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 CV131176

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

INVESTIGATORS: 255 investigators

STUDY CENTERS: 255 sites (130 sites in the US, 30 in Canada, 16 in Russia, 10 in Israel, 24 in Germany, 25 in France, 10 in Netherlands, and 10 in Belgium) received drug product; 185 of these sites enrolled subjects into the study.

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 19-Sep-2004

Date last subject completed: 11-May-2005

CLINICAL PHASE: 3

OBJECTIVES: The primary objective of this study was to compare the proportion of subjects whose seated diastolic blood pressure (SeDBP) was controlled (SeDBP < 90 mmHg) at Week 5 when initiating irbesartan 150 mg/HCTZ 12.5 mg combination therapy and titrating to irbesartan 300 mg/HCTZ 25 mg as first-line treatment, as compared to initiating irbesartan 150 mg monotherapy and titrating to irbesartan 300mg.

METHODOLOGY: This was a multicenter, randomized, double-blind, active controlled, 8-week, parallel arm study in untreated, uncontrolled hypertensive (SeDBP ≥ 110 mmHg) subjects and in subjects with uncontrolled hypertension (SeDBP ≥ 100 mmHg) who were currently treated with antihypertensive monotherapy. Qualifying subjects were withdrawn from their antihypertensive medications, where applicable, and entered into a 7-day placebo lead-in period (Period A). Following Period A, subjects who fulfilled the randomization criterion (SeDBP ≥ 110 mmHg at 2 consecutive visits off of medication) were randomized in a 2:1 ratio to receive either combination therapy (irbesartan plus HCTZ) or irbesartan monotherapy for 7 weeks (Period B). The starting doses of the regimens were irbesartan 150 mg/HCTZ 12.5 mg and irbesartan 150 mg, respectively. Study medication was force titrated after the first week in all subjects.

NUMBER OF SUBJECTS/PATIENTS: 468 subjects in irbesartan/HCTZ treatment group, 229 subjects in irbesartan monotherapy treatment group

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Untreated adult male and female subjects with uncontrolled hypertension defined as SeDBP of at least 110 mmHg, and adult male and female

subjects currently receiving antihypertensive monotherapy with uncontrolled hypertension defined as SeDBP of at least 100 mmHg on 2 consecutive visits prior to randomization.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: irbesartan/hydrochlorothiazide 150mg/12.5mg tablets, administered orally once a day (batch number: 4G84833).

DURATION OF TREATMENT: 7 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: placebo tablets administered orally once a day for a maximum of 7 days in the Lead-in Period A (batch number: 3A67550); irbesartan 150 mg tablets administered orally once a day for 7 weeks (batch numbers: 4G86226, 8MAE421, 3A67555), matching placebo irbesartan tablets administered orally once a day for 7 weeks (batch numbers: 4G86228, 8MAE420, 3A67533), and matching placebo irbesartan/hydrochlorothiazide tablets administered orally once a day for 7 weeks (batch number: 4G84834).

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy outcome measure was the proportion of subjects with SeDBP < 90 mmHg at Week 5.

Other efficacy outcome measurements were the proportion of subjects with SeDBP < 90 mmHg (at Week 1, Week 3, and Week 7), the change from baseline in SeSBP and SeDBP at Week 1, Week 3, Week 5, and Week 7, and the proportion of subjects with simultaneous SeSBP < 140 mmHg and SeDBP < 90 mmHg at Week 1, Week 3, Week 5, and Week 7.

Safety: Safety measurements included the frequency of treatment discontinuations due to adverse events (AEs), the frequencies of hypotension, dizziness, and syncope, the frequency of headaches, and the frequencies of hypokalemia and hyperkalemia.

STATISTICAL METHODS: The primary analysis was a test comparing the proportions of subjects with SeDBP < 90 mmHg in the 2 treatment groups at the end of Week 5.

The sample size and the power of the test was calculated based on Fisher's exact test performed at a two-sided 5% level of significance. The proportion of subjects normalized under irbesartan monotherapy was assumed to be 0.10 for this sample size calculation. Using 2:1 randomization scheme it was determined that a total of 430 subjects in the combination therapy group and 215 subjects in the monotherapy group would provide 90% power to detect a doubling (to 0.20) in the proportion of normalized subjects for combination therapy relative to the monotherapy.

EFFICACY RESULTS: Mean baseline blood pressures were approximately 172/113 mmHg in each treatment group. The proportion of subjects achieving SeDBP < 90 mmHg at Week 5 revealed a statistically significant difference between the treatment groups (0.472 for the combination therapy arm and 0.332 for the monotherapy arm; $p<0.001$). The proportions controlled at Week 5 according to JNC VII criteria (SeDBP < 90 mmHg and SeSBP < 140 mmHg) also differed significantly between groups (0.346 versus 0.192, $p<0.0001$ in favor of combination therapy).

Mean decreases in SeDBP at Week 5 were 24.0 mmHg and 19.3 mmHg for the combination therapy and monotherapy arms, respectively (mean difference of 4.7 mmHg, $p < 0.0001$). Mean decreases in SeSBP were 30.8 mmHg and 21.1 mmHg for combination therapy and monotherapy, respectively (mean difference of 9.7 mmHg, $p < 0.0001$).

SAFETY RESULTS: The overall frequency of subjects with AEs reported during the 7-week, double-blind period was lower in the combination therapy group than in the monotherapy group (29.9% versus 36.1%). Adverse events and laboratory abnormalities of pre-specified interest (dizziness, hypotension, syncope, headache, and abnormalities of serum potassium) were found collectively to occur less frequently

in the combination therapy group than in the monotherapy group (8.8% versus 11.5%). No syncope was reported during the study in either treatment group, and AEs of hypotension and dizziness occurred with similar frequency in the 2 treatment groups. Headache was the most frequent of the pre-specified AEs and was reported by 19 (4.3%) subjects treated with combination therapy and by 15 (6.6%) monotherapy subjects.

One subject in each group experienced a serious adverse event (SAE) during double-blind therapy: Subject [redacted] (irbesartan 300 mg/HCTZ 25 mg) experienced colitis secondary to irritable bowel syndrome and polynephritis (both of moderate intensity), and Subject [redacted] (irbesartan 150 mg) experienced renal artery stenosis of mild intensity. Each SAE was categorized as unrelated to study therapy. Neither subject was discontinued from the study due to their SAE. Ann additional subject (Subject [redacted]) in the irbesartan 300 mg /HCTZ 25 mg combination group experienced a transient ischemic attack that the investigator did not report as serious, and did not consider related to study medication. The subject discontinued from the study due to that AE.

Nine subjects (1.9%) in the combination group and 5 subjects (2.2%) in the monotherapy group were discontinued from the study due to AEs. Of those, 3 discontinuations in the combination group were categorized as certainly related to the drug. Those were due to dizziness, fatigue, and hypotension. The intensity of the events was severe, moderate, and mild, respectively. All other AEs leading to discontinuation were categorized as probable, possible, or unrelated to study medication.

Laboratory test results for serum potassium were considered of particular interest because they are of clinical concern in subjects with severe hypertension. The prespecified marked abnormality (MA) criterion for serum potassium was < 3.0 or > 6.0 mmol/L. Six subjects had a serum potassium MA: 3 subjects (0.6%) in the irbesartan/HCTZ group and 3 (1.3%) subjects in the irbesartan monotherapy group had serum potassium levels > 6.0 mmol/L. None had serum potassium < 3.0 mmol/L. A mean decrease of 0.12 mmol/L from baseline in potassium was seen with irbesartan/HCTZ combination by the end of the double-blind period. A mean increase of 0.01 mmol/L from baseline in potassium was seen with irbesartan monotherapy by the end of the double-blind period.

CONCLUSIONS:

- Irbesartan/HCTZ started at 150 mg/12.5 mg and titrated to 300 mg/25 mg after one week in severely hypertensive (SeDBP >110mmHg) subjects lowers BP more rapidly and to a greater extent than irbesartan monotherapy, started at 150 mg and titrated to 300 mg after one week.
- The maximum dose of irbesartan monotherapy controls approximately one-third of subjects with severe hypertension to SeDBP < 90 mmHg, and one-fifth to the JNC VII treatment goal of <140/<90 mmHg. First line Irbesartan/HCTZ therapy is more effective, controlling approximately one-half and one-third, respectively.
- First line treatment of severely hypertensive subjects with irbesartan/HCTZ is safe and well tolerated, with a safety profile similar to that for irbesartan monotherapy.

DATE OF REPORT: 31-Oct-05