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: Irbesartan		

SYNOPSIS

Clinical Study Report for Study CV131186

TITLE OF STUDY: Irbesartan in the Treatment of Hypertensive Patients with Metabolic Syndrome

INVESTIGATORS/STUDY CENTERS: A total of 50 investigative sites participated (5 in France, 6 in Germany, 5 in Italy, 4 in Spain, 5 in Norway and 25 in Russia).

PUBLICATIONS: None.

STUDY PERIOD: Study Initiation Date: 18-Nov-2005 **CLINICAL PHASE:** 4

Study Completion Date: 22-Feb-2007

OBJECTIVES:

The primary objective was to compare the change from baseline in insulin resistance (IR), as measured by the Matsuda Index (MI) in subjects with hypertension and metabolic syndrome after 16 weeks of monotherapy with irbesartan relative to hydrochlorothiazide (HCTZ).

The secondary objectives were:

1) To compare the change from baseline in insulin resistance (as measured by the Quicki Index) after 16 weeks of monotherapy with irbesartan relative to HCTZ.
2) To compare the change from baseline in triglycerides after 16 weeks of monotherapy with irbesartan relative to HCTZ.
3) To compare the change from baseline in blood pressure (BP) after 16 weeks of monotherapy with irbesartan relative to HCTZ.
4) To compare the change from baseline in high sensitivity-C reactive protein (hs-CRP) after 16 weeks of monotherapy with irbesartan relative to HCTZ.
5) To compare the change from baseline in albumin/creatinine ratio after 16 weeks of monotherapy with irbesartan relative to HCTZ.
6) To describe the changes from baseline in Matsuda Index, Quicki index, BP, triglycerides, hs-CRP, and albumin/creatinine ratio after 28 weeks of treatment with a regimen of irbesartan and HCTZ.
7) To describe the changes from Week 16 to Week 28 in Matsuda Index, Quicki index, BP, and triglycerides in the two randomized treatment groups.
8) To assess the safety and tolerability of irbesartan and HCTZ alone and in combination.

Other objectives included:

9) To summarize the change from baseline in total cholesterol, HDL and LDL fractions after 16 weeks and 28 weeks of treatment with an irbesartan-based regimen relative to a HCTZ-based regimen.
10) To describe the changes from baseline in beta-cell function indices at Week 16 and 28: insulinogenic index (IGI) calculated from oral glucose tolerance testing (OGTT) insulin and glucose measurements and HOMA-derived beta-cell function model (HOMA%B) evaluations.
11) To explore modeling of the therapeutic benefit of irbesartan compared with HCTZ by estimating the absolute and relative risk reduction in projected cardiovascular outcomes. The modeled benefit can be derived from a combination of blood pressure lowering, changes in the Matsuda index, and changes in rates of metabolic syndrome. *Note: this analysis was not performed.*

Biomarker Substudy Objectives:

The primary objective of the biomarkers substudy was to compare the changes in serum adiponectin levels from baseline to Week 16 between the irbesartan and HCTZ treatment groups. The secondary objective was to compare the changes in serum levels of leptin, Interleukin-6 (IL-6) and monocyte chemoattractant protein (MCP-1) from baseline to Week 16 between the irbesartan and HCTZ groups.

METHODOLOGY: This study was a multicenter, randomized, double-blind, active-controlled, parallel-group study to evaluate the efficacy and safety of irbesartan as compared with HCTZ in the treatment of subjects with hypertension and metabolic syndrome. The study consisted of two phases, a 4-week placebo lead-in phase and a 28-week, double-blind treatment phase. During the placebo lead-in phase, eligible subjects discontinued their current antihypertensive therapy (if any) and were treated with placebo for 4 weeks. Subjects who continued to meet eligibility criteria were entered into the double-blind phase and were randomized in a 1:1 ratio to treatment with either irbesartan 150 mg or HCTZ 12.5mg given once daily (QD). Subjects were scheduled to return for study visits at Weeks 2, 4, 10, 16, 18, 22 and 28 during the double-blind phase.

At the Week 2 visit during the double-blind phase, subjects whose seated systolic BP (SeSBP) was ≥100 mmHg and who had no clinical signs of hypotension were uptitrated to 300 mg in the irbesartan group or to 25 mg in the HCTZ group for the remaining 26 weeks of treatment. At any time up to Week 16, subjects who were unable to tolerate the increased doses of either irbesartan or HCTZ could have their dose reduced to the original starting dose (150 mg for irbesartan and 12.5 mg for HCTZ) and continue in the study; the doses of irbesartan and HCTZ remained constant from Week 16 to the end of the study.

At Week 16, subjects whose SeSBP was ≥100 mmHg began concomitant treatment; those who had received double-blind treatment with HCTZ received irbesartan 150 mg QD, and those who had received double-blind treatment with irbesartan received HCTZ 12.5 mg QD. If the SeSBP remained ≥100 mmHg at Week 22, subjects receiving combination irbesartan/HCTZ therapy had their daily irbesartan dose increased to 300 mg (HCTZ group), or their HCTZ dose increased to 25 mg (irbesartan group). If a subject did not receive additional treatment with HCTZ or irbesartan at Week 16, blinded concomitant treatment was added at the Week 22 visit if SeSBP was ≥100 mmHg. Subjects who were unable to tolerate the increased doses of the concomitant medication added at Week 22 (either irbesartan or HCTZ) could have the dose of the added medication reduced to the original starting dose (150 mg for irbesartan and 12.5 mg for HCTZ) and continue in the study.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 540 subjects were planned to be enrolled at approximately 50 study sites worldwide. Of these, 400 subjects were expected to be eligible for randomization into the 28-week, double-blind treatment phase.

A total of 604 subjects were enrolled in the 4-week placebo lead-in phase. Of these, 426 were entered into the double-blind phase and received treatment with either irbesartan (211) or HCTZ (215).

For the biomarkers substudy, 212 enrolled subjects (106 in each treatment group) had blood samples drawn at baseline and at Week 16 for analysis of biomarkers. The first 212 evaluable subjects who were randomized in sequential order starting from Day X were included in this sub-study; Day x was the first day of sample stability at the time sample analysis started. A total of 211 subjects were included in the biomarkers substudy.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Adult male or female subjects (≥18 years) with uncontrolled mild to moderate hypertension (averaged SeSBP ≥140 mmHg or averaged seated diastolic BP [SeDBP] ≥90 mmHg), who were either treatment naive or were uncontrolled while receiving antihypertensive monotherapy were eligible for enrollment into the placebo Lead-in Phase. Subjects also must have met at least 2 of the modified National Cholesterol Adult Treatment Panel III (ATP III) criteria:

- Abdominal obesity waist circumference (WC) ≥ 94 cm (≥ 37 in) for men and ≥ 80 cm (≥ 32 in) for women
- Elevated plasma triglycerides (>150 mg/dL)
- High Density Lipid (HDL) cholesterol <40 mg/dL for men and <50 mg/dL for women
- Elevated fasting plasma glucose ≥100 mg/dL, but < 126 mg/dL.

Laboratory results obtained either at Screening (Week -5), or within 12 months prior to entry into the Lead-in Phase were used to document qualifying levels of triglycerides, cholesterol and glucose for enrollment.

Laboratory results obtained either at Screening (Week -5) or at Week -2 were used to document qualifying levels of triglycerides, cholesterol and glucose for randomization.

Women of childbearing potential who were using an adequate method of contraception to avoid pregnancy throughout the study and up to 4 weeks after study completion also were eligible for enrollment. A negative serum or urine pregnancy test was required at enrollment, at randomization into the double-blind treatment phase, at Week 16 and at the final study assessment/Week 28.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Irbesartan was supplied as a 150-mg tablet and was taken orally, once daily in the morning. Placebo was supplied as a tablet that matched the irbesartan 150 mg tablet, and was taken orally, once daily in the morning. Batch numbers were:

Irbesartan 150 mg tablet: 8MAE421, 4G84835, 5M07559

Placebo (matching Irbesartan 150 mg): 3A67533, 5M07546

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: HCTZ was supplied as a 12.5-mg tablet and was taken orally, once daily in the morning. Placebo was supplied as a tablet that matched the HCTZ 12.5-mg tablet, and was taken orally, once daily in the morning. During the placebo Lead-in Phase, placebo was supplied as a white tablet and was taken orally in the morning. Batch numbers were:

HCTZ 12.5-mg tablet: 5H05258, 5H05263, 5C08516, 5C08525

Placebo (matching HCTZ 12.5 mg) : 5H05259, 5H05262, 5C08524, 5C08523

Placebo (Lead-in Phase): 3M61862

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy assessment was the determination of insulin resistance using the Matsuda Index, which was calculated from the fasting glucose and fasting insulin values, and the averaged glucose and insulin values obtained during the 2-hour OGTT. Secondary efficacy assessments included: insulin resistance assessed using the Quicki index; blood pressure measurements in the seated position taken 24 hours post-dose; albumin/creatinine ratio, triglyceride levels, hs-CRP values; total cholesterol, HDL, and

LDL levels; IGI; and HOMA-derived beta-cell function model evaluations at baseline, Week 16 and at the final visit.

Safety: Safety assessments included the occurrence of adverse events, clinical laboratory test results, physical examinations and vital signs measurements.

Other: In the biomarkers substudy, blood samples for analysis of the key biomarkers associated with metabolic syndrome that were taken at baseline and at Week 16 have been analyzed in 211 subjects. These biomarkers included adiponectin, leptin, IL-6, and MCP-1. The primary efficacy assessment was the mean change in adiponectin level from baseline to Week 16, before and after treatment with irbesartan or HCTZ.

Exploratory modeling of the therapeutic benefit of irbesartan compared to HCTZ in terms of estimated absolute and relative risk reduction in projected cardiovascular outcomes (stroke, myocardial infarction, revascularization, CV death) was to be performed at Weeks 16 and 28. *Note: this analysis was not performed because the glucose parameters did not change.*

STATISTICAL CONSIDERATIONS: The disposition of all enrolled subjects was presented by treatment group for the placebo lead-in phase and the randomized double-blind Phase. The randomized data set, which included all randomized subjects, was used to summarize demographic and baseline characteristics, and for all efficacy analyses. For the primary efficacy variable, change in the Matsuda Index (MI) from baseline to Week 16, an analysis of covariance (ANCOVA) on log-transformed data using treatment as the main effect and the natural log of the baseline value as covariate, was used to compare the irbesartan and HCTZ treatment groups. The covariate-adjusted mean difference between treatment groups was tested at the two-sided 5% significance level. Mean changes from baseline to Week 16 in the components of the MI were summarized, and 95% confidence intervals for the difference between treatment groups were calculated. A similar analysis was performed for mean changes from baseline to Week 16 for the Quicki Index and fasting triglyceride levels. Subgroup analyses characterized by the presence or absence of the pre-diabetic state were conducted for the results of the MI at Weeks 16 and 28.

All randomized subjects who took at least one dose of double-blind study medication were included in the safety dataset. Duration of exposure to double-blind medication (initial as well as add-on therapies) was presented by treatment group and by dose. The number of subjects discontinuing the study prematurely was summarized by treatment group and by reason for discontinuation. The incidences of adverse events, serious adverse events, discontinuations of treatment for adverse events, and clinical laboratory test abnormalities during the double-blind period were summarized by treatment group.

For the Biomarkers Sub-study, demographic data and baseline characteristics were summarized by treatment group. Mean change from baseline to Week 16 for adiponectin (the primary response variable), leptin, IL-6 and MCP-1 before and after treatment with irbesartan or HCTZ were summarized by treatment group. One-way ANCOVA was used to compare treatments using baseline values as the covariate; 95% confidence intervals for the differences between treatment groups were provided.

Exploratory modeling of the therapeutic benefit of irbesartan as compared with HCTZ was not performed because the glucose parameters did not change.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

A total of 604 subjects were enrolled in the study and 530 entered the single-blind placebo lead-in phase. Of these, 426 were randomized into the double-blind treatment phase: 211 to irbesartan and 215 to HCTZ. A total of 29 randomized subjects discontinued double-blind treatment (see table below). A majority of subjects in the irbesartan group who discontinued did so due to withdrawn consent. More subjects in the HCTZ group discontinued due to an adverse event than in the irbesartan group.

Subject Disposition

	Irbesartan n (%)	HCTZ n (%)	Total n (%)
Total Number of Subjects Randomized	211 (100.0)	215 (100.0)	426 (100.0)
Number of Subjects Treated	211 (100.0)	215 (100.0)	426 (100.0)
Number of Subjects Discontinued from the Study	11 (5.2)	18 (8.4)	29 (6.8)
Adverse Event	2 (0.9)	10 (4.7)	12 (2.8)
Subject Withdrew Consent	7 (3.3)	5 (2.3)	12 (2.8)
Administrative Reason By Sponsor	0	1 (0.5)	1 (0.2)
Subject No Longer Meets Study Criteria	1 (0.5)	0	1 (0.2)
Lack of Efficacy	0	1 (0.5)	1 (0.2)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Number of Subjects Completing	200 (94.8)	197 (91.6)	397 (93.2)

DATASET: Randomized Subjects

Baseline Characteristics

The treatment groups were comparable with regard to demographic and baseline characteristics. Most subjects in both groups were female and white. The mean age was 53.5 years. The groups were comparable with regard to baseline values for Matsuda Index, Quicki index, 30-minute insulinogenic Index, HOMA-B Index, ACR, hs-CRP, triglycerides and blood pressure.

Efficacy Results:

With respect to the primary endpoint, no significant differences were observed between the 2 treatment groups relative to the Matsuda index at Week 16. The effects of irbesartan on the metabolic profile were maintained when HCTZ was added to the subject's treatment regimen, and when irbesartan was added to the HCTZ regimen. The differences between the groups in the mean changes from baseline in Matsuda Index were not statistically significant.

Change from Baseline in Matsuda Index at Week 16 and Week 28

	Irbesartan N = 186	**HCTZ N = 182**
Baseline (mean ± SE)	2.66 ± 0.12	2.65 ± 0.12
Week 16 (mean ± SE)	2.69 ± 0.12	2.67 ± 0.11
Week 28 (mean ± SE)	2.88 ± 0.14	2.70 ± 0.12
P value	0.8813	0.2856

No significant differences were observed between the 2 treatment groups with respect to the Quicki index. The effects of irbesartan on the metabolic profile were maintained when HCTZ was added to the subject's treatment regimen, and when irbesartan was added to the HCTZ regimen. The differences between the groups in the mean changes from baseline in the Quicki Index were not statistically significant.

Subjects treated with irbesartan had mild decreases in fasting serum triglyceride levels at Week 16, while serum triglyceride levels remained about the same among subjects treated with HCTZ monotherapy. The between-group ratio of adjusted geometric mean values was not statistically significant. At Week 28, the

effect of the irbesartan-based regimen on serum triglyceride levels was maintained; HCTZ-treated subjects had an increase in serum triglyceride. The between-group ratio of adjusted geometric mean values was statistically significant (P = 0.0256).

Antihypertensive therapy with either irbesartan or HCTZ was effective in reducing SeSBP and SeDBP in hypertensive subjects with metabolic syndrome. Irbesartan resulted in a slightly better non-significant reduction in BP. This difference was carried over to the 28 week period when HCTZ was added.A decrease in the adjusted geometric mean percent change in hs-CRP level from baseline to Week 16 was seen for irbesartan-treated subjects; HCTZ-treated subjects had an increase from baseline. The difference between the 2 treatment groups was statistically significant (P = 0.0024). The beneficial effect of an irbesartan-based regimen on hs-CRP level was maintained at Week 28, and remained statistically significant (P = 0.0016).

A decrease in the adjusted mean percent change from baseline in urinary albumin/creatinine ratio (ACR) at Week 16 was seen for irbesartan-treated subjects, while HCTZ-treated subjects had a mean adjusted percent increase from baseline. The between-group comparison showed that this was a highly statistically significant difference (P = 0.0041). The beneficial effect of an irbesartan-based regimen on urinary ACR remained statistically significant (P = 0.0182) at Week 28.

Change from Baseline in Secondary Endpoints

	Irbesartan	**HCTZ**	**P value**
Quicki Index, N	186	182	
Baseline (mean ± SE)	0.138 ± 0.001	0.139 ± 0.001	
Week 16 (mean ± SE)	0.138 ± 0.001	0.139 ± 0.001	0.6901
Week 28 (mean ± SE)	0.139 ± 0.001	0.139 ± 0.001	0.8146
Triglycerides (mg/dL), N	200	197	
Baseline (mean ± SE)	156.14 ± 5.96	160.50 ± 5.67	
Week 16 (mean ± SE)	153.82 ± 6.31	161.43 ± 5.51	0.4520
Week 28 (mean ± SE)	150.41 ± 5.67	167.60 ± 5.97	0.0256
Blood Pressure (mm Hg), N	202	203	
Baseline (mean)	152/95	152/95	
Week 16 (mean)	133/85	135/86	0.3124/0.2424
Week 28 (mean)	129/82	131/83	0.3167/0.2421
hs-CRP (mg/L), N	199	202	
Baseline (mean ± SE)	2.14 ± 0.14	2.37 ± 0.16	
Week 16 (mean ± SE)	2.07 ± 0.14	2.79 ± 0.19	0.0024
Week 28 (mean ± SE)	1.87 ± 0.13	2.52 ± 0.17	0.0016
ACR, N	194	201	
Baseline (mean ± SE)	6.60 ± 0.48	6.62 ± 0.48	
Week 16 (mean ± SE)	5.74 ± 0.36	7.19 ± 0.53	0.0041
Week 28 (mean ± SE)	5.89 ± 0.38	7.09 ± 0.49	0.0182

Subjects treated with either irbesartan or HCTZ had minimal changes in total cholesterol, HDL, LDL, insulinogenic index and HOMA-B values during 16 weeks of monotherapy. Results for Week 28 followed similar patterns.The percent of subjects who met 3 or more of the modified ATPIII criteria for metabolic syndrome decreased in both the irbesartan group and in the HCTZ group after 16 weeks of monotherapy. The beneficial effects of an irbesartan-based regimen on metabolic profile were maintained at Week 28, since there was an overall shift toward fewer ATPIII criteria per subject in both dose groups.

A total of 211 subjects (108 in the irbesartan group, 103 in the HCTZ group) participated in the biomarker sub-study. Demographic and baseline characteristics for these subjects were similar between the two treatment groups.

The ratio of the geometric mean for the levels of all measured serum biomarkers from baseline to Week 16 was not close to 1 or statistically significant for both irbesartan- and HCTZ-treated subjects.Since treatment with irbesartan did not result in any statistical advantage for the primary objective in this study, the sponsor has not conducted the proposed analyses for modeling of therapeutic benefit.

Safety Results: Except where noted, adverse event information is reported for the cumulative experience (ie, Weeks 1-28) in the double-blind phase regardless of when subjects added a second antihypertensive medication.

Overall, irbesartan and HCTZ were well tolerated by subjects in this trial. The same percentage of subjects in the irbesartan and HCTZ groups experienced at least 1 AE; more subjects in the HCTZ group discontinued due to an AE (see table below).

Overall Adverse Events at Week 28

Event	Irbesartan (N = 211)	HCTZ (N = 215)
AE, total (% of Subjects)	97 (46.0%)	99 (46.0%)
Related AE*	33 (15.6%)	38 (17.7%)
SAE*	3 (1.4%)	5 (2.3%)
Death	0	0
Discontinuation due to AE*	2 (0.9%)	10 (4.7%)

Note: AE during Double-Blind Period until last dosing date + 1 day
SAE during Double-Blind Period until last dosing date + 30 days or the last visit date whichever occurs last
Abbreviation: AE=Adverse Event; SAE=Serious Adverse Event
* Subsets of all AEs: Subjects may be represented in more than one AE category
Related AE: relationship to study drug is certain, probable, possible or missing
MEDDRA VERSION: 9.1
DATASET: Treated Subjects

No deaths occurred during the lead-in phase or double-blind phase. The proportion of subjects who experienced SAEs during 28 weeks of double-blind treatment was lower in the irbesartan group than in the HCTZ group. A total of 8 subjects had one or more SAEs during the study: 3 subjects (1.4%) in the irbesartan group (coronary artery disease, concussion, and metrorrhagia) and 5 subjects (2.3%) in the HCTZ group (retinal hemorrhage, chronic otitis media, osteochondrosis, acute pancreatitis, and colon cancer). All SAEs were considered to be not likely related or not related to study drug in both groups.

A total of 12 subjects discontinued study therapy because of an AE: 2 subjects (0.9%) in the irbesartan group and 10 subjects (4.7%) in the HCTZ group. Each AE leading to discontinuation in the irbesartan-

treated subjects was considered to be not likely related or not related to study drug; 5 of the events in the HCTZ-treated subjects were considered to be possibly or probably related to study medication, and 8 were considered not likely related or not related. The most common individual AEs (≥1% in either treatment group) were hypertension and headache.

Overall, 138 of the 426 subjects (32.4%) had one or more AEs during double-blind treatment with monotherapy (up to Week 16): 31.3% of subjects on irbesartan compared with 33.5% of subjects on HCTZ. Headache was the most frequent individual AE experienced by both groups (4.3% in the irbesartan group and 4.2% in the HCTZ group).

A total of 71 of the 426 subjects (16.7%) had one or more related ADEs during double-blind treatment: 15.6% of subjects on irbesartan compared with 17.7% of subjects on HCTZ. The most frequent of the common individual ADEs (≥ 1% in either treatment group) were hypotension and asthenia.

During the double-blind period, most subjects who experienced AEs had events of mild or moderate intensity (31.3% and 20.4% in the irbesartan group, and 31.6% and 22.8% in the HCTZ group, respectively). Only one subject in the irbesartan group experienced AEs considered to be severe (nasopharyngitis and acute tonsillitis). In the HCTZ-treated group, 5 subjects experienced severe AEs (orthostatic hypotension, headache, nausea, proteinuria, hyperhidrosis, and colon cancer).

CONCLUSIONS:

- No significant changes were observed between the two treatment groups with respect to the Matsuda index. Therefore, the study is considered to be neutral with respect to achieving the primary endpoint of the trial at Week 16.
- Significant changes in hs-CRP & ACR were observed with irbesartan compared to HCTZ at Week 16 favoring irbesartan. Both treatments lowered BP to a similar extent. These findings suggest that irbesartan compared to HCTZ may have beneficial effects in managing hypertensive subjects with metabolic syndrome.
- The results of the biomarker substudy revealed no significant changes in either treatment group from baseline to Week 16 in adiponectin, leptin, IL-6, or MCP-1.
- Irbesartan is safe and well-tolerated in the studied population.

DATE OF REPORT: 25-Jul-2007