihypertensive Monotherapy:** SeSBP ≥150mmHg and <180mmHg, and SeDBP <110mmHg **or** SeDBP ≥95mmHg and <110mmHg and SeSBP ≥130mmHg and <180mmHg.

Subjects who completed the lead-in period and continued to satisfy the selection criteria and the following blood pressure (BP) criteria at the last 2 lead-in visits qualified for randomization to Period B:

- averaged SeSBP ≥ 160 mmHg and <180 mmHg and averaged SeDBP <110 mmHg or
- averaged SeDBP ≥100 mmHg and <110 mmHg and averaged SeSBP ≥ 130 mmHg and <180 mmHg

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**
Irbesartan 150mg/HCTZ 12.5 mg tablets, administered orally, once a day for 2 weeks. Dosage was then titrated to irbesartan 300mg/HCTZ 25 mg for ten weeks. Batch number: 4G84833

**DURATION OF TREATMENT:** 12 weeks.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:**

150 mg irbesartan tablets, 12.5 mg HCTZ tablets, and their matching placebo tablets were administered orally once a day for 2 weeks. Matching placebo tablets for the 150mg irbesartan/HCTZ 12.5 mg tablets were administered orally once a day. Then subjects in the irbesartan arm were titrated to 300 mg irbesartan; those in the HCTZ arm to 25 mg HCTZ daily. Subjects continued at these dosages for the remaining 10 weeks of the study. Matching placebo tablets were also administered orally once a day for 10 weeks. **Batch numbers**: 150 mg irbesartan tablets - 3M61863, matching placebo - 8MAE420; 12.5 mg HCTZ tablets - 4H70431, matching placebo - 4H68496; matching placebo for the 150 mg irbesartan/HCTZ 12.5 mg tablets - 4G84834.

**CRITERIA FOR EVALUATION:**

The primary efficacy outcome measure was the change from baseline in SeSBP at Week 8.

The secondary outcome measurements were the frequency of treatment discontinuations due to adverse events, the frequencies of hypotension, dizziness, and syncope, the frequency of headaches, and the frequencies of hypokalemia and hyperkalemia over 12 weeks of therapy, the change from baseline in SeDBP at Weeks 8 and 12, the change from baseline in SeSBP at Week 12, the proportion of subjects with simultaneous SeSBP <140 mmHg and SeDBP <90 mmHg at Weeks 8 and 12, and the change from baseline in high sensitivity C-reactive protein (hs-CRP) at Week 12.

The other efficacy outcome measurements were the change from baseline in SeSBP and SeDBP at Weeks 2 and 4, the proportion of subjects with simultaneous SeSBP <140 mmHg and SeDBP <90 mmHg at Weeks 2 and 4, and the change from baseline in hs-CRP at Week 8.

**STATISTICAL METHODS:** Changes from baseline to Week 8 in SeSBP and SeDBP were compared between treatment groups using one-way analysis of covariance, where the baseline blood pressure value served as the covariate. A sample size of 298 subjects in irbesartan/HCTZ group and 99 subjects in both irbesartan and HCTZ groups provided 90% power to detect a 6.0 mmHg difference between the combination treatment group and each of the monotherapy treatment groups in SeSBP changes from baseline at Week 8. A standard deviation of 14 mmHg was assumed for the change in SeSBP. Additionally a 5% allowance for dropouts was factored in. The same sample size given above provided 90% power to detect a 3.2 mmHg overall difference between the combination group and each of the monotherapy treatment groups in change from baseline in SeDBP at Week 8. A standard deviation of 7.5 mmHg was assumed for the change in SeDBP.

**EFFICACY RESULTS:**

At Week 8, the reduction from baseline in SeSBP was -27.1 mmHg, -22.1 mmHg, and -15.7 mmHg in the irbesartan/HCTZ combination therapy, irbesartan monotherapy, and HCTZ monotherapy, respectively. The reduction from baseline in SeDBP was -14.6 mmHg, -11.6 mmHg, and -7.3 mmHg in the irbesartan/HCTZ, irbesartan, and HCTZ groups, respectively. The reduction was greatest in the combination therapy arm for both SeSBP and SeDBP ($p \leq 0.0016$).

The proportions of subjects whose blood pressures were controlled (<140/90 mmHg) were statistically significantly greater ($p <= 0.026$) for irbesartan/HCTZ therapy than for either irbesartan or HCTZ

monotherapies. At Week 8, the proportions of subjects with blood pressure less than 140/90 mmHg were 53.4%, 40.6%, and 20.2% with irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy, respectively.

The main focus of the analysis of hs-CRP was the Week 12 timepoint (evaluated later in the study to accommodate the slow rate of change in hs-CRP). There was no significant change in hs-CRP from baseline to Week 12 in either irbesartan/HCTZ or HCTZ monotherapy. The decline in the irbesartan group differed significantly (p=0.004) from the small increase observed in the combination therapy group. No significant between group differences were observed at Week 8.

**SAFETY RESULTS:**

There were no deaths reported for any of the 3 treatment groups. Across the 3 treatment groups, 9 subjects reported SAEs. Six (6) SAEs occurred in 6 subjects (1.8%) in the irbesartan/HCTZ combination-therapy group. Only 1 SAE was considered by the investigator to be probably related to study drug. The case was reported as “severe hypokalemia”, but had only a minor decrease in potassium in a subject presenting with atypical chest pain. Other SAEs in the irbesartan/HCTZ combination-therapy group included 2 reports of duodenal ulcer; and 1 each of diffuse, large, B-cell lymphoma; coronary artery disease (CAD); and transient ischemic attack (TIA). These events ranged in intensity from mild to severe. No SAEs occurred in the irbesartan monotherapy group. In the HCTZ group, 3 subjects (2.9%) reported 4 SAEs (depression, diabetes mellitus, rhabdomyolysis, and nerve compression). These events ranged from mild to moderate in intensity.

The irbesartan/HCTZ-combination therapy group had 47 subjects (14.3%) for whom AEs were considered to be related to study medication. Dizziness, the most commonly reported related adverse drug experience (ADE) in the combination therapy group, was reported in 8 subjects (2.4%). There were 12 subjects (11.3%) in the irbesartan monotherapy group and 8 subjects (7.7%) in the HCTZ monotherapy group who reported AEs judged to be related to study drug. In the irbesartan monotherapy group, ADEs of dizziness and diarrhoea were most commonly reported (2 subjects [1.9%] each). In the HCTZ monotherapy group, headache was the most commonly reported ADE (3 subjects [2.9%]).

The forced-titration design of this study addressed the potential for AEs related to a rapid reduction of blood pressure. If the incidences of dizziness and hypotension were low in the context of such a study design, one would have expected the incidences of these events to be even lower under a flexible-titration design. Safety events and laboratory abnormalities designated as being of special interest that were pre-specified included hypotension, dizziness, syncope, headache, hyperkalemia and hypokalemia, and the laboratory abnormalities of serum potassium < 3 mEq/L and serum potassium> 6 mEq/L. Syncope was the most important of these pre-specified AEs; 1 case of syncope was reported, occurring in the HCTZ monotherapy group. The irbesartan/HCTZ combination arm had a total of 35 subjects (10.7%) with a pre-specified AE, whereas there were 7 subjects in each of the monotherapy arms (6.6% and 6.7% in the irbesartan and HCTZ groups, respectively).

In the irbesartan/HCTZ combination-therapy, irbesartan monotherapy, and HCTZ monotherapy groups, 6.7%, 3.8%, and 4.8% of subjects, respectively, discontinued study therapy due to AEs. Although there were some discontinuations due to dizziness (4 subjects) or hypotension (3 subjects) in the irbesartan/HCTZ combination therapy group, these events were infrequent and occurred primarily when forced-titration was applied to subjects whose blood pressure was already well-controlled on the starting dose of irbesartan/HCTZ.

At Week 12, there was a mean decrease from baseline in potassium of -0.14 mEq/L in the irbesartan/HCTZ combination-therapy group, none in the irbesartan monotherapy group, and -0.30 mEq/L in the HCTZ monotherapy group. There were no clinically significant changes from baseline in ECG intervals or HR.

**CONCLUSIONS:**

- The irbesartan/HCTZ combination (150 mg/12.5 mg titrated to 300 mg/25 mg) was more effective than either irbesartan monotherapy (150 mg titrated to 300 mg) or HCTZ (12.5 mg titrated to 25 mg) in reducing seated BP in subjects with moderate hypertension.
- Irbesartan was safe used in combination with the non-loop diuretic HCTZ.
- One event of syncope was reported (occurring in the HCTZ monotherapy group following upward titration). Both dizziness and hypotension were uncommon and occurred at frequencies consistent with the current product label.
- Subjects with moderate hypertension can achieve blood pressure control promptly and safely with combination irbesartan and HCTZ.

**DATE OF REPORT:** 20-Jan-2006