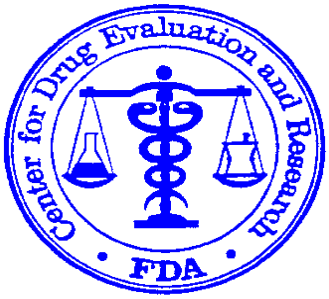

FDA/CDER
DIVISION OF CARDIOVASCULAR AND RENAL DRUG PRODUCTS

BACKGROUND MATERIAL

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

APRIL 18, 2007

NDA 20-758/S-037
AVALIDE (irbesartan/hydrochlorothiazide)
Sponsor: Bristol-Myers Squibb

MEDICAL OFFICER’S REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-758
Submission Code	SE1; s-037
Letter Date	12/15/2005
Stamp Date	12/16/2005
PDUFA Goal Date	10/15/2006
Reviewer Name	Karen A. Hicks, M.D.
Review Completion Date	August 4, 2006 Addendum September 1, 2006
Established Name	irbesartan/hydrochlorothiazide
(Proposed) Trade Name	Avalide®
Therapeutic Class	antihypertensive
Applicant	Bristol-Myers Squibb
Priority Designation	S
Formulation	oral
Dosing Regimen	Irbesartan 300 mg/HCTZ 25 mg
Indication	First line therapy
Intended Population	Severe Hypertension

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of Avalide® (irbesartan/hydrochlorothiazide) for the treatment of hypertension for patients whose blood pressure is not adequately controlled on monotherapy. This fixed dose combination is not indicated for initial therapy of hypertension except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

1.2 Recommendation on Postmarketing Actions

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In this supplemental NDA (sNDA), Bristol-Myers Squibb Company submitted 1 clinical study to support the use of Avalide® as initial therapy for severe hypertension and 1 clinical study demonstrating the efficacy of Avalide® in moderate hypertension. The studies include

1. Study CV131176 ("The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Severe Hypertension")
2. Study CV131185 ("The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Patients with Moderate Hypertension")

1.3.2 Efficacy

In Study CV131176, the primary efficacy endpoint was the proportion of subjects with seated diastolic blood pressure (SeDBP) < 90 mm Hg at Week 5 of the double-blind period. At Week 5, a significantly greater proportion of subjects on irbesartan/hydrochlorothiazide (HCTZ) achieved seated diastolic blood pressure (SeDBP) < 90 mm Hg, compared to irbesartan monotherapy (47.2% on irbesartan/hydrochlorothiazide (HCTZ) versus 33.2% on irbesartan monotherapy, $p = 0.0005$).

Study CV131176 had numerous secondary efficacy outcome measures. Although the sponsor did not make adjustments in the statistical analysis plan for multiple testing at each of the study visits, the p-values for the secondary efficacy outcome measures were highly significant and supported the efficacy of irbesartan/HCTZ in treating patients with severe hypertension. The proportion of subjects controlled (SeDBP < 90 mm Hg) on irbesartan/HCTZ combination therapy was significantly greater than irbesartan monotherapy at Weeks 1 ($p = 0.0317$), 3 ($p = 0.0002$), and 7 ($p < 0.0001$). Additionally, there was a significantly greater proportion of

subjects achieving trough SeDBP < 90 mm Hg AND trough seated systolic blood pressure (SeSBP) < 140 mm Hg at Weeks 1 ($p = 0.0230$), 3 ($p < 0.0001$), 5 ($p < 0.0001$), and 7 (< 0.0001) on combination therapy, compared with monotherapy. Lastly, the mean changes from baseline in SeSBP and SeDBP at Weeks 1 ($p \leq 0.0006$), 3 ($p < 0.0001$), 5 ($p < 0.0001$), and 7 ($p < 0.0001$) were significantly greater in the irbesartan/HCTZ group, compared with irbesartan monotherapy.

In Study CV131185, the primary efficacy endpoint was the change from baseline in SeSBP at Week 8. At Week 8, combination therapy with irbesartan/HCTZ significantly reduced trough SeSBP from baseline a mean of 5.0 mm Hg over irbesartan monotherapy ($p = 0.0016$) and a mean of 11.3 mm Hg over HCTZ monotherapy ($p < 0.0001$). At Week 8, irbesartan/HCTZ also significantly reduced trough SeDBP from baseline a mean of 3.0 mm Hg over irbesartan monotherapy ($p = 0.0013$) and a mean of 7.4 mm Hg over HCTZ monotherapy (< 0.0001).

Although the sponsor did not make adjustments in the statistical analysis plan for multiple testing at each study visit, all secondary efficacy outcome measurements in Study CV131185 were highly significant except for one parameter. The proportion of subjects with trough SeDBP < 90 mm Hg AND trough SeSBP < 140 mm Hg at Week 2 was not significantly different between the irbesartan/HCTZ combination and irbesartan monotherapy treatment groups ($p = 0.2492$). Nevertheless, in all secondary analyses of mean changes from baseline in trough SeSBP or trough SeDBP at Weeks 2, 4, and 12, combination therapy was significantly more effective than either irbesartan or HCTZ monotherapy.

In addition to demonstrating the efficacy of irbesartan/HCTZ combination therapy, Studies CV131176 and CV131185 demonstrated the efficacy of irbesartan monotherapy. In Study CV131176, at Week 1 when subjects were receiving either irbesartan 150 mg/HCTZ 12.5 mg or irbesartan 150 mg, 15.2% and 9.2% of subjects in the combination and monotherapy treatment groups, respectively, had trough SeDBP < 90 mm Hg. After one week, subjects in CV131176 were force titrated to either irbesartan 300 mg/HCTZ 25 mg or irbesartan 300 mg. By Week 3, 41.0% and 26.2% of subjects in the combination and monotherapy treatment groups, respectively, achieved SeDBP < 90 mm Hg. By Week 5, 47.2% and 33.2% of subjects and by Week 7, 51.9% and 32.8% of subjects in the combination and monotherapy treatment groups, respectively, had controlled SeDBP (SeDBP < 90 mm Hg). The sponsor did not prove futility for irbesartan monotherapy because 33.2% of subjects achieved the SeDBP goal at Week 5. Furthermore, irbesartan monotherapy was not futile in regards to the proportion of subjects achieving simultaneous SeDBP < 90 mm Hg AND SeSBP < 140 mm Hg at Weeks 3 (12.7%), 5 (19.2%), and 7 (21.4%).

In Study CV131185, subjects received irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 150 mg, or HCTZ 12.5 mg for two weeks prior to being force titrated to irbesartan 300 mg/HCTZ 25 mg, irbesartan 300 mg, or HCTZ 25 mg for an additional 10 weeks of therapy. At Week 2, 26.5%, 20.8%, and 14.4% of subjects in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively, achieved trough SeDBP < 90 mm Hg AND trough SeSBP < 140 mm Hg. At Week 4, 44.5%, 29.2%, and 17.3 % of subjects in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively, had simultaneous control of SeDBP and SeSBP. At Week 8, 53.4%, 40.6%, and

20.2% of subjects and at Week 12, 55.8%, 34.0%, and 25.0% of subjects in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively, achieved simultaneous seated diastolic and systolic blood pressure control. The sponsor did not prove futility for irbesartan monotherapy because at Weeks 2, 4, 8, and 12, 20.8%, 29.2%, 40.6%, and 34.0% of subjects, respectively, achieved simultaneous control of SeDBP and SeSBP. Furthermore, Study CV131185 demonstrated irbesartan 150 mg was more effective than HCTZ 12.5 mg and irbesartan 300 mg was more effective than HCTZ 25 mg. However, the 50 mg HCTZ dose was not studied.

1.3.3 Safety

Overall, no new safety signals were seen in Studies CV131176 and CV131185. In both the combination and monotherapy treatment groups, there were more adverse events at the highest treatment doses than at the lowest treatment doses. During the double-blind phase of Study CV131176, the percentage of subjects experiencing adverse events was lower in the irbesartan/HCTZ group (140/468 or 29.9%) than in the irbesartan monotherapy group (82/227 or 36.1%). However, subjects in the combination therapy group experienced 64.2% of the adverse events, compared with subjects in the irbesartan monotherapy treatment group who experienced 35.8% of the adverse events. In Study CV131185, the percentage of subjects experiencing adverse events during the double-blind period was higher in the irbesartan/HCTZ group (154/328 or 47.0%) than in the irbesartan monotherapy (48/106 or 45.3%) or HCTZ monotherapy (41/104 or 39.4%) treatment groups.

Hypotension appeared to be underreported in these studies, since vital signs were not recorded during peak symptoms in a number of patients.

1.3.4 Dosing Regimen and Administration

Avalide® is currently indicated for the treatment of hypertension. However, this fixed dose combination is not indicated for initial therapy. The recommended initial dose of irbesartan is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume (e.g., patients treated vigorously with diuretics or on hemodialysis). Hydrochlorothiazide (HCTZ) is effective in doses of 12.5 to 50 mg once daily.

In Study CV131176, subjects received one week of either irbesartan 150 mg/HCTZ 12.5 mg or irbesartan 150 mg and were then force titrated to irbesartan 300 mg/25 mg or irbesartan 300 mg for an additional 6 weeks.

In Study CV131185, subjects received two weeks of irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 150 mg monotherapy, or HCTZ 12.5 mg monotherapy. At two weeks, subjects were force titrated to irbesartan 300 mg/HCTZ 25 mg, irbesartan 300 mg monotherapy, or HCTZ 25 mg monotherapy for an additional 10 weeks.

For the initial treatment of severe hypertension, the sponsor recommends a starting dose of one tablet of Avalide® 150/12.5 mg once daily. The dosage may be increased after one week of therapy to a maximum of one 300/25 mg tablet once daily. Avalide® is not recommended as initial therapy in patients with intravascular volume depletion.

1.3.5 Drug-Drug Interactions

The sponsor did not perform any drug-drug interaction studies.

1.3.6 Special Populations

Study CV131176 was comprised of patients with severe hypertension, and Study CV131185 was comprised of patients with moderate hypertension. In both studies, Blacks and patients ≥ 65 years of age were underrepresented. Children were not studied, and the Division granted a deferral of pediatric studies for the severe hypertension indication.

2 INTRODUCTION AND BACKGROUND

2.1 Currently Available Treatment for Indications

Hyzaar® (losartan potassium-hydrochlorothiazide tablets) is indicated for the treatment of hypertension. The fixed dose combination is "not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients."[1]

2.2 Important Issues With Pharmacologically Related Products

Avalide® is a typical angiotensin II receptor antagonist and diuretic combination and has a low incidence of adverse effects. Class specific risks include angioedema, cough, rhabdomyolysis, hyperkalemia/hypokalemia, hepatitis, increases in blood urea nitrogen and creatinine, and mild decreases in hemoglobin.

2.3 Presubmission Regulatory Activity

In a meeting with the sponsor on November 4, 2003, there was a discussion of what would constitute futility with irbesartan monotherapy.[2] For Hyzaar, Merck had made a successful futility argument for losartan monotherapy, as 9-10% of patients only had adequate control of blood pressure despite maximum doses. Merck demonstrated that the benefit of combination therapy was greater in more than 10% of patients receiving the drug.

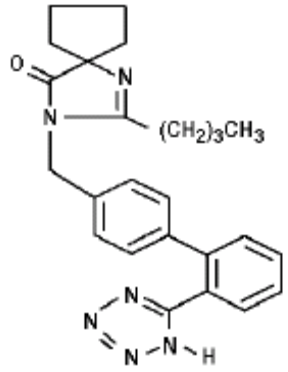
[1]Hyzaar® Label (Physician's Desk Reference)
[2]Meeting Minutes dated November 4, 2003.

In a meeting with the sponsor on November 10, 2005, the sponsor asked the Division if "failure to control 81% of subjects to levels below 140/90 mm Hg at Week 5 (or 87% at week 3) on full-dose monotherapy supported an indication for first-line combination therapy."[3] The Division responded that it would depend upon a review of the data, but the Division noted this metric was different from the primary endpoint of the study.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

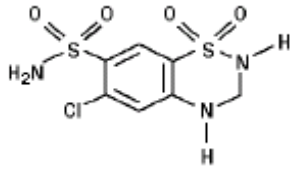
3.1 CMC (and Product Microbiology, if Applicable)

Avalide® is a combination of an angiotensin II receptor antagonist (AT_1 subtype), irbesartan, and a thiazide diuretic, hydrochlorothiazide (HCTZ). Irbesartan is a non-peptide compound with an empirical formula of $C_{25}H_{28}N_6O$ and the following structural formula:



Irbesartan

HCTZ has an empirical formula of $C_7H_8ClN_3O_4S_2$ and the following structural formula:



HCTZ

Supplement 037 provides for the use of Avalide® in the treatment of patients with uncontrolled severe hypertension. The 300/25 mg strength was approved by Ram Mittal, Ph.D. under Supplement #032 dated 3/9/2005. No changes have been proposed to the chemistry, manufacturing and controls section or to the description, dosage and administration, and how supplied section of labeling. In Supplement 037, Nallaperumal Chidambaram, Ph.D. found the

[3] **Meeting Minutes dated November 10, 2005.**

sponsor's claim for categorical exclusion from filing an environmental assessment document to be acceptable.

3.2 Animal Pharmacology/Toxicology

The sponsor did not perform any pharmacology or toxicology studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the sNDA submission dated December 15, 2005. This submission included electronic study reports for Studies CV131176 and CV131185, SAS data sets, and case report forms.

4.2 Tables of Clinical Studies

The studies included in this sNDA are displayed in Table 1.

Table 1. Table of Clinical Studies

Studies	Country/Sites	N	Design	Follow-Up
CV131176	255 Sites (US, Canada, Russia, Israel, Germany, France, Netherlands, Belgium)	697 subjects (Irbesartan/HCTZ: 468 subjects; Irbesartan monotherapy: 229 subjects)	Multicenter, randomized, double-blind, active-controlled, parallel group trial in untreated uncontrolled hypertensive (SeDBP ≥ 110 mm Hg) subjects and in subjects with uncontrolled hypertension (SeDBP ≥ 100 mm Hg) who were currently treated with antihypertensive monotherapy.	7 Weeks
CV131185	135 Sites (US, Canada, Germany, France)	538 subjects (Irbesartan/HCTZ: 328 subjects; Irbesartan monotherapy: 106 subjects; HCTZ monotherapy: 104 subjects)	Multicenter, randomized, double-blind, active-controlled, 12-week, parallel group study in untreated and treated subjects with uncontrolled hypertension.	12 Weeks

4.3 Review Strategy

I reviewed the Protocols, Administrative Letters, Clinical Study Reports, and data sets for CV131176 and CV131185. I performed additional analyses as necessary using JMP.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) audited Site #100 in Ocoee, Florida and Site #118 in Pembroke Pines, Florida. John Cappleman, M.D. and Larry Gilderman, D.O. were the

investigators for Sites #100 and #118, respectively. Dr. Gilderman was inspected in May 2006, and the conduct of Study CV131176 was found to be acceptable. Dr. Cappleman was inspected in June 2006 and was issued a VAI (voluntary action indicated) for failure to maintain adequate and accurate case histories that recorded all observations and data pertinent to the investigation. Specifically, Dr. Cappleman did not record treatment progress notes for Subject #100-12 at the Week 5 Visit that occurred on December 15, 2004 and for Subject #100-19 at the Week 7 Visit that occurred on April 7, 2005. Additionally, Subject #100-15 experienced a headache during Visit 2 on January 13, 2005, and this was recorded in the subject's progress notes but not on the case report forms. Subject #100-15 was in the placebo lead-in period on this date but subsequently received irbesartan/HCTZ up to the maximum dose.

In my opinion, these findings did not alter the overall efficacy and safety results for this sNDA.

4.5 Compliance with Good Clinical Practices

Studies CV131176 and CV131185 were conducted following Good Clinical practices and in accordance with the current Declaration of Helsinki.

4.6 Financial Disclosures

Both studies were conducted by Bristol-Myers Squibb Company. The sponsor provided categorical assurance there were no financial arrangements with the clinical investigators.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The sponsor's proposed indication is the use of Avalide® for the "treatment of hypertension for patients whose blood pressure is not adequately controlled on monotherapy . . and as initial treatment when hypertension is sufficiently severe that rapid control of blood pressure (within days to weeks) is of primary clinical importance."

5.1.1 Methods

In this sNDA, there are two reviewable studies (CV113176 and CV131185), considered separately.

5.1.2 General Discussion of Endpoints

In Study CV131176, the primary efficacy outcome measure was the proportion of subjects whose seated diastolic blood pressure (SeDBP) was controlled (SeDBP < 90 mm Hg) at Week 5.

In Study CV131185, the primary efficacy outcome measure was the change from baseline in seated systolic blood pressure (SeSBP) at Week 8.

5.1.3 Study Design

Study CV131176 was a multicenter, randomized, double-blind, active-controlled, parallel group trial in untreated uncontrolled hypertensive (SeDBP ≥ 110 mm Hg) subjects and in subjects with uncontrolled hypertension (SeDBP ≥ 100 mm Hg) who were currently treated with antihypertensive monotherapy.

Study CV131185 was a multicenter, randomized, double-blind, active-controlled, 12-week, parallel group study in untreated and treated subjects with uncontrolled hypertension. Uncontrolled hypertension in Study CV131185 was defined as follows:

Untreated Subjects:

- averaged seated systolic blood pressure (SeSBP) ≥ 160 mm Hg and < 180 mm Hg and averaged seated diastolic blood pressure (SeDBP) < 110 mm Hg

or

- averaged SeDBP ≥ 100 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

Subjects Receiving Antihypertensive Monotherapy:

- averaged SeSBP ≥150 mm Hg and < 180 mm Hg and averaged SeDBP < 110 mm Hg

or

- averaged SeDBP ≥ 95 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

5.1.4 Efficacy Findings

In Study CV131176, a significantly greater proportion of subjects treated with irbesartan/HCTZ achieved SeDBP < 90 mm Hg at Week 5, compared with irbesartan monotherapy (p = 0.0005). The primary efficacy results for CV131176 are shown in Table 2.

Table 2. Proportion of Subjects Controlled (SeDBP < 90 mm Hg) at Week 5 (CV131176)

	Trough Seated DBP < 90 mm Hg	
	Irbesartan/HCTZ N = 468	**Irbesartan N = 229**
n at Baseline	468	229
n at Week 5	423	206
Proportion Controlled (No. Controlled)	0.472 (221)	0.332 (76)
Est. Difference between Treatments	0.140	
95% CI for Estimated Difference	(0.061, 0.220)	
P-value for Between Group Comparison	0.0005	

Reproduced from Sponsor, Clinical Study Report, Table 10.1, page 64. Source: Appendix 10A, Appendix 6, Supplemental Table S.10.1A.
N=number of subjects randomized
n=number of subjects with available efficacy data at Week 5
Proportion controlled=number controlled/number randomized.
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

In Study CV131185, subjects treated with irbesartan/HCTZ had a significantly greater change from baseline in mean SeSBP at Week 8, compared with irbesartan (p = 0.0016) and HCTZ (p < 0.0001) monotherapies. The primary efficacy results for CV131185 are displayed in Table 3.

Table 3. Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP and SeDBP to Week 8 of Period B: Randomized Subjects (CV131185)

	Irbesartan/HCTZ N = 328	Irbesartan N = 106	HCTZ N = 104
SeSBP			
n	303	95	95
Baseline Mean (SD)	161.8 (12.30)	161.5 (10.29)	161.6 (10.75)
On-Therapy Mean (SD)	134.7 (15.06)	139.5 (14.25)	145.9 (13.61)
Adjusted Mean Change from Baseline (SE)	-27.1 (0.76)	-22.1 (1.36)	-15.7 (1.36)
Estimated Difference between Combo and mono Group*		-5.0	-11.3
95% CI for Estimated Difference		(-8.0, -1.9)	(-14.4, -8.3)
P-value for Combo and Mono Group Comparison**		0.0016	< 0.0001
SeDBP			
n	303	95	95
Baseline Mean (SD)	97.6 (8.13)	98.0 (7.10)	97.4 (7.65)
On-Therapy Mean (SD)	83.0 (8.95)	86.2 (8.80)	90.2 (8.91)
Adjusted Mean Change from Baseline (SE)	-14.6 (0.45)	-11.6 (0.81)	-7.3 (0.81)
Estimated Difference between Combo and mono Group*		-3.0	-7.4
95% CI for Estimated Difference		(-4.8, -1.2)	(-9.2, -5.5)
P-value for Combo and Mono Group Comparison**		0.0013	< 0.0001

Reference: Supplemental Tables S.10.1A
Randomized Subjects
***Difference = Combo Group – Mono Group**
****p-value of two-sided tests**
Note: N = number of subjects randomized into Period B
n = number of subjects with available efficacy data at Week 8
Source: Appendix 6.0, Appendix 10A
Reproduced from Sponsor, Clinical Study Report, Table 10.1.1, page 69
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

In Studies CV131176 and CV131185, the sponsor had numerous secondary efficacy outcome measures but did not adjust for multiple testing at each of the study visits. Nevertheless, with one exception, these results were highly significant and supported the efficacy of irbesartan/HCTZ in the treatment of moderate and severe hypertension. In Study CV131185, there was no significant difference between the irbesartan/HCTZ combination and irbesartan monotherapy treatment groups in the proportion of subjects with trough SeDBP < 90 mm Hg AND trough SeSBP < 140 mm Hg at Week 2 (p = 0.2492). For a full discussion of the secondary outcome measures, please see the individual study reviews in Appendix 10.

In addition to demonstrating the efficacy of irbesartan/HCTZ in the treatment of patients with moderate and severe hypertension, these studies demonstrated the efficacy of irbesartan monotherapy.

5.1.5 Efficacy Conclusions

In Study CV131176, a significantly greater proportion of subjects treated with irbesartan/HCTZ achieved SeDBP < 90 mm Hg at Week 5, compared with irbesartan monotherapy (p = 0.0005). In Study CV131185, subjects treated with irbesartan/HCTZ had a significantly greater change from baseline in mean SeSBP at Week 8, compared with irbesartan (p = 0.0016) and HCTZ (p < 0.0001) monotherapies. Combination therapy with irbesartan/HCTZ was highly effective in treating subjects with moderate and severe hypertension.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

For the evaluation of safety issues related to Avalide®, I relied upon the data and tabulations provided in this submission for Studies CV131176 and CV131185.

6.1.1 Deaths

There were no deaths in studies CV131176 or CV131185.

6.1.2 Other Serious Adverse Events

Study CV131176
In total, there were six serious adverse events that occurred during Study CV131176, including three serious adverse events in the lead-in phase (Period A) and three serious adverse events in the double-blind period (Period B).

The three serious adverse events that occurred during Period A include the following patients:

1. Subject 245-11 (50 year old (yo) Caucasian male) started the placebo lead-in phase on 3/9/2005 and continued until 3/17/2005. On 3/18/2005, lead-in medication was discontinued because the subject's sitting average diastolic blood pressure fell below 110 mm Hg (sitting average blood pressure, 136/98 mm Hg), and he requested to be withdrawn from the study. Treatment with study drug was never initiated. On [redacted], he developed a moderate/grade II headache and was hospitalized. His initial blood pressure was 160/95 and increased to 180/110. He was treated with acetaminophen and was discharged on [redacted].

2. Subject 182-4 (46 yo Caucasian female) started the placebo lead-in phase on 1/11/2005 and was discontinued on 1/12/2005. Treatment with study drug was never initiated. On 1/12/2005, she experienced a non-ST-segment elevation myocardial infarction, and her troponin peaked at 1.05 (units not specified). She subsequently underwent cardiac catheterization.

3. Subject 167-3 (45 yo Black female) signed the Informed Consent on 10/21/2004. Her past medical history was notable for congestive heart failure, cardiomegaly, elevated liver function tests, alcohol use, tobacco use, and substance abuse. On [redacted] she was admitted for a moderate/grade II hypertensive crisis, transient ischemic attack, and substance abuse (cocaine). Her symptoms included a 3 hour history of word-finding difficulty, tingling in the right upper and lower extremities, and facial droop. The Emergency Medical Services (EMS) recorded the subject's blood pressure at 210/110 mmHg. In the Emergency Room, her troponin was positive (second troponin 0.12 (units not specified)) and urine toxicology was positive for marijuana, cocaine, and benzodiazepines. Brain natriuretic peptide was markedly elevated at 2200-3140 (units not specified). An echocardiogram showed an ejection fraction of 35% and "marked atrial enlargement." Her electrocardiogram (ECG) reportedly showed no dynamic changes. She was treated medically with intravenous nitroglycerin, clopidogrel 75 mg, aspirin 325 mg, and Atorvastatin. She was discharged on [redacted] on metoprolol 25 mg po bid, furosemide 40 mg po qd, lisinopril 40 mg po qd, and aspirin 325 mg po qd. No other adverse events were reported. The patient had not received study drug.

There were three serious adverse events (SAEs) reported by two subjects receiving irbesartan/HCTZ and one subject receiving irbesartan monotherapy during Period B or within 30 days of the last Period B dose date. These serious adverse events are described below:

1. Subject 288-1 (68 yo Caucasian male) had 2 serious adverse events (SAEs) (colitis on Day 43 and chronic pyelonephritis on Day 49) after receiving double-blind (DB) irbesartan 300 mg/HCTZ 25 mg.

2. Subject 245-1 (31 yo Caucasian female) experienced a serious adverse event (possible renal artery stenosis) on day 8 of the double-blind phase while receiving irbesartan 150 mg.

3. Subject 240-4 (74 yo Caucasian female) experienced a transient ischemic attack on Day 9 of the double-blind period. The patient was initiated on irbesartan 150 mg/HCTZ 12.5 mg on 12/3/2004. On Day 8 (12/10/2004), the study drug was increased to irbesartan 300 mg/HCTZ 25 mg. Average sitting blood pressure (BP) on Day 8 was 168/73. On Day 9 (12/11/2004), the patient reported a moderate/grade II transient ischemic attack and no treatment was given. The symptoms resolved on the same day. The investigator considered the event to be of moderate intensity and unrelated to study medication. The investigator did not report this event as a SAE. However, on Day 10 (12/12/2004), the study drug was discontinued and the patient was withdrawn from the study due to this adverse event. The patient was not receiving any concomitant medications at the time of this event. Average sitting blood pressure on Day 11 (12/13/2004) was 190/104 mm Hg. Post randomization, the subject reported no other adverse events. In retrospect, I believe this adverse event should have been coded as serious.

Study CV131185

Thirteen serious adverse events (SAEs) occurred in Study CV131185 during Periods A and B, including 6 adverse events in the irbesartan/HCTZ treatment group, 3 adverse events in the

HCTZ monotherapy group, and 4 adverse events in Period A prior to the subjects receiving double-blind therapy. The serious adverse events are displayed in Table 4.

Table 4. Serious Adverse Events (SAEs) (CV131185)

#	Subject ID Age/Race/Gender	Dose at SAE Onset	Days from First Double-Blind Dose	SAE	Duration (Days)
1	Subject 23-5 66/Caucasian/F	DB Irbesartan 150/HCTZ 12.5	13	Follicular and Diffuse Large B-Cell Lymphoma, Stage IIIA	Ongoing
2	Subject 23-15 72/Caucasian/M	DB Irbesartan 300/HCTZ 25	77	Duodenal Ulcer (GI Bleed)	2
3	Subject 29-4 46/Black/F	DB Irbesartan 300/HCTZ 25	25	Abdominal Pain due to healing duodenal ulcer	5
4	Subject 34-1 58/Black/M	DB Irbesartan 150/HCTZ 12.5	10	Coronary artery disease (Patient was asymptomatic, but he had an abnormal cardiac stress test during his evaluation for Hepatitis C. Subject was referred for cardiac catheterization)	2
5	Subject 100-1 50/Caucasian/F	DB Irbesartan 300/HCTZ 25	49	Symptomatic hypokalemia. This subject developed three days of recurrent, substernal chest pressure and heaviness radiating to her back, as well as worsening muscle spasms in her chest, and cramping in both hands. She was treated with sublingual nitroglycerin x 3 and taken to the hospital on Day 49. CPK and troponin on admission were normal. She was treated with oxygen, oral metoprolol, and intramuscular hydralazine hydrochloride. Cardiac catheterization was normal on Day 51, but her serum potassium was 3.2 mEq/L. On Day 52, potassium was 4.2 mEq/L, CPK was 413 U/L (normal 28-152 U/L), and her average sitting blood pressure was 163/99 mm Hg. Study drug was discontinued.	3
6	Subject 141-6 68/Caucasian/M	DB Irbesartan 150/HCTZ 12.5	2	Moderate/Grade II Transient Ischemic Attack (TIA) with aphasia. Study drug was discontinued on Day 2 due to this event. The investigator did not think hypotension caused the TIA.	10
7	Subject 8-1 57/Caucasian/M	DB HCTZ 12.5	4	Worsening of depression	50
8	Subject 12-4 81/Caucasian/F	PSTB HCTZ 25	48	Rhabdomyolysis and new diagnosis of Type II diabetes mellitus	Diabetes was ongoing

#	Subject ID Age/Race/Gender	Dose at SAE Onset	Days from First Double-Blind Dose	SAE	Duration (Days)
9	Subject 18-4 56/Caucasian/M	DB HCTZ 25 mg	48	Right cubital nerve compression	4
10	Subject 84-3 67/Black/M	No study drug	Lead-in Phase	Grade I prostate cancer. Double-blind therapy was never initiated.	Ongoing
11	Subject 103-3 47/Caucasian/M	No study drug	Lead-in Phase	Hospitalization for abnormal stress cardiolite and ischemic cardiomyopathy. Patient was treated medically from a cardiac perspective. Double-blind therapy was never initiated.	2
12	Subject 121-1 48/Caucasian/M	No study drug	Lead-in Phase	Moderate/Grade II hypertensive crisis (patient came to the Emergency Room with "TIA-like" symptoms and blood pressure of 170/120 mm Hg). Patient was withdrawn from the study. Double-blind therapy was never initiated.	1
13	Subject 141-4 77/Caucasian/F	No study drug	Lead-in Phase	Acute anterior ST-elevation myocardial infarction. Patient underwent placement of 2 drug eluting stents. Double-blind therapy was never initiated.	15

DB: double-blind; F: female; M: male; HCTZ: hydrochlorothiazide; PSTB: Post Period B.
Source: Clinical Study Report, Table 12.3, page 96 and Patient Narratives (pages 1581-1621)
Compiled by Karen A. Hicks, M.D.

6.1.3 Dropouts and Other Significant Adverse Events

In Study CV131176, 48 (10.3%) subjects in the irbesartan/HCTZ group and 28 (12.2%) subjects in the irbesartan monotherapy group discontinued the study during the double-blind period. Ten (2.1%) patients in the irbesartan/HCTZ group and 5 (2.2%) patients in the irbesartan monotherapy group discontinued the study for adverse events during the double-blind period.

In Study CV131185, 31 subjects experienced adverse events leading to discontinuation, including 22 (6.7%) subjects in the irbesartan/HCTZ group, 4 (3.8%) subjects in the irbesartan monotherapy group, and 5 (4.8%) subjects in the HCTZ monotherapy group.

6.1.3.1 Overall profile of dropouts

Study CV131176
The overall profile of dropouts for Study CV131176 is displayed in Table 5. Subject 60-4, a 32 year old Caucasian female, was randomized to the irbesartan monotherapy treatment group. However, she was found to be pregnant at the prerandomization visit and was discontinued from the study before receiving any study drug.

In my opinion, one of the discontinued subjects (Subject 96-6) classified as "subject withdrew consent," should actually have been classified as withdrawn due to an "adverse event." Subject 96-6 was a 44 year old Black man weighing 146.1 kg and was randomized to the irbesartan/HCTZ treatment group. On 11/20/2004, his baseline seated blood pressure was 149/114, with a heart rate of 67. He received his first dose of study medication (placebo) the same day. On Day 18 post randomization (12/17/2004), the patient began experiencing a severe Grade III headache and mild dizziness. The patient self-discontinued his medication on 12/24/2004. His symptoms were still ongoing as of 12/28/2004 when his seated blood pressure was 190/131 and heart rate was 81 bpm. The sponsor coded Subject 96-6 as discontinued from the double-blind period due to "[withdrawn] consent." However, after reviewing the case report form, I believe the discontinuation should be coded as withdrawn due to an "adverse event" since the case report form states "withdrew consent due to adverse event."

Table 5. Agency Analysis: Summary of Subjects Discontinued During Period B and Reason for Discontinuation (CV131176)

	Irb/HCTZ (n, %)	Irbesartan (n, %)	Total (n, %)
Total Number of Subjects Randomized	468 (100.0)	229 (100.0)	697 (100.0)
Number of Subjects Treated	468 (100.0)	227 (99.1)	695 (99.7)
Number of Subjects who Discontinued the Study during the Double-Blind Period	48 (10.3)	28 (12.2)	76 (10.9)
Adverse event*	10 (2.1)	5 (2.2)	15 (2.2)
Subject withdrew consent*	9 (1.9)	4 (1.7)	13 (1.9)
Pregnancy	0	1 (0.4)	1 (0.1)
Lost to follow-up	4 (0.9)	3 (1.3)	7 (1.0)
Administrative reason by sponsor	1 (0.2)	0	1 (0.1)
Subject no longer meets study criteria	8 (1.7)	3(1.3)	11 (1.6)
Lack of efficacy	15 (3.2)	12 (5.2)	27 (3.9)
Poor/non-compliance	1 (0.2)	0	1 (0.1)
Number of Subjects Completing	420 (89.7)	201 (87.8)	621 (89.1)

***Table 8.1 in the Clinical Study Report on page 53 reports 10 subjects (2.1%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to "withdrawn consent" and 9 subjects (1.9%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to adverse events. Since I believe one of the irbesartan/HCTZ subjects (Subject 96-6) who was originally placed in the "withdrew consent" column in the sponsor's analysis should actually have been placed in the "adverse event" column, I retabulated the values for the "adverse event" and "withdrew consent" rows in this Table and made adjustments to the respective "Total" columns for these rows.**
Irb = Irbesartan
Analysis by Karen A. Hicks, M.D.

6.1.3.2 Adverse events associated with dropouts

Study CV131176

There were 15 discontinuations due to adverse events, including 10 subjects (2.1%) in the irbesartan/HCTZ group and 5 subjects (2.2%) in the irbesartan monotherapy group. The discontinuations due to adverse events in the double-blind period or due to serious adverse

events in the double-blind period or within 30 days of last Period B dose date are listed in Table 6.

At the highest doses in both the combination and monotherapy treatment groups, there was a higher percentage of withdrawals due to adverse events than at the lowest doses. In the irbesartan/HCTZ treatment group, 8 patients (1.7%) receiving irbesartan 300 mg/HCTZ 25 mg and 2 subjects (0.4%) receiving irbesartan 150 mg/HCTZ 12.5 mg discontinued the study due to adverse events. In the irbesartan monotherapy treatment group, 3 subjects (1.3%) receiving irbesartan 300 mg and 2 subjects (0.9%) receiving irbesartan 150 mg discontinued the study due to adverse events.

Table 6. Agency Analysis: Discontinuations Due to Adverse Events in the Double-Blind Period and Discontinuations Due to Serious Adverse Events in the Double-Blind Period or Within 30 Days of Last Period B Dose Date (CV131176)

#	Subject Age/Gender/ Race	Study Drug	Onset Day†	Duration	Type	Preferred Term/ Additional Information
Irbesartan/HCTZ						
1	Subject 3-1 38/M/W	Irb 300/ HCTZ 25	8	6	AE	Dizziness Pt complained of dizziness from 2/2/2005 through 2/4/2005 and from 2/9/2005 (Day 8) through 2/14/2005. The last dose of medication was on 2/13/2005. Pt was not orthostatic.
2	Subject 27-2 61/M/W	Irb 300/ HCTZ 25	43	9	AE	Fatigue
3	Subject 65-3 58/F/W	Irb 300/ HCTZ 25	12	4	AE	Chest Discomfort
			12	4	AE	Polyuria
			12	4	AE	Asthenia
4	Subject 141-2 50/M/W	Irb 300/ HCTZ 25	12	-	AE	Erectile Dysfunction
5	Subject 160-6 (47/F/W)	Irb 150/ HCTZ 12.5	6	49	AE	Rash
6	Subject 175-7 63/F/W	Irb 150/ HCTZ 12.5	1	13	AE	Abdominal Pain
			1	13	AE	Headache
7	Subject 240-4 74/F/W	Irb 300/ HCTZ 25	9	1	SAE	Transient Ischemic Attack
8	Subject 248-1 32/F/W	Irb 300/ HCTZ 25	30	7	AE	Hypotension (Please see further discussion under Section 6.1.7, Vital Signs)
9	Subject 305-1 48/F/W	Irb 300/ HCTZ 25	23	6	AE	Dizziness
			23	7	AE	Muscle Fatigue
			27	2	AE	Dyspnoea Exertional
10	Subject 96-6 44/M/B	Irb 300/ HCTZ 25	18	Ongoing	AE	Headache/Dizziness
Irbesartan						
11	Subject 5-6 39/M/W	Irb 150	2	8	AE	Headache
			2	8	AE	Nausea
12	Subject 121-6 47/M/W	Irb 150	2	6	AE	Fatigue
			2	6	AE	Lethargy
			2	6	AE	Muscle Spasms
			2	6	AE	Muscular Weakness

#	Subject Age/Gender/ Race	Study Drug	Onset Day†	Duration	Type	Preferred Term/ Additional Information
13	Subject 175-5 54/F/W	Irb 300	12	-	AE	Wrist Fracture
14	Subject 226-1 46/M/W	Irb 300	7	1	AE	Dizziness
			7	1	AE	Nausea
15	Subject 240-7 53/F/W	Irb 300	15	-	AE	Urticaria (angioedema)

†Adverse Event Days Relative to First Study Medication Dose
B = Black; Irb = Irbesartan; HCTZ = Hydrochlorothiazide; AE = Adverse Event; SAE = Serious Adverse Event.
Source: Derived Adverse Event data set and Appendix 8.1.2
Analysis by Karen A. Hicks, M.D.

Subject 65-3, a 58 year old Caucasian woman, was initiated on irbesartan 150 mg/HCTZ 12.5 mg on 2/7/2005. On Day 12 (2/18/2005), while she was receiving irbesartan 300 mg/HCTZ 25 mg, she developed moderate/grade II chest discomfort, weakness, and polyuria that did not require treatment. Study medication was discontinued on Day 15 (2/21/2005), and the events were considered resolved. Average standing blood pressure was 166/115 mm Hg on Day 1 (2/7/2005), 114/76 mm Hg on Day 8 (2/14/2005), and 151/83 mm Hg on Day 15 (2/21/2005). At the time of her symptoms, she was also receiving Simvastatin 40 mg. The subject did not report any other adverse events post randomization.

Study CV131185

Table 7 displays the subjects who discontinued the study during Period B due to adverse events. There were 31 subjects who discontinued the study due to adverse events in the double-blind period, including 13 patients receiving irbesartan 300 mg/HCTZ 25 mg, 9 subjects receiving irbesartan 150 mg/HCTZ 12.5 mg, 1 patient receiving irbesartan 300 mg, 3 subjects receiving irbesartan 150 mg, 3 patients receiving HCTZ 25 mg, and 2 patients receiving HCTZ 12.5 mg.

Table 7. Subjects who Discontinued from Double-Blind Period Due to Adverse Events (CV131185)

#	Subject Age/Gender/Race	Study Drug	Onset Day†	Duration	Type	Preferred Term/ Comments
1	Subject 17-11 34/M/W	Irb 300/ HCTZ 25	29	40	AE	Hyperkalemia (Potassium 7.6 mEq/L)
2	Subject 23-15 72/M/W	Irb 300/ HCTZ 25	77	2	SAE	Duodenal Ulcer
3	Subject 33-3 53/M/H	Irb 300/ HCTZ 25	29	32	AE	Decreased serum potassium (Potassium 3.1 mEq/L)
4	Subject 35-5 64/M/W	Irb 300/ HCTZ 25	76	1	AE	Worsening dizziness
5	Subject 36-14 52/M/W	Irb 300/ HCTZ 25	64	Continuing	AE	Vertigo
6	Subject 52-7 81/F/W	Irb 300/ HCTZ 25 mg	15	4	AE	Elevated potassium (Potassium 5.8 mEq/L)

#	Subject Age/Gender/Race	Study Drug	Onset Day†	Duration	Type	Preferred Term/ Comments
7	Subject 66-6 37/F/B	Irb 300/ HCTZ 25 mg	16	22	AE	Dizziness (2/10/2005 – 2/23/2005 and 2/23/2005 – 3/16/2005) (NOTE: Patient began study on 1/19/2005 with 21 days of placebo therapy. Patient first experienced dizziness during first two weeks of therapy with irbesartan 150 mg/HCTZ 12.5 mg, instead of irbesartan 300 mg/HCTZ 25 mg)
			29	9	AE	Hypokalemia (Potassium 3.2 mEq/L (normal range 3.6 – 5.2 mEq/L))
			29	9	AE	Orthostatic hypotension (3/8/2005-3/16/2005) (On 3/8/2005, sitting average blood pressure was 98/76 mm Hg with heart rate 94 bpm. Standing average blood pressure was 86/50 mm Hg with heart rate 80 bpm. Final dose was on 3/13/2005.)
8	Subject 69-26 58/M/W	Irb 300/ HCTZ 25	19	20	AE	Headache
9	Subject 90-1 57/M/W	Irb 300/ HCTZ 25	69	10	AE	Dizziness (On Day 66, the patient experienced a fall that the investigator attributed to **hypotension, but no blood pressure was recorded on this date**. On Day 69, the patient experienced lightheadedness due to hypotension, followed by a fall with rib contusion. His blood pressure was 98/52 mm Hg.)
10	Subject 99-6 53/F/W	Irb 300/ HCTZ 25	14	1	AE	Asthenia (weak legs)
			15	2	AE	Palpitations
			15	7	AE	Pruritic rash (itchy burning rash on inside of both legs & arms)
11	Subject 100-1 50/F/W	Irb 300/ HCTZ 25	49	3	SAE	Symptomatic hypokalemia (Potassium 3.2 mEq/L)
12	Subject 126-2 57/M/B	Irb 300/ HCTZ 25	30	Continuing	AE	Increased creatinine (Creatinine 1.6 mg/dL (normal range 0.7 – 1.3 mg/dL))
13	Subject 143-4 63/M/W	Irb 300/ HCTZ 25	53	10	AE	Orthostatic hypotension **(no vital signs were recorded during symptomatic period)**. Medication was discontinued on Day 58. Symptoms resolved on Day 62. On Day 63, sitting average blood pressure was 146/81 mm Hg with heart rate 66 bpm. Standing average blood pressure was 128/77 mm Hg with heart rate 68 bpm.
14	Subject 9-5 44/F/W	Irb 150/ HCTZ 12.5	9	8	AE	Erythema
15	Subject 21-6 59/M/A	Irb 150/ HCTZ 12.5	11	3	AE	Hypotension (dizziness due to low blood pressure; **blood pressure on Day 11 was not recorded**)
16	Subject 23-5 66/F/W	Irb 150/ HCTZ 12.5	13	Continuing	SAE	Follicular and Diffuse Large B-Cell Lymphoma

#	Subject Age/Gender/Race	Study Drug	Onset Day†	Duration	Type	Preferred Term/ Comments
17	Subject 75-3 58/F/W	Irb 150/ HCTZ 12.5	4	40	AE	Fatigue
18	Subject 81-7 47/M/W	Irb 150/ HCTZ 12.5	1	72	AE	Arthralgia (joint pains)
		Same	1	72	AE	Muscle spasms (muscle cramps)
19	Subject 89-6 50/F/W	Irb 150/ HCTZ 12.5	4	10	AE	Pruritus generalized
		Same	5	10	AE	Rash
20	Subject 127-3 86/M/W	Irb 150/ HCTZ 12.5	8	4	AE	Dizziness **(no blood pressure was recorded during symptoms)**. On Day 24, sitting average blood pressure was 138/90 mm Hg with heart rate 75 bpm. Standing average blood pressure was 108/66 with heart rate 66 bpm.
21	Subject 141-6 68/M/W	Irb 150/ HCTZ 12.5	2	10	SAE	Transient Ischemic Attack
22	Subject 142-4 56/F/A	Irb 150/ HCTZ 12.5	1	Continuing	AE	Blood potassium increased (peak potassium was 5.9 mEq/L)
23	Subject 127-4 87/F/W	Irb 300	82	9	AE	Diarrhea
			82	9	AE	Vomiting
24	Subject 14-1 82/F/W	Irb 150	1	3	AE	Dizziness **(no vital signs were recorded during symptoms)**
			1	3	AE	Hypotonia
25	Subject 68-1 44/M/W	Irb 150	12	20	AE	Rash (face)
26	Subject 125-5 51/M/W	Irb 150	13	5	AE	Stomach discomfort
			14	4	AE	Diarrhea
			14	4	AE	Nervousness
27	Subject 12-4 81/F/W	PSTB HCTZ 25	34	22	SAE	Rhabdomyolysis
28	Subject 30-6 77/M/B	HCTZ 25	42	2	AE	Pain in extremity (right leg)
29	Subject 122-3 61/M/W	HCTZ 25	31	23	AE	Hypertension (uncontrolled) (average sitting blood pressure on Day 31 was 157/101 mm Hg)
30	Subject 8-1 57/M/W	HCTZ 12.5	4	50	SAE	Depression (worsening of depression)
31	Subject 40-3 80/M/W	HCTZ 12.5	1	5	AE	Fibromyalgia (worsening fibromyalgia)

†Adverse Event Days Relative to First Study Medication Dose
A: Asian; B: Black; W: White; F: Female; M: Male; Irb: Irbesartan; HCTZ: Hydrochlorothiazide; PSTB: Post Period B.
Table Compiled by Karen A. Hicks, M.D. using Clinical Study Report, Appendix 12.4 (pages 1623-1631), Patient Narratives (pages 1581-1621), Case Report Forms, and Adverse Event data set.

6.1.3.3 Overall Incidence of Adverse Events

Study CV131176

During the placebo lead-in, double-blind phase, and post B periods of Study CV131176, 274 patients experienced a total of 494 adverse events. Of these 274 patients, 33 patients were ≥ 65 years of age and experienced 60 adverse events.

During the double-blind period or within 30 days of the last Period B dose date, a total of 222 patients (140 subjects (140/468 or 29.9%) in Treatment Group 1 and 82 subjects (82/227 or 36.1%) in Treatment Group 2) experienced 344 adverse events. Of these 222 patients, 27 patients were ≥ 65 years of age and experienced 49 (14.2%) of the 344 adverse events. In patients ≥ 65 years of age, a total of 28 of the adverse events occurred in patients receiving irbesartan 300 mg/HCTZ 25 mg, while 2, 17, and 2 adverse events occurred in patients receiving irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 300 mg, and irbesartan 150 mg, respectively.

In both the combination and monotherapy treatment groups, there were more adverse events at the highest treatment doses than at the lowest treatment doses.

During the double-blind period, a total of 140 subjects in Treatment Group 1 (irbesartan/HCTZ) experienced 221 (64.2%) adverse events, including 158 adverse events on irbesartan 300 mg/HCTZ 25 mg and 63 adverse events on irbesartan 150 mg/HCTZ 12.5 mg.

During the double-blind period, a total of 82 subjects in Treatment Group 2 (irbesartan monotherapy) experienced 123 (35.8%) adverse events, including 87 adverse events on irbesartan 300 mg and 36 adverse events on irbesartan 150 mg.

Table 8 displays the overall incidence of adverse events (AE) during the double-blind period in Study CV131176. The overall percentage of unique subjects experiencing adverse events was lower in the irbesartan/HCTZ group (29.9%) than in the irbesartan monotherapy group (36.1%). However, this smaller percentage of subjects in the combination therapy group experienced 64.2% of the adverse events, compared with patients in the irbesartan monotherapy treatment group who experienced 35.8% of the adverse events.

Table 8. Sponsor's Analysis: Overall Incidence of Adverse Events During Double-Blind Treatment Period (CV131176)

Event	Irbesartan/HCTZ (N = 468) N (%)	Irbesartan (N = 227) N (%)
Total Subjects with Adverse Events (AE)‡	140 (29.9%)	82 (36.1%)
Total Subjects with Treatment-Related AE	53 (11.3%)	23 (10.1%)
Total Subjects with Serious Adverse Events (SAE)	**1 (0.2%)†**	1 (0.4%)
Total Subjects with Discontinuations due to AE	**9 (1.9%)***	5 (2.2%)
Deaths	0	0

‡Adverse Event = unique subjects experiencing adverse events. Total unique subjects experiencing adverse events = 222.

†If one includes Subject 240-4, the 74 year old white female who experienced a transient ischemic attack one day after her study medication was increased to irbesartan 300 mg/HCTZ 25 mg, the irbesartan/HCTZ

combination group has 2 serious adverse events (0.43%).
***In the irbesartan/HCTZ treatment group, I counted 10 discontinuations due to AE (2.2%), not 9 (1.9%). The additional AE involved Subject 96-6 who had been coded as a "withdrew consent" as opposed to "withdrew due to an adverse event."**
Reproduced from Sponsor, Clinical Study Report, Table 12.1, page 76.
Source: Supplemental Tables S.12.1.1, S.12.1.2, S.12.2, S.12.3; Appendix 12.4.
Analysis verified by Karen A. Hicks, M.D.

Study CV131185
In Study CV131185, there were no pregnancies.

Throughout the study, 311 patients experienced a total of 653 adverse events. Ninety-nine of these adverse events occurred in patients ≥ 65 years of age.

During the double-blind period or within 30 days of the last Period B dose date, 243 subjects experienced a total of 415 adverse events or serious adverse events. Seventy-one (17.1%) of these adverse events occurred in 46 patients ≥ 65 years of age.

In Treatment Group 1 (irbesartan/HCTZ) during the double-blind phase, 154 subjects (47.0%) experienced a total of 247 adverse events. At different times during the double-blind phase, some subjects received irbesartan 150 mg/HCTZ 12.5 mg or irbesartan 300 mg/HCTZ 25 mg. Seventy-five of the 247 adverse events occurred in 58 subjects receiving irbesartan 150 mg/HCTZ 12.5 mg, and 172 of the 247 adverse events occurred in 119 subjects receiving irbesartan 300 mg/HCTZ 25 mg.

In Treatment Group 2 (irbesartan monotherapy) during the double-blind phase, 48 subjects (45.3%) experienced 96 adverse events. Thirty-six of the 96 adverse events occurred in 20 subjects receiving irbesartan 150 mg. Sixty of the 96 adverse events occurred in 35 subjects receiving irbesartan 300 mg.

In Treatment Group 3 (HCTZ monotherapy) during the double-blind phase, 41 subjects (39.4%) experienced a total of 72 adverse events. At different times during the double-blind phase, some subjects received HCTZ 12.5 mg or HCTZ 25 mg. Twenty-nine of the 72 adverse events occurred in 24 subjects receiving HCTZ 12.5 mg. Forty-one of the 72 adverse events occurred in 25 subjects receiving HCTZ 25 mg. Additionally, Subject 12-4, an 81 year old Caucasian female, experienced 2 serious adverse events, including diabetes and rhabdomyolysis, during the post-B phase while receiving HCTZ 25 mg.

An overview of adverse events for Study CV131185 is displayed in Table 9. The irbesartan/HCTZ combination group had the highest percentage of subjects with adverse events, serious adverse events, and discontinuations due to adverse events.

Table 9. Overview of Adverse Events During Period B (CV131185)

Event	Irbesartan/HCTZ (N = 328) n (%)	Irbesartan (N = 106) n (%)	HCTZ (N = 104) n (%)
Total Subjects with Adverse Events (AE)	154 (47.0)	48 (45.3)	41 (39.4)
Total Subjects with Treatment-Related AE	47 (14.3)	12 (11.3)	8 (7.7)
Total Subjects with Serious Adverse Events (SAE)	6 (1.8)	0	3 (2.9)
Total Subjects with Discontinuations due to AE	22 (6.7)	4 (3.8)	5 (4.8)
Deaths	0	0	0
Source: Table 2.12.1.1B, Table S.12.1.1C, Table @.12.2, Table S.12.3, Table S.12.4 Reproduced from Sponsor, Clinical Study Report, Table 12.1, page 83.			

6.1.3.4 Prespecified Adverse Events

Study CV131176

Prespecified secondary safety outcome measures in CV131176 included

- the frequency of treatment discontinuations due to adverse events
- the frequency of hypotension, dizziness, and syncope
- the frequency of headaches
- the frequencies of hypokalemia and hyperkalemia

Treatment Discontinuations Due to Adverse Events

During the double-blind period of CV131176, 10 subjects (2.2%) in the irbesartan/HCTZ group and 5 subjects (2.2%) in the irbesartan monotherapy group discontinued the study due to adverse events.

Hypotension

In the irbesartan/HCTZ group, hypotension was reported in 2 subjects (0.4%), including one subject with postural dizziness and one subject with orthostatic hypotension. There were no reports of hypotension in the irbesartan monotherapy group.

Dizziness

In the irbesartan/HCTZ group, dizziness was reported in 16 subjects (3.4%). Eleven out of 16 subjects were receiving irbesartan 300 mg/HCTZ 25 mg and 5 subjects were receiving irbesartan 150 mg/HCTZ 12.5 mg. In the high-dose combination group, the mean onset of dizziness was 27.5 days relative to first study medication dose. In the low-dose combination group, the mean onset of dizziness was 2.6 days relative to first study medication dose.

In the irbesartan monotherapy group, dizziness occurred in 9 subjects (4.0%). At the time of symptoms, six subjects were receiving irbesartan 300 mg and 3 subjects were receiving irbesartan 150 mg. In the high- and low-dose monotherapy groups, the mean onset of dizziness was 20.7 and 1.7 days, respectively, after the first study medication dose.

Two patients ≥ 65 years of age experienced dizziness during the double-blind period. One patient receiving irbesartan 300 mg/HCTZ 25 mg began experiencing dizziness on Day 42, but

the symptoms resolved in 2 days. Another patient receiving irbesartan 300 mg began experiencing dizziness on Day 32, but the symptoms resolved in 1 day.

Syncope
There were no reports of syncope in either treatment group.

Headaches
Headaches occurred in 4.1% (19 subjects) and 6.6% (15 subjects) of the patients in the irbesartan/HCTZ and irbesartan monotherapy groups, respectively. One additional patient (0.2%) in the irbesartan/HCTZ group reported a migraine.

Hypokalemia and Hyperkalemia
In the irbesartan/HCTZ group, hypokalemia was reported in 3 (0.6%) subjects and hyperkalemia were reported in 1 (0.2%) subject. In the irbesartan monotherapy group, hypokalemia was reported in 1 subject (0.4%), but there were no reported cases of hyperkalemia. No subjects in either treatment group had a serum potassium < 3.0. Three subjects (0.6%) in the irbesartan/HCTZ group and 3 subjects (1.3%) in the irbesartan monotherapy group had a serum potassium > 6.0 mEq/L. The Agency Analysis for the number of subjects with prespecified adverse events is displayed in Table 10.

Table 10. Agency Analysis: Subjects with Prespecified Adverse Events and Discontinuations During the Double-Blind Treatment Period (CV131176)

Adverse Event (AE) (Preferred Term)	Irbesartan/HCTZ (N = 468) N (%)	Irbesartan (N = 227) N (%)
Subjects with Discontinuations due to AE	10 (2.1%)	5 (2.2%)
Subjects with Prespecified Adverse Events		
Hypotension	**2 (0.4%)**	**0**
Postural Dizziness	1 (0.2%)	0
Orthostatic Hypotension	1 (0.2%)	0
Dizziness (includes light-headedness)	**16 (3.4%)**	**9 (4.0%)**
Syncope	**0**	**0**
Headaches	**20 (4.3%)**	**15 (6.6%)**
Headache	19 (4.1%)	15 (6.6%)
Migraine Headache	1 (0.2%)	
Hypokalemia	**3 (0.6%)**	**1 (0.4%)**
Hyperkalemia*	**1 (0.2%)**	**0**
Serum Potassium < 3.0	**0**	**0**
Serum Potassium > 3.0	**3 (0.6%)**	**3 (1.3%)**
***Please note that although hyperkalemia was reported as an adverse event in one subject randomized to irbesartan/HCTZ only, there were three subjects (0.6 %) in the irbesartan/HCTZ group and three subjects**		

in the irbesartan monotherapy group (1.3%) who achieved elevated potassium levels meeting the "laboratory marked abnormality criteria." Please see Table 19 **for full details.**
Analysis by Karen A. Hicks, M.D.. Source: Derived Adverse Event Data set.

Study CV131185

The number of subjects with prespecified adverse events for Study CV131185 is displayed in Table 11. The irbesartan/HCTZ combination therapy group had the highest percentage of subjects (10.7%) with selected adverse events, compared with 6.6% of the irbesartan monotherapy and 6.7% of the HCTZ monotherapy treatment groups. In the age group ≥ 65 years, one 80 year old patient experienced hyperkalemia on HCTZ 12.5 mg.

A total of 15 subjects experienced dizziness, including 10 subjects in the irbesartan/HCTZ combination group, 4 subjects in the irbesartan monotherapy group, and 1 subject in the HCTZ monotherapy group. A total of 7, 3, 3, 1, and 1 subject(s) receiving irbesartan 300 mg/HCTZ 25 mg, irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 300 mg, irbesartan 150 mg, and HCTZ 12.5 mg, respectively, experienced dizziness.

A total of 22 subjects experienced nonsinus headaches during the double-blind period or within 30 days of the last period B dose date, including 14 subjects in the irbesartan/HCTZ group, 3 subjects in the irbesartan monotherapy group, and 5 subjects in the HCTZ monotherapy group. In the irbesartan/HCTZ group 7 subjects received irbesartan 300 mg/HCTZ 25 mg and 7 subjects received irbesartan 150 mg/HCTZ 12.5 mg. In the irbesartan monotherapy group, all 3 subjects received 300 mg. In the HCTZ monotherapy group, 4 subjects received HCTZ 12.5 mg and 1 subject received HCTZ 25 mg.

Table 11. Number (Percent) of Subjects with Pre-Specified Adverse Events During Double-Blind Period by AE and PT (CV131185)

Adverse Events (AE) Preferred Term (PT)	Irbesartan/HCTZ		Irbesartan		HCTZ	
	(N = 328) n (%)	95% CI	(N = 106) n (%)	95% CI	(N = 104) n (%)	95% CI
Subjects with Selected Adverse Events	**35 (10.7)**	**(7.5, 14.5)**	**7 (6.6)**	**(2.7, 13.1)**	**7 (6.7)**	**(2.7, 13.4)**
Dizziness	10 (3.0)	(1.4, 5.4)	4 (3.8)	(1.0, 9.3)	1 (1.0)	(0.0, 5.2)
Headache	18 (5.5)	(3.2, 8.4)	4 (3.8)	(1.0, 9.3)	5 (4.8)	(1.6, 10.8)
Headache	14 (4.3)		3 (2.8)		5 (4.8)	
Sinus Headache	4 (1.2)		1 (0.9)		0	
Hyperkalemia/Increased Potassium	4 (1.2)	(0.3, 3.0)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.2)
Blood Potassium Increased	2 (0.6)		0		1 (1.0)	
Hyperkalemia	2 (0.6)		0		0	
Hypokalemia/Decreased Potassium	3 (0.9)	(0.2, 2.6)	0	(0.0, 3.4)	0	(0.0, 3.5)
Blood Potassium Decreased	1 (0.3)		0		0	
Hypokalemia	2 (0.6)		0		0	
Hypotension	3 (0.9)	(0.2, 2.6)	0	(0.0, 3.4)	0	(0.0, 3.5))
Hypotension	1 (0.3)		0		0	

Adverse Events (AE) Preferred Term (PT)	Irbesartan/HCTZ		Irbesartan		HCTZ	
	(N = 328) n (%)	95% CI	(N = 106) n (%)	95% CI	(N = 104) n (%)	95% CI
Orthostatic Hypotension	2 (0.6)		0		0	
Syncope	0	(0.0, 1.1)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.2)
Syncope Vasovagal	0		0		1 (1.0)	
Serum Potassium < 3.0	0	(0.0, 1.1)	0	(0.0, 3.4)	0	(0.0, 3.5)
Serum Potassium > 6.0	4 (1.2)	(0.3, 3.0)	0	(0.0, 3.4)	0	(0.0, 3.5)
Reproduced from Sponsor, Clinical Study Report, Table S.12.1.1A, page 259. Analysis verified by Karen A. Hicks, M.D.						

Five subjects experienced hyperkalemia/increased blood potassium, including 1 subject receiving HCTZ 12.5 mg, 3 subjects receiving irbesartan 300 mg/HCTZ 25 mg, and 1 subject receiving irbesartan 150 mg/HCTZ 12.5 mg.

Three subjects experienced hypokalemia. All subjects were receiving irbesartan 300 mg/HCTZ 25 mg.

Three subjects experienced hypotension, including two subjects on irbesartan 300 mg/HCTZ 25 mg and one subject on irbesartan 150 mg/HCTZ 12.5 mg.

One subject on HCTZ 25 mg experienced vasovagal syncope.

During the course of the study, there were no patients in any of the treatment groups with serum potassium < 3.0 mEq/L.

A total of 6 subjects experienced 8 episodes of potassium > 6.0 mEq/L. Two episodes occurred in the lead-in phase. The remaining six episodes occurred in 4 patients in the combination group during the double-blind phase. Three patients were receiving irbesartan 300 mg/HCTZ 25 mg, and one subject was receiving irbesartan 150 mg/HCTZ 12.5 mg. The episodes of potassium > 6.0 mEq/L are summarized in Table 12. These findings suggest potassium needs to be monitored closely with irbesartan/HCTZ combination therapy. In particular, Subjects 115-2 and 17-11 had extremely high potassium values which could have been potentially life-threatening. Subject 38-3 was on naproxen at the time of the hyperkalemia. The other subjects were not on any concomitant medications that would have contributed to the hyperkalemia.

Table 12. Potassium > 6.0 mEq/L (CV131185)

#	Subject	Phase	Potassium (meq/l)	Treatment
1	**Subject 101-5 (58 yo caucasian male)**	**Pre-Lead In (Day -23)**	**6.1**	**Pre-Lead In**
2	**Subject 115-2 (65 yo Black male)**	**Double-Blind (Day 30)**	**6.5**	**Irbesartan 300/HCTZ 25**
	Subject 115-2	**Double-Blind (Day 86)**	**6.1**	**Irbesartan 300/HCTZ 25**
3	**Subject 117-13**	**Pre-Lead In**	**6.1**	**Pre-Lead In**

#	Subject	Phase	Potassium (meq/l)	Treatment
4	**Subject 17-11 (34 yo caucasian male)**	**Double-Blind (Day 29)**	**7.6**	**Irbesartan 300/ HCTZ 25**
	Subject 17-11	**Double-Blind (Day 56)**	**6.9**	**Irbesartan 300/HCTZ 25**
5	**Subject 38-3 (47 yo caucasian female)**	**Double-Blind (Day 85)**	**6.1**	**Irbesartan 300/HCTZ 25**
6	**Subject 50-8 (59 yo Black male)**	**Double-Blind (Day 11)**	**6.1**	**Irbesartan 150/HCTZ 12.5**
Analysis by Karen A. Hicks, M.D.				

6.1.4 Other Search Strategies

I reviewed the submitted data sets to determine if the adverse events were consistent with what was reported in the Clinical Study Reports. I also performed analyses for adverse events the sponsor had not prespecified.

6.1.5 Common Adverse Events

6.1.5.1 Common adverse event tables

In Study CV131176, the most common adverse events as reported by at least 1% of subjects in either treatment group during the double-blind period are displayed by preferred term in Table 13. The most frequently reported adverse events in both treatment groups were headache and dizziness.

Table 13. Sponsor's Analysis: Most Common Adverse Events As Reported by At Least 1 Percent of Subjects In Either Treatment Group During Double-Blind Period, by Preferred Term (CV131176)

	Number (%) of Subjects	
Preferred Term (PT) (%)	**Irb/HCTZ N = 468**	**Irbesartan N = 227**
Total Subjects with at least 1 AE	140 (29.9%)	82 (36.1%)
Headache	19 (4.1%)	15 (6.6%)
Dizziness	16 (3.4%)	9 (4.0%)
Nasopharyngitis	8 (1.7%)	10 (4.4%)
Bronchitis	6 (1.3%)	6 (2.6%)
Fatigue	6 (1.3%)	1 (0.4%)
Upper Respiratory Tract Infection	6 (1.3%)	4 (1.8%)
Erectile Dysfunction	5 (1.1%)	0
Nausea	5 (1.1%)	5 (2.2%)
Diarrhea	4 (0.9%)	3 (1.3%)
Sinusitis	4 (0.9%)	3 (1.3%)
Cough	3 (0.6%)	4 (1.8%)
Muscle Spasms	2 (0.4%)	3 (1.3%)
Reproduced from Sponsor, Clinical Study Report, Table 12.1.1B, page 81. Source: Appendix 12.0.		

In Study CV131185, the most common adverse events as reported by at least 1 percent of subjects in any treatment group during the double-blind period were similar to those seen in Study CV131176.

By preferred term and age group, the most common adverse events in Study CV131176 as reported by at least 1 percent of subjects in either treatment group during the double-blind period are displayed in Table 14. A total of 91 subjects ≥ 65 years of age were enrolled in the study, representing 13.1% of the randomized subjects only.

Table 14. Sponsor's Analysis: Number (Percent) of Subjects with Adverse Events Occurring in At Least 1% of Subjects in Either Treatment Group During Double-Blind Period by Preferred Term and Age-Group (CV131176)

	Number (%) of Subjects	
Preferred Term (PT) (%)	**Irb/HCTZ**	**Irbesartan**
Age < 65 Years	**N = 415**	**N = 189**
Total Subjects with AE	**126 (30.4%)**	**69 (36.5%)**
Nasopharyngitis	7 (1.7%)	9 (4.8%)
Bronchitis	6 (1.4%)	3 (1.6%)
Upper Respiratory Tract Infection	6 (1.4%)	4 (2.1%)
Sinusitis	4 (1.0%)	3 (1.6%)
Influenza	2 (0.5%)	2 (1.1%)
Headache	17 (4.1%)	13 (6.9%)
Dizziness	15 (3.6%)	8 (4.2%)
Diarrhea	4 (1.0%)	3 (1.6%)
Nausea	4 (1.0%)	4 (2.1%)
Fatigue	5 (1.2%)	1 (0.5%)
Chest Pain	2 (0.5%)	2 (1.1%)
Chest Discomfort	1 (0.2%)	2 (1.1%)
Muscle Spasms	2 (0.5%)	3 (1.6%)
Cough	2 (0.5%)	4 (2.1%)
Erectile Dysfunction	5 (1.2%)	0
Hot flush	1 (0.2%)	2 (1.1%)
Age ≥ 65 years	**N = 53**	**N = 38**
Total Subjects with AE	**14 (26.4%)**	**13 (34.2%)**
Blood creatinine increased	2 (3.8%)	0
Blood glucose increased	1 (1.9%)	0
Blood uric acid increased	1 (1.9%)	0
Electrocardiogram abnormal	1 (1.9%)	0
Urine output increased	1 (1.9%)	0
Colitis	1 (1.9%)	0
Constipation	1 (1.9%)	0
Nausea	1 (1.9%)	1 (2.6%)
Dry Mouth	0	1 (2.6%)
Nasopharyngitis	1 (1.9%)	1 (2.6%)
Pyelonephritis chronic	1 (1.9%)	0
Rhinitis	1 (1.9%)	1 (2.6%)
Viral infection	1 (1.9%)	0

Preferred Term (PT) (%)	Number (%) of Subjects	
	Irb/HCTZ	Irbesartan
Bronchitis	0	3 (7.9%)
Urinary tract infection	0	1 (2.6%)
Headache	2 (3.8%)	2 (5.3%)
Dizziness	1 (1.9%)	1 (2.6%)
Transient ischaemic attack	1 (1.9%)	0
Somnolence	0	1 (2.6%)
Cataract	1 (1.9%)	0
Retinopathy Hypertensive	0	1 (2.6%)
Fatigue	1 (1.9%)	0
Pyrexia	0	1 (2.6%)
Hyponatremia	1 (1.9%)	0
Back Pain	1 (1.9%)	0
Arthralgia	0	1 (2.6%)
Pain in Extremity	0	1 (2.6%)
Nervousness	1 (1.9%)	0
Hypertensive nephropathy	1 (1.9%)	0
Pollakiuria	1 (1.9%)	0
Cough	1 (1.9%)	0
Pruritus	1 (1.9%)	0
Psoriasis	0	1 (2.6%)
Supraventricular extrasystoles	0	1 (2.6%)
Humerus fracture	0	1 (2.6%)
Reproduced from Sponsor, Clinical Study Report, Table S.12.1.4, pages 247-256.		

In Study CV131185, adverse event findings by age-group were similar although diarrhea was reported in 3 (4.4%) irbesartan/HCTZ subjects, 1 (5.3%) irbesartan subject, and 1 (4.3%) HCTZ subject ≥ 65 years of age.

6.1.5.2 Identifying common and drug-related adverse events

In Study CV131176, the most common related adverse events as reported by at least 1 percent of subjects in either treatment group during the double-blind period are displayed by preferred term in Table 15. Dizziness was the most common related adverse event in both treatment groups.

Table 15. Sponsor's Analysis: Most Common Related Adverse Events As Reported by At Least 1 Percent Of Subjects In Either Treatment Group During Double-Blind Period, by Preferred Term (CV131176)

Preferred Term (PT) (%)	Number (%) of Subjects	
	Irb/HCTZ N = 468	Irbesartan N = 227
Total Subjects with at least 1 AE	53 (11.3%)	23 (10.1%)
Dizziness	12 (2.6%)	7 (3.1%)
Headache	6 (1.3%)	5 (2.2%)
Erectile Dysfunction	5 (1.1%)	0
Fatigue	5 (1.1%)	1 (0.4%)
Nausea	3 (0.6%)	3 (1.3%)
Reproduced from Sponsor, Clinical Study Report, Table 12.1.2, page 83. Source: Appendix 12.0.		

In Study CV131185, dizziness was also the most common related adverse event as reported by at least 1 percent of subjects in any treatment group during the double-blind period and occurred in 8 (2.4%), 2 (1.9%), and 0 subjects in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively.

Hypotension was also a treatment related adverse event, but this adverse event was underreported in Studies CV131176 and CV131185. A number of patients in both studies did not have vital signs checked at peak symptoms.

6.1.5.3 Additional analyses and explorations

Study CV131176
A total of 9 subjects reported the adverse event of cough, including one subject receiving irbesartan 150 mg, three subjects receiving irbesartan 300 mg, one subject receiving irbesartan 150 mg/HCTZ 12.5 mg, two subjects receiving irbesartan 300 mg/HCTZ 25 mg, and two subjects in the placebo lead-in phase. All subjects were Caucasian, except for Subject 192-11, a 32 year old Black male who experienced cough during the placebo lead-in phase. The overall percentage of cough by treatment group is 3/468 (0.64%) in the irbesartan/HCTZ combination group and 4/227 (1.8%) in the irbesartan monotherapy group.

I also searched the sponsor's derived adverse events table for all terms falling into the angioedema standardized MedDRA query (SMQ). Subject 240-7, a 53 year old Caucasian female developed an urticarial rash on irbesartan 300 mg, 15 days after receiving her first dose of irbesartan. She did not require hospitalization, but she was discontinued from the trial. Subject 256-1, a 59 year old Caucasian man developed a swollen tongue in the pre-randomization phase and was subsequently not enrolled in the study. Subject 107-1, a 45 year old Caucasian woman developed facial edema and peripheral edema during the placebo lead-in phase, and was not enrolled in the study. Lastly, Subject 27-2, a 61 year old Caucasian man developed edema on irbesartan 300 mg/HCTZ 25 mg, 10 days after receiving his first dose of combination therapy. The edema lasted 6 days, but the case report form did not specify the location of the edema. Subject 27-2 later discontinued the study on Day 47 due to the ongoing adverse event of fatigue.

Other Analyses:
Adverse Events in the Double-Blind Period by Baseline SeDBP Quartile (CV131176)
By baseline quartile of SeDBP and by treatment group, Table 16 displays the number of patients having adverse events in the double-blind period and SAEs in the double-blind period and within 30 days of the last Period B dose date. Quartile 1 had the lowest number of adverse events in both treatment groups.

Table 16. Number of Patients with Adverse Events by Baseline SeDBP Quartile (CV131176)

Baseline SeDBP Quartile	N (Treatment Group 1: N = 468) (Treatment Group 2: N = 227)	Number of Adverse Events in Double-Blind Period and SAEs in Double-Blind Period and Within 30 Days of Last Period B Dose Date (N = 341*)
Treatment Group 1 (Irbesartan/HCTZ)	**138 subjects (2 subjects missing BP data)**	**218 (63.9%)**
Quartile 1 (104.2 – 110.67 mm Hg)	23	37 (10.9%)
Quartile 2 (111 – 112.6 mm Hg)	43	63 (18.5%)
Quartile 3 (112.7 – 114.3 mm Hg)	35	56 (16.4%)
Quartile 4 (114.7 – 127.3 mm Hg)	37	62 (18.2%)
Treatment Group 2 (Irbesartan)	**82 subjects**	**123 (36.1%)**
Quartile 1 (109.0 – 110.7 mm Hg)	15	21 (6.2%)
Quartile 2 (111.0 – 112.0 mm Hg)	26	36 (10.6%)
Quartile 3 (112.7 – 114.3 mm Hg)	25	38 (11.1%)
Quartile 4 (114.7 – 135.0 mm Hg)	16	28 (8.2%)
BP = blood pressure ***3 AEs missing from 2 subjects missing blood pressure data in Treatment Group 1** **Analysis by Karen A. Hicks, M.D.**		

Adverse Events in the Double-Blind Period by Weight (CV131176)

Table 17 displays the adverse events by weight and treatment group. Most adverse events occurred in patients ≥ 75 kg.

Table 17. Number of Adverse Events in Double-Blind Period and SAEs in Double-Blind Period and Within 30 Days of Last Period B Dose Date by Weight (CV131176)

Weight	N (Treatment Group 1: N = 468) (Treatment Group 2: N = 227)	Number of Adverse Events in Double-Blind Period and SAEs in Double-Blind Period and Within 30 Days of Last Period B Dose Date (N = 344)
Treatment Group 1 (Irbesartan/HCTZ)	**140 subjects (29.9%) (but only 139 subjects had weights)**	**221 (66.2%)**
Wt < 75 kg	36	67 (19.5%)
Wt ≥ 75 kg	103	153 (44.5%)
Treatment Group 2	**82 subjects (36.1%)**	**123 (35.8%)**
Wt < 75 kg	19	28 (8.1%)
Wt ≥ 75 kg	63	95 (27.6%)
Analysis by Karen A. Hicks, M.D.		

6.1.6 Laboratory Findings

6.1.6.1 Overview of laboratory testing in the development program

In Study CV131176, laboratory tests were performed at 6 visits including enrollment (Visit A00), randomization (Visit A99/B00), titration visit (Week 1/B01), Week 3 (B02), Week 5 (B03), and end of treatment (Week 7/B99).

Summary statistics for laboratory values did not demonstrate any substantial median changes from baseline in the combination and monotherapy treatment groups. The following median changes were noted:

- Chloride decreased 2.0 meq/L in the combination group compared to 0.0 meq/L in the monotherapy group
- Alkaline phosphatase increased 4.0 U/L from baseline in the monotherapy group compared to 1.0 U/L in the combination group
- BUN increased 2.0 mg/dL from baseline in the combination group compared to 0 mg/dL in the monotherapy group
- Creatine kinase increased 8.0 U/L from baseline in the combination group compared to 5.0 U/L in the monotherapy group
- Serum glucose increased 3.0 mg/dL from baseline in the combination group compared to 1.0 mg/dL in the monotherapy group
- Lactate dehydrogenase decreased 6.0 U/L from baseline in the combination group compared to a decrease of 2.0 U/L in the monotherapy group
- Uric acid increased 0.55 mg/dL from baseline in the combination group compared to a decrease of 0.10 in the monotherapy group
- Alkaline phosphatase increased 1.0 U/L in the combination group compared to 4.0 U/L in the monotherapy group
- Platelet count increased by 8.0 x 10^9 c/L in both treatment groups

6.1.6.1.1 Marked outliers and dropouts for laboratory abnormalities

Table 18 summarizes the laboratory marked abnormality criteria for Studies CV131176 and CV131185.

Table 18. Laboratory Marked Abnormality Criteria (Studies CV131176 and CV131185)

Lab Test	Units	Safety Criteria
Hemoglobin	g/dL	> 3 g/dL decrease from pre Rx
Platelet Count	X 10*9 c/L	< 0.5X pre Rx and < 100,000/mm^3
Neutrophils + Bands (absolute)	X 10*3 c/uL	If value < 1000/mm^3
Creatinine	mg/dL	> 1.5X pre Rx
Alanine Aminotransferase (ALT)	U/L	> 3X ULN, or If pre Rx > ULN then use > 4X pre Rx
Aspartate Aminotransferase (AST)	U/L	>3X ULN, or If pre Rx > ULN then use > 4X pre Rx
Bilirubin, Total	mg/dL	>2X ULN, or If pre Rx > ULN then use > 4X pre Rx

Lab Test	Units	Safety Criteria
Serum Potassium	mEq/L	< 3.0 or > 6.0
Serum Sodium	mEq/L	< 0.95X LLN or > 1.05X ULN; or if pre Rx< LLN then use < 0.95X pre Rx or > ULN; if pre Rx > ULN then use > 1.05X pre Rx or < LLN
Creatine Kinase (CK)	U/L	> 4X pre Rx
Serum Glucose	mg/dL	< 60 mg/dL or > 300 mg/dL
Total Cholesterol (TC)	mg/dL	> 2X pre Rx
Uric Acid	mg/dL	> 2X pre Rx
Albumin	g/dL	< 0.75X pre Rx
Pre Rx: Pretreatment; LLN: lower limit of normal; ULN: upper limit of normal **Reproduced from Sponsor, Clinical Study Report, Table S.12.5.1, pages 304-305.**		

Study CV131176

Table 19 displays the number (percent) of evaluable subjects with laboratory abnormalities meeting the laboratory marked abnormality (MA) criteria. An increase in creatinine was the most frequent MA. Creatinine increases from baseline meeting the marked laboratory abnormality criteria occurred in 14 (3.0%) subjects receiving combination therapy and in 4 (1.8%) subjects receiving monotherapy. Of these 18 subjects, 16 subjects were under 65 years of age. The maximum creatinine measurement was 2.1 mg/dL. In the irbesartan/HCTZ group at Week 5, the mean change from baseline in serum creatinine was 0.04 mg/dL, compared to -0.01 mg/dL for irbesartan monotherapy. The incidence of other marked laboratory abnormalities was < 1% in each treatment group.

Table 19. Sponsor's Analysis: Number (Percent) of Evaluable Subjects with Laboratory Abnormalities Meeting the Laboratory Marked Abnormality Criteria (CV131176)

Lab Test Description	Irb/HCTZ			Irbesartan		
	n	Low (%)	High (%)	n	Low (%)	High (%)
Hemoglobin	448	1 (0.2)	NE	219	0	NE
Platelet Count	444	0	NE	218	0	NE
Neutrophils + Bands (absolute)	449	0	NE	220	0	NE
Creatinine	461	NE	14 (3.0)	225	NE	4 (1.8)
Alanine Aminotransferase (ALT)	455	NE	1 (0.2)	222	NE	0
Aspartate Aminotransferase (AST)	455	NE	0	222	NE	0
Bilirubin, Total	455	NE	0	222	NE	0
Serum Potassium	463	0	3 (0.6)	226	0	3 (1.3)
Serum Sodium	461	3 (0.7)	1 (0.2)	225	0	1 (0.4)
Creatine Kinase (CK)	455	NE	5 (1.1)	220	NE	2 (0.9)
Serum Glucose	457	1 (0.2)	4 (0.9)	223	1 (0.4)	0
Total Cholesterol	455	NE	0	222	NE	0
Uric Acid	455	NE	1 (0.2)	221	NE	0
Albumin	455	1 (0.2)	NE	222	0	NE
NE = Not Evaluated **Treated Subjects** **Reproduced from Sponsor, Clinical Study Report, Table 12.6, page 96.**						

In Study CV131176, there were 5 discontinuations for potassium abnormalities. Three subjects (0.6%) in the irbesartan/HCTZ group and 1 subject (0.4%) in the irbesartan monotherapy group

were discontinued due to hypokalemia. One subject (Subject 56-5) (0.2%) in the irbesartan/HCTZ group was discontinued due to hyperkalemia (potassium of 5.6 mmol/l).

Hyperkalemia
Three subjects (0.6%) in the irbesartan/HCTZ treatment group and three subjects (1.3%) in the irbesartan monotherapy group achieved elevated potassium levels meeting the "marked abnormality criteria." The normal range for potassium was 3.6 to 5.2 mEq/L. Most of these subjects were not on concomitant medications that would contribute to the hyperkalemia. All subjects had normal potassium values in the pre lead-in period except for Subjects 15-8 (potassium 5.5 mEq/L, irbesartan monotherapy) and Subject 153-7 (potassium 5.5 mEq/L, irbesartan/HCTZ).

In the irbesartan monotherapy group, Subject 24-6, a 76 year old female, had a potassium of 7.1 mEq/Lon Day 36 while receiving irbesartan 300 mg. She was also receiving allopurinol, theophylline, clarithromycin, dihydrocodeine, and ibuprofen. Subject 15-8, a 61 year old male, had a potassium of 6.1 mEq/L on Day 8 while receiving irbesartan 150 mg. He continued to have potassium levels of 5.9 mEq/L on Day 36 and 5.6 mEq/L on Day 50. Subject 194-5, a 52 year old male, had a potassium of 6.1 mEq/L on Day 50 while receiving irbesartan 300 mg.

In the irbesartan/HCTZ combination group, Subject 24-2, a 64 year old female, had a potassium of 6.2 mEq/L on Day 22 while receiving irbesartan 300/HCTZ 25. Subject 28-5, a 38 year old male, had a potassium of 6.5 mEq/L on Day 43 while receiving irbesartan 300/HCTZ 25. Subject 153-7, a 43 year old female, had a potassium of 6.1 mEq/L on Day 1 of irbesartan 150/HCTZ 12.5 therapy. Her potassium pre lead-in was also elevated at 5.5 mEq/L. She was receiving amoxicillin and aspirin at the time of her MA.

Elevated Creatine Phosphokinase (CPK)
Five subjects (1.1%) in the irbesartan/HCTZ combination group and 2 subjects (0.9%) in the irbesartan monotherapy group developed creatine phosphokinase elevations meeting the "marked abnormality criteria."

Subjects 10-5, 101-1, 164-1, 215-3, and 247-5 had CPK values of 193.0, 800.0, 786.0, 1471.0, and 254.0 U/L, respectively, on Days 50, 22, 51, 53, and 52, respectively, while receiving irbesartan 300 mg/HCTZ 25 mg. Subject 215-3, a 57 year old man with a CPK of 1471 U/L on Day 53, was also receiving Atorvastatin.

In the irbesartan 300 mg monotherapy group, Subjects 25-1 and 283-6 had CPKs of 1267 and 338 U/L, respectively.

Study CV131185
Table 20 displays the number (percent) of evaluable subjects with laboratory abnormalities meeting the laboratory marked abnormality criteria in Study CV131185. In the irbesartan/HCTZ treatment group, increases in creatinine, potassium, liver function enzymes, and creatine kinase were evident, as were decreases in serum sodium and glucose.

Table 20. Number (Percent) of Evaluable Subjects with Laboratory Abnormalities Meeting the Laboratory Marked Abnormality Criteria (CV131185)

Lab Test	Irb/HCTZ			Irbesartan			HCTZ		
	n	Low (%)	High (%)	n	Low (%)	High (%)	n	Low (%)	High (%)
Hemoglobin	313	0	NE	102	0	NE	97	0	NE
Platelet Count	309	0	NE	102	0	NE	95	0	NE
Neutrophils and Bands (absolute)	315	1 (0.3)	NE	102	0	NE	97	0	NE
Creatinine	325	NE	10 (3.1)	105	NE	3 (2.9)	102	NE	5 (4.9)
Alanine Aminotransferase (ALT)	312	NE	3 (1.0)	103	NE	1 (1.0)	97	NE	0
Aspartate Aminotransferase (AST)	312	NE	3 (1.0)	103	NE	1 (1.0)	97	NE	0
Bilirubin, Total	312	NE	1 (0.3)	103	NE	0	97	NE	0
Serum Potassium	325	0	4 (1.2)	105	0	0	102	0	0
Serum Sodium	325	3 (0.9)	0	105	0	0	102	0	1 (1.0)
Creatinine Kinase	312	NE	1 (0.3)	103	NE	1 (1.0)	97	NE	0
Serum Glucose	312	2 (0.6)	0	103	1 (1.0)	1 (1.0)	97	0	0
Total Cholesterol	312	NE	0	103	NE	0	97	NE	0
Uric Acid	312	NE	0	103	NE	0	97	NE	0
Albumin	312	0	NE	103	1 (1.0)	NE	97	0	NE
Reproduced from Sponsor, Clinical Study Report, Table S.12.4.2A, pages 306-307.									

6.1.7 Vital Signs

In Study CV131176, vital signs were obtained at seven visits including the enrollment visit (A00), qualifying visit (A01), randomization visit (A99/B00), titration visit (Week 1/B01), Week 3 (B02), Week 5 (B03), and end of treatment (Week 7/B99).

There were no cases of hypotension in the irbesartan monotherapy group and three reported cases of hypotension, including 2 cases of hypotension and 1 case of orthostatic hypotension, in the irbesartan/HCTZ treatment group. All three cases occurred after medication was titrated to the highest dose. Blood pressures according to week for these three patients are displayed in Table 21.

Table 21. Sponsor's Analysis: Mean Seated Blood Pressures (mm Hg) in Subjects with an Adverse Event of Hypotension on Irbesartan/HCTZ (CV131176)

Patient ID	Age/Race/ Sex	Randomization	Week 1	Week 3	Week 5	End of Study
248-1	32 WF	140/111	133/86	133/83	-	138/96
288-4	62 WF	156/113	153/105	131/79	133/81	133/78
293-2	38 WF	190/125	145/109	133/97	142/103	134/96
W = White; F = Female; M = Male **Reproduced from Sponsor, Clinical Study Report, Table 12.5.1B, page 94.**						

According to the adverse events data set, Subjects 248-1, 288-4, and 293-2 experienced hypotension on Days 30, 19, and 16, respectively. Subjects 248-1 and 288-4 did not have vital signs recorded when they were on medication and symptomatic.

Subject 248-1 had vital signs checked on the last day of symptoms, one day after study medication was discontinued. According to the case report form, Subject 248-1 experienced hypotension from 2/12/2005 (Day 30) through 2/18/2005. The last date of study drug was 2/17/2005. On 2/10/2005, seated blood pressure was 136/86 with a heart rate of 78 bpm. Standing blood pressure was 136/87 with a heart rate of 74 bpm. On 2/18/2005, seated blood pressure was 139/96 with a heart rate of 81 bpm. Standing blood pressure was 125/91 with a heart rate of 76 bpm. There were no additional blood pressures or heart rates recorded between 2/12/2005 and 2/18/2005 when the patient was on medication and symptomatic. Although her systolic blood pressure dropped 15 mm Hg with standing, her heart rate did not increase. It is possible her blood pressure and heart rate changes would have been more prominent if vital signs were checked on medication during peak symptoms.

Subject 293-2 began the study on 3/14/2005. From 4/2/2005 through 4/10/2005, the patient experienced weakness and sleepiness, interpreted by the physician as "hypotension." On 4/6/2005, average sitting blood pressure was 133/97 with a heart rate of 88 bpm. Standing blood pressures were 138/108, 135/102, and 134/102 with a heart rate of 98 bpm. Based on these blood pressures, the patient was not hypotensive, although she had been diagnosed as hypotensive by the study physician.

The proportion of subjects with systolic blood pressure less than 110 mm Hg is displayed in Table 22 and was 0% in the Irbesartan monotherapy group and ≤ 1.07% (5 subjects) in the irbesartan/HCTZ treatment group. The lowest seated systolic blood pressure achieved was 99 mm Hg, and the lowest standing systolic blood pressure achieved was 102 mm Hg.

Table 22. Sponsor's Analysis: Proportion of Subjects with Systolic Blood Pressure Less than 110 mm Hg

Week	Irbesartan/HCTZ n (%) (N = 468)	Irbesartan n (%) (N = 229)
Week 1	0 (0%)	0 (0%)
Week 3	4 (0.85%)	0 (0%)
Week 5	2 (0.43%)	0 (0%)
Week 7	5 (1.07%)	0 (0%)
Reproduced from Sponsor, Clinical Study Report, Table 12.5.1C, page 94. Source: Appendix 10A.		

However, in many cases, patients did not have vital signs recorded during their actual symptoms, so I believe the number of patients experiencing systolic blood pressures less than 110 mm Hg is underrepresented.

6.1.8 Electrocardiograms (ECGs)

Study CV131176
In Study CV131176, twelve-lead electrocardiograms (12-lead ECGs) were performed at enrollment and end of treatment (Week 7/B99). There was no central reading of ECGs, and the type of QT correction used was the decision of each individual investigator. Study CV131176 was not a thorough QT study, and there were no previous concerns regarding QT prolongation in the initial approval of Avalide®.

Overall, there were no significant mean or median changes in ECG parameters during the double-blind period. However, the summarized ECG measurements presented in this NDA for Study CV131176 were *not reliable*. In Table S12.8.1 of the NDA, for example, the sponsor listed the following maximum values for PR, QRS, QT, and QTc in the irbesartan/HCTZ group at baseline: 1.2 seconds, 9.4 seconds, 4.270 seconds, and 4.850 seconds. Similar maximum values were reported in the combination treatment group at Week 7. All of these values belonged to Subject 116-1, a 27 year old female, and were confirmed on the Case Report Forms. I reviewed the ECGs and found all values to be within normal limits.

Study CV131185
There were no significant mean or median changes in heart rate, QRS width, PR interval, QT interval, or QTc interval from baseline to Week 12.

6.1.8.1.1 Analyses focused on outliers or shifts from normal to abnormal

Study CV131176
Subject 191-1, a 74 year old Caucasian woman assigned to the irbesartan/HCTZ treatment group, had a reported baseline QTc of 0.503 seconds. I reviewed her 12-lead ECG and measured a QTcB of 0.440 seconds. No follow-up ECG was performed. Subject 286-3, a 63 year old Caucasian woman in the irbesartan monotherapy group, had a reported baseline QTc of 0.414 seconds and a follow-up QTc of 0.561 seconds. After reviewing her 12-lead ECGs, I measured a QTcB of 0.450 seconds on 3/14/2005 and a QTcB of 0.438 seconds on 4/12/2005. Concomitant medications for Subject 286-3 during the double-blind period included Amaryl, ASA, folic acid, metformin, and nexium.

Given the lack of centralized ECG reading, I viewed results from more detailed analyses with skepticism. For example, according to the sponsor's data set, there were 17 subjects with a change in QTc > 60 ms from baseline, including 11 subjects in the irbesartan/HCTZ group and 6 subjects in the irbesartan monotherapy group. I reviewed ECGs for 13 of these 17 subjects, including Subjects 96-11, 121-4, 150-1, 176-2, 210-6, 245-2, 275-7, and 275-9 in the irbesartan/HCTZ group and Subjects 24-1, 60-3, 192-9, 275-13, and 286-3 in the irbesartan monotherapy group. The ECG tracings for Subject 60-003 were technically poor and could not be interpreted. None of the other ECG tracings I reviewed suggested drug-related QTc prolongation. At the time of this addendum, I am awaiting the following tracings from the sponsor: ECGs for Subjects 55-19, 55-20, and 80-3 in the irbesartan/HCTZ group and ECGs for Subject 10-4 in the irbesartan monotherapy group.

6.1.8.1.2 Marked outliers and dropouts for ECG abnormalities

There were no dropouts for ECG abnormalities. Please see the section above for a discussion of QTc outliers.

6.1.9 Immunogenicity

Immunogenicity was not evaluated.

6.1.10 Human Carcinogenicity

Based on the safety data from Studies CV131176 and CV131185 as well as post-marketing adverse events reporting, there does not appear to be a signal for human carcinogenicity with Avalide®.

6.1.11 Special Safety Studies

No special safety studies were performed.

6.1.12 Withdrawal Phenomena and/or Abuse Potential

No withdrawal studies were done.

6.1.13 Human Reproduction and Pregnancy Data

There have been no clinical studies of the effects of Avalide® or irbesartan in pregnant women.

6.1.14 Assessment of Effect on Growth

Adult patients only were studied.

6.1.15 Overdose Experience

There were no overdoses in the clinical studies.

6.1.16 Postmarketing Experience

The sponsor recently updated the post-marketing experience section of the Avalide® label to report rare cases of rhabdomyolysis in patients receiving angiotensin II receptor blockers. The sponsor is also in the process of adding "hepatitis" to the adverse events post-marketing section of the label.

6.2 Adequacy of Patient Exposure and Safety Assessments

Blacks and subjects ≥ 65 years of age were underrepresented in both studies. Therefore, safety assessments in these subjects is limited.

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Patients with moderate and severe hypertension were evaluated in Studies CV131185 and CV131176, respectively. In Studies CV131185 and CV131176, subjects had a mean exposure of 78.6 and 47.2 days, respectively, in the irbesartan/HCTZ treatment group.

6.2.1.1 Study type and design/patient enumeration

The two multicenter, randomized, double-blind, active-controlled, parallel group trials that provide safety data for this sNDA are identified in Table 1.

6.2.1.2 Demographics

The demographics of the safety population are shown in Table 23.

Table 23. Demographics (CV131176 and CV131185)

	CV131176		CV131185		
	Irbesartan/HCTZ	**Irbesartan**	**Irbesartan/HCTZ**	**Irbesartan**	**HCTZ**
N	**468**	**229**	**328**	**106**	**104**
Age (Mean ± SD)	52.2 ±10.5	52.9 ± 10.9	55.1 ± 11.3	55.3 ±10.8	56.0 ± 12.7
Male (n, %)	277 (59.2%)	124 (54.1%)	181 (55.2%)	49 (46.2%)	62 (59.6%)
Black (n, %)	67 (14.3%)	34 (14.8%)	50 (15.2%)	9 (8.5%)	15 (14.4%)

6.2.1.3 Extent of exposure (dose/duration)

The extent of exposure is shown in Table 24 and Table 25.

Table 24. Extent of Exposure to Double-Blind Study Drug by Treatment Group (CV131176 and CV131185)

Extent of Exposure	**CV131176**		**CV131185**		
	Irbesartan/HCTZ	**Irbesartan**	**Irbesartan/HCTZ**	**Irbesartan**	**HCTZ**
N	**468**	**227**	**328**	**106**	**104**
1-7 Days	8 (1.7%)	6 (2.6%)	3 (0.9%)	2 (1.9%)	3 (2.9%)
8-14 Days	6 (1.3%)	1 (0.4%)	6 (1.8%)	2 (1.9%)	0
15-30 Days	21 (4.5%)	11 (4.8%)	12 (3.7%)	5 (4.7%)	4 (3.8%)
31-60 Days	426 (91.0%)	208 (91.6%)	13 (4.0%)	2 (1.9%)	5 (4.8%)
61-90 Days	7 (1.5%)	1 (0.4%)	279 (85.1%)	90 (84.9%)	88 (84.6%)
91-180 Days			15 (4.6%)	5 (4.7%)	4 (3.8%)
Mean Duration of Exposure	47.2 Days	46.8 Days	78.6 Days	78.1 Days	77.7 Days

Extent of Exposure	CV131176		CV131185		
	Irbesartan/HCTZ	Irbesartan	Irbesartan/HCTZ	Irbesartan	HCTZ
Mean Total Dose	13009.9/1084.2	12849.1	21397.4/1783.1	21233.5	1756.3
Reproduced from Sponsor, Clinical Study Report CV131176, Table 9.1, page 60 and Clinical Study Report CV131185, Table 9.1, page 65.					

Table 25. Distribution of Subjects During Double-Blind Period by Week and Dose Received on Day Prior to the Visit (CV131176 and CV131185)

Treatment Group Dose (mg/mg)	Week 1 n (%)	Week 3 n (%)	Week 5 n (%)	Week 7 n (%)
CV131176				
Irbesartan/HCTZ				
0	3 (0.7)	3 (0.7)	1 (0.2)	3 (0.7)
0/0	1 (0.2)	0	0	0
150/12.5	456 (99.1)	8 (1.8)	2 (0.5)	3 (0.7)
300/25	0	441 (97.6)	420 (99.3)	420 (98.6)
Irbesartan				
0	0	1 (0.5)	1 (0.5)	2 (1.0)
150	219 (100.0)	6 (2.7)	3 (1.5)	1 (0.5)
300	0	212 (96.8)	202 (98.1)	200 (98.5)
Treatment Group Dose (mg/mg)	**Week 2 n (%)**	**Week 4 n (%)**	**Week 8 n (%)**	**Week 12 n (%)**
CV131185				
Irbesartan/HCTZ				
0	1 (0.3)	2 (0.6)	3 (1.0)	2 (0.7)
150/12.5	315 (99.7)	6 (1.9)	2 (0.7)	1 (0.3)
300/25	0	308 (97.5)	298 (98.3)	288 (99.0)
Irbesartan				
0	1 (1.0)	0	0	1 (1.1)
150	101 (99.0)	1 (1.0)	0	0
300	0	99 (99.0)	95 (100.0)	93 (98.9)
HCTZ				
0	2 (1.9)	0	1 (1.1)	2 (2.2)
12.5	101 (98.1)	2 (2.0)	1 (1.1)	1 (1.1)
25	0	98 (98.0)	92 (96.8)	88 (96.7)
> 30 PST	0	0	1 (1.1)	0
Reproduced from Sponsor, Clinical Study Report CV131176, Table S.9.1.B, page 125 and Clinical Study Report CV131185, Table S.9.1.1, page 153.				

6.2.2 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In Study CV131176, there were more adverse events and more discontinuations due to adverse events in the irbesartan/HCTZ treatment group and at the highest doses in both the combination and monotherapy treatment arms. Increases in creatinine, potassium, creatine phosphokinase, and glucose were evident in the irbesartan/HCTZ treatment group.

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The sponsor recommends a starting dose of one tablet of Avalide® 150/12.5 mg once daily for initial treatment of severe hypertension. The dosage may be increased after one week of therapy to a maximum of one 300/25 mg tablet once daily. Avalide® is not recommended as initial therapy in patients with intravascular volume depletion.

7.2 Drug-Drug Interactions

The sponsor did not perform any drug-drug interaction studies.

7.3 Special Populations

The elderly and Blacks/African Americans were underrepresented in the clinical studies.

7.4 Pediatrics

The Division granted the sponsor a pediatric deferral.

7.5 Advisory Committee Meeting

This sNDA has not been and is not planned to be discussed at an advisory committee meeting.

8 OVERALL ASSESSMENT

8.1 Conclusions

In Study CV131176, a significantly greater proportion of subjects treated with irbesartan/HCTZ achieved a SeDBP < 90 mm Hg at Week 5, compared with irbesartan monotherapy ($p = 0.0005$). In Study CV131185, subjects treated with irbesartan/HCTZ had a significantly greater change from baseline in mean SeSBP at Week 8, compared with irbesartan ($p = 0.0016$) and HCTZ ($p < 0.0001$) monotherapies. Numerous secondary efficacy measures in both studies were highly significant and supported the efficacy of combination therapy, although the sponsor did not

adjust for multiple testing at the study visits. Combination therapy with irbesartan/HCTZ was highly effective in treating subjects with moderate and severe hypertension.

Studies CV131176 and 131185 also proved the efficacy of irbesartan monotherapy. In Study CV131176, the proportion of subjects achieving simultaneous SeSBP < 140 mm Hg AND SeDBP < 90 mm Hg on irbesartan monotherapy was 12.7%, 19.2%, and 21.4% at Weeks 3, 5, and 7, respectively. In Study CV131185, 10.8%, 19.2%, 40.6%, and 34.0% of subjects receiving irbesartan monotherapy at Weeks 2, 4, 8, and 12 achieved simultaneous seated systolic and diastolic blood pressure control. Therefore, the sponsor did not demonstrate the futility of irbesartan monotherapy.

Patients receiving irbesartan/HCTZ had more adverse events than those receiving irbesartan monotherapy. At the highest doses in all treatment groups, there were more adverse events than in the lowest doses. Therefore, combination therapy is not indicated for initial therapy of severe hypertension unless the perceived benefits outweigh the known risks.

8.2 Recommendation on Regulatory Action

Approval of Avalide (irbesartan/hydrochlorothiazide) for the treatment of hypertension for patients whose blood pressure is not adequately controlled on monotherapy. This fixed dose combination is not indicated for initial therapy of hypertension except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

8.3 Recommendation on Postmarketing Actions

I recommend the sponsor create a monitoring system to track the development of creatine phosphokinase increases in subjects receiving either irbesartan monotherapy or irbesartan/HCTZ combination therapy, and to determine if concomitant medications such as lipid-lowering agents (i.e., statins, fibrates) contribute to this risk.

8.3.1 Risk Management Activity

Please see Section 7.3.

8.4 Labeling Review

The labeling review will be discussed in the upcoming labeling meetings.

8.5 Comments to Applicant

The recommendations in Section 8.3 should be communicated to the sponsor.

9 APPENDICES

9.1 Review of Individual Study Reports

9.2 Study CV131176, The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Severe Hypertension

9.2.1 Protocol, Amendment and Post Hoc Changes

This study description was based upon the protocol dated June 11, 2004. There were no amendments. There were 6 letters which made various administrative changes.[4]

9.2.2 Study Design

This was a multicenter, randomized, double-blind, active-controlled, parallel group trial in untreated uncontrolled hypertensive (SeDBP ≥ 110 mm Hg) subjects and in subjects with uncontrolled hypertension (SeDBP ≥ 100 mm Hg) who were currently treated with antihypertensive monotherapy.

9.2.2.1 Objectives

The primary objective was to compare the proportion of subjects whose seated diastolic blood pressure (SeDBP) was controlled (SeDBP < 90 mm Hg) at Week 5 when initiating combination therapy as first-line treatment (irbesartan 150 mg/HCTZ 12.5 mg titrated to irbesartan 300 mg/HCTZ 25 mg), to that when initiating irbesartan monotherapy (irbesartan 150 mg titrated to 300 mg).

The secondary objective was to characterize the safety and tolerability of the two treatment groups over the seven-week study period.

By treatment group, other objectives included the comparison of the proportion of subjects whose SeDBP was controlled (SeDBP < 90 mm Hg) at Weeks 1, 3, and 7, the comparison of the proportion of subjects whose blood pressure was controlled, defined as simultaneous SeDBP < 90 mm Hg and seated systolic blood pressure (SeSBP) < 140 mm Hg at Weeks 1, 3, 5, and 7, and the comparison of the change from baseline in Se SBP and SeDBP at Weeks 1, 3, 5, and 7.

[4]**There were 6 Administrative letters dated September 1, 2004, October 20, 2004, November 11, 2004, February 25, 2005, March 24, 2005, and May 17, 2005. These administrative letters corrected the IND number, clarified handling of serious adverse events, clarified exclusion criteria, and corrected the EUDRACT Number.**

9.2.2.2 Inclusion and Exclusion Criteria

Inclusion Criteria (Based on Protocol, page 22)

1. Men and women, ages 18 and older, with women of childbearing potential (WOCBP) using an adequate method of contraception to avoid pregnancy throughout the study and for up to one week after the study to minimize the risk of pregnancy
2. Signed written informed consent
3. Subjects with uncontrolled hypertension defined as:
   - Currently untreated with an SeDBP ≥ 110 mm Hg
     OR
   - Currently receiving antihypertensive monotherapy with and SeDBP ≥ 100 mm Hg. Monotherapy was defined as treatment with one antihypertensive medication for at least four weeks; fixed combination therapy did not represent monotherapy.
4. Subjects willing to discontinue their antihypertensive medication, if applicable.
   - To qualify for randomization to double-blind therapy:
     - All evaluations including laboratory testing from the Enrollment Visit were completed and the results satisfied all selection criteria
     - Blood pressure measurement of an averaged SeDBP ≥ 110 mm Hg was demonstrated at two consecutive visits (A01 and A99) off of medication and immediately prior to randomization.

Exclusion Criteria (Based on Protocol, page 23)

Sex and Reproductive Status

1. Women of childbearing potential (WOCBP) who were **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to one week after the study.
2. Women who were pregnant or breastfeeding
3. Women with a positive pregnancy test on enrollment or prior to study drug administration

Target Disease Exceptions

4. SeSBP ≥ 220 mm Hg or SeDBP ≥ 130 mm Hg and/or evidence of malignant or accelerated hypertension or clinical evidence that the subject required immediate lowering of his/her blood pressure within hours, including, but not limited to coronary ischemia or neurological signs and symptoms
5. Known or suspected secondary hypertension

Medical History and Concurrent Diseases

6. Hypertensive encephalopathy, stroke, or transient ischemic attack within the past 12 months
7. Myocardial infarction, percutaneous transluminal coronary revascularization, coronary artery bypass graft, or unstable angina pectoris within the past six months
8. New York Heart Association functional class III-IV congestive heart failure, or LV dysfunction requiring ACE inhibitor
9. Hemodynamically significant cardiac valvular disease

10. Heart block greater than first degree atrioventricular block, preexcitation syndrome, sick sinus syndrome, chronic atrial fibrillation, or chronic atrial flutter, or other significant arrhythmias that may interfere with the blood pressure measurements
11. Significant chronic renal impairment, or renovascular disease
12. Significant liver disease
13. Systemic lupus erythematosus
14. Gastrointestinal disease or surgery that may interfere with drug absorption
15. Malignancy during the past five years excluding localized squamous cell or basal cell carcinoma of the skin
16. Currently pregnant or lactating
17. Mental condition (psychiatric or organic cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study, or mental retardation or language barrier such that the subject is unable to give informed consent
18. Drug or alcohol abuse within the last five years
19. Any medical condition that in the judgment of the Investigator would jeopardize the subject's safety or evaluation of the study drug for efficacy and safety

Physical and Laboratory Test Findings

20. Obesity that would limit accurate blood pressure measurement
21. Positive pregnancy test
22. Serum creatinine ≥ 1.5 mg/dL
23. AST, ALT, or total bilirubin ≥ 3 times the upper limit of normal
24. Plasma glucose > 240 mg/dL (if high, may be repeated once)
25. Hemoglobin A1c ≥ 10%
26. Serum potassium < 3.3 or > 5.5 mmol/l
27. White blood cell count < 2,600/µl
28. Platelet count < 100,000 µl
29. Hemoglobin < 10 g/dL
30. Any laboratory test value that in the judgment of the Investigator would jeopardize the subject's safety or the study drug's evaluation for efficacy and safety

Allergies and Adverse Drug Reactions

31. Known hypersensitivity to irbesartan, angiotensin receptor blockers (ARB), hydrochlorothiazide (HCTZ), or other thiazide diuretics

Prohibited Therapies and/or Medications (Reproduced from Sponsor, Section 6.4.1, page 31)

Concomitant vasoactive drugs, including the following, are not permitted throughout the study:

32. Nitrates
33. Angiotensin converting enzyme (ACE inhibitors), calcium antagonists, diuretics, angiotensin II receptor antagonists
34. Beta-adrenergic blocking agents including eye drops
35. Chronic sympathomimetic drugs including bronchodilators, nasal sprays, and oral decongestants
36. Other bronchodilators

37. Other antihypertensive drugs and arterial vasodilators

Also prohibited were:
38. Potassium supplements
39. Antibiotics other than short (≤ 2 week) courses
40. Protease inhibitors and reverse transcriptase inhibitors
41. Oral contraceptive therapy (must have been initiated at least one month prior to study enrollment. If taking, oral contraception must have been at a stable dose throughout the study)
42. Antacid ingestion within two hours of study treatment
43. Lithium
44. Chronic nonsteroidal anti-inflammatory drugs (NSAIDs) (chronic defined as for seven days or more) with the exception of low-dose aspirin therapy (≤ 325 mg daily) and occasional aspirin or NSAID use in customary doses (not to exceed 7 days and not to be ingested within the 4 days preceding a clinic visit)
45. Psychotropic drug therapy (occasional anxiolytics and stable doses of selective serotonin reuptake inhibitors, except venflaxine, are permitted), anticonvulsant, and antidepressant drugs
46. Herbal medications, food supplements, vitamin or mineral supplements found to have ingredients, which have the potential to effect blood pressure, e.g., ephedra

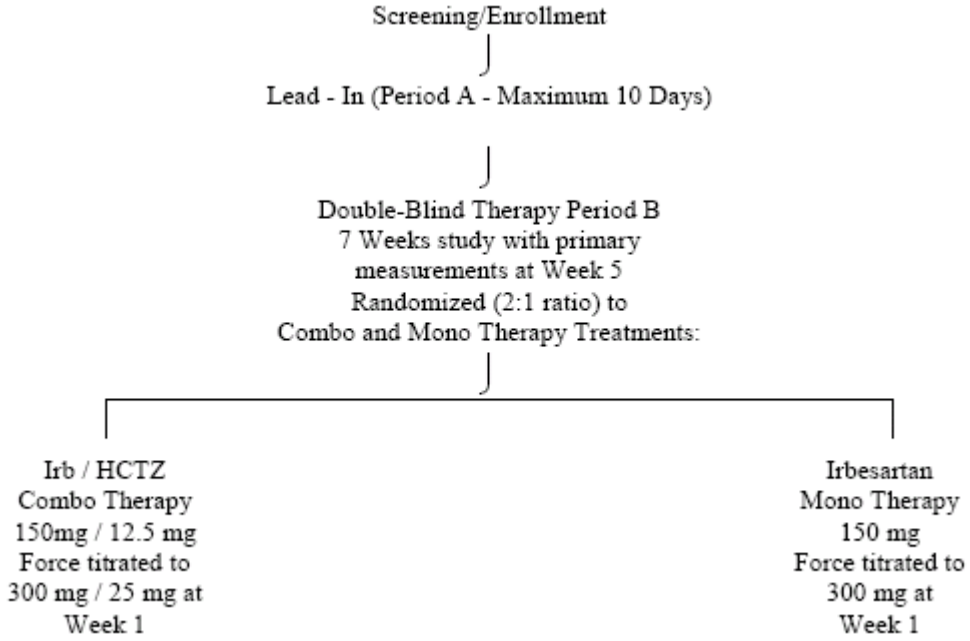
Other Exclusion Criteria
47. Potential for non-compliance with the requirements of the protocol or geographic or social factors that made study participation impractical
48. Simultaneous or previous participation (in the 30 days prior to study entry) in a clinical study using an experimental drug or device, or previous participation in this study
49. Prisoners or subjects who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study

Restricted Therapies
- Chronic NSAIDs (chronic defined as for 7 days or more) with the exception of low-dose aspirin therapy (≤ 325 mg daily) and occasional aspirin or NSAID use in customary does (not to exceed 7 days and not to be ingested within the 4 days preceding a clinic visit
- Antibiotics other than short (≤ 2 week) courses
- Oral contraceptive therapy (must have been initiated at least one month prior to study enrollment. If taking, oral contraception must have been at a stable dose throughout the study)
- Antacid ingestion within 2 hours of study treatment
- Herbal medications, food supplements, vitamin or mineral supplements were permitted unless the specific preparation was reviewed by the Investigator and found to have ingredients which had the potential to effect blood pressure, e.g., ephedra

9.2.2.3 Study Plan

Following screening and completion of the informed consent process, investigators or designees telephoned the central randomization system (IVRS) to enroll subjects into the study. The study was comprised of two periods, A and B. Period A was the single-blind placebo lead in phase, and Period B was the double-blind treatment phase. The duration of Period A was up to 10 days, and the duration of Period B was 7 weeks. The study schematic is displayed in Figure 1.

Figure 1. Study Schematic (CV131176)



Reproduced from Sponsor, Clinical Study Report, Figure 5.1, page 23). Source: Appendix 5.1.

During Period A, subjects who were currently untreated immediately began taking single-blind placebo therapy. Subjects currently receiving antihypertensive monotherapy were withdrawn from therapy and were to also immediately begin receiving single-blind placebo therapy.

Following Period A, if subjects fulfilled the randomization criterion of SeDBP ≥ 110 mm Hg at 2 consecutive visits (A01 and A99 visits) off of medication, the subjects 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.

During Periods A and B, study medication was to be taken between 6 am and 11 am. On the morning of all study visits, study medication was to be withheld so trough blood pressure was measured (24 ± 3 hours following the last dose of study medication). Following randomization, study visits occurred at Weeks 1 (B01), 3 (B02), 5 (B03), and 7 (B99). Medication use was assessed from the Qualifying Visit (A01) through the End of Treatment (Week 7/Visit B99).

Blood and urine were collected and analyzed at 3 visits, A00, A99/B00, and the final B99 visit. At 3 visits, B01, B02, and B03 blood was collected only.

The schedule of procedures/events is summarized in Table 26.

Table 26. Flow Chart/Time and Events Schedule (CV131176)

Procedure	Enrollment Visit A00	Qualifying Visit A01	Randomization Visit A99/B00	Titration Visit Week 1/B01	Week 3/B02	Week 5/B03	End of Treatment Week 7/B99
Eligibility Assessments	|<----------7 - 10 Days---------->			|<----------7 Weeks---------->			
Informed Consent	X						
Telephone IVRS	X		X				X
Inclusion/Exclusion Criteria	X	X	X				
Medical History	X						
Pregnancy Test	X		X				X
Efficacy/Safety Assessments							
Physical Examination and ECG	X						X
Blood Pressure/Heart Rate	X	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X	X
Laboratory Tests	X		X	X	X	X	X

9.2.2.4 Dosage, Duration, and Adjustment of Therapy

The starting dose was irbesartan 150 mg/HCTZ 12.5 mg or irbesartan 150 mg. After one week, subjects were titrated to irbesartan 300 mg/HCTZ 25 mg and irbesartan 300 mg, respectively. Subjects remained on the titrated doses for 6 weeks. No other dose adjustments were permitted.

9.2.2.5 Concomitant Therapy

No concomitant antihypertensive therapy was allowed.

9.2.2.6 Efficacy Endpoints

The primary efficacy outcome measure was the proportion of subjects whose SeDBP was controlled (SeDBP < 90 mm Hg) at Week 5.

The other efficacy outcome measures were

- the proportion of subjects with SeDBP < 90 mm Hg (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)
- the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg (at Week 1, Week 3, Week 5, and Week 7).

9.2.2.7 Safety Endpoints

The secondary outcome measures were

- the frequency of treatment discontinuations due to adverse events
- the frequencies of hypotension, dizziness, and syncope
- the frequency of headaches
- the frequencies of hypokalemia and hyperkalemia.

Withdrawal of Subjects from Study (Based on Section 6.6, page 32 of Protocol)
Subjects were to be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy and participation in the trial is not in the best interest of the subject, including
    - Clinical signs and symptoms which, in the opinion of the investigator, indicate a need for more aggressive blood pressure treatment than specified in the protocol
    - Clinical signs and symptoms of hypotension to a degree which, in the opinion of the investigator, indicate a need for less aggressive blood pressure treatment than specified in the protocol
- Severe hypertension unresponsive to therapy. Severe hypertension is average SeDBP ≥ 110 mm Hg or average SeSBP ≥ 200 mm Hg. The parameter in question (whether SeSBP or SeDBP) should be confirmed above its threshold at two consecutive visits after B00. Both unscheduled and scheduled visits should be considered in this assessment. Response to therapy is a decline of at least 10 mm Hg **average** SeDBP from visit B00.
- Pregnancy
- Termination of the study by Bristol-Myers Squibb
- Subjects who become prisoners or become involuntarily incarcerated for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

9.2.2.8 Statistical Considerations

No interim analyses were performed. Efficacy analyses utilized intent-to-treat data from all randomized patients. The primary analysis was a test comparing the proportions of subjects with SeDBP < 90 mm Hg in the 2 treatment groups at the end of Week 5. Subjects with no blood pressure measurements at Week 5 were classified as uncontrolled.

The sample size and the power of the test were calculated based on Fisher's exact test performed at a two-sided 5% level of significance. Using a 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.

For the proportions of subjects in each treatment group with simultaneous systolic and diastolic blood pressure control (at Week 1, Week 3, Week 5, and Week 7) as well as the proportions of subjects with SeDBP < 90 mm Hg in each treatment group compared at Week 1, Week 3, and Week 7 were carried out the same way as for the primary efficacy variable.

Change from baseline in mean SeSBP and mean SeDBP at Week 1, Week 3, Week 5, and Week 7 were analyzed using analysis of covariance (ANCOVA) to compare the combination therapy and monotherapy groups, with treatment as the main effect and the baseline value as covariate. The covariate-adjusted mean difference between treatment groups was tested at the two-sided 5% significance level.

There were no adjustments in the statistical analysis plan for multiple testing at each of the study visits.

Safety analyses utilized data from all treated patients (randomized subjects who received at least one dose of double-blind study medication). For safety summaries, the data was truncated to exclude non-serious AEs occurring after the day of last double-blind treatment, and serious AEs occurring more than 14 days after the last dose date. Safety listings, however, were not truncated and included all available data.

9.2.3 Results

9.2.3.1 Sites, Investigators, and Study Dates

The study was conducted from September 19, 2004 through May 11, 2005. There were 255 investigators at a total of 255 sites, including 130 sites in the US, 30 in Canada, 16 in Russia, 10 in Israel, 24 in Germany, 25 in France, 10 in the Netherlands, and 10 in Belgium. Although 185 sites enrolled subjects, only 156 sites randomized subjects. Individual sites randomized 1 – 30 subjects.

9.2.3.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the current Declaration of Helsinki.

The sponsor audited a total of 9 sites (118, 096, 170, 100, 167, 055, 015, 028, and 040), including 5 in the United States and 4 in Europe.

Significant patient level protocol violations included the lack of informed consent, calculated age < 18 years at the time of enrollment, date and time of first dose preceding date and time of last qualifying (A99/B00) BP measurement, receipt of prohibited medications expected to have a significant effect on BP during Period B (medication numbers 32 (nitrates), 33 (ACE inhibitors, calcium antagonists, diuretics, angiotensin II receptor antagonists), 34 (beta-adrenergic blocking agents including eye drops), and 37 (other antihypertensive drugs and arterial vasodilators) listed

under Prohibited Therapies), last qualifying (A99) SeSBP ≥ 220 mm Hg or SeDBP ≥ 130 mm Hg, and Kit ID dispensed not matching kit ID assigned by IVRS.

A significant visit level protocol violation was defined as the time for last dose to BP measurement < 20.5 or > 27.5 hours at Week 5 (Visit B03).

There were 35 patient level protocol violations and 5 visit level protocol violations in the Irbesartan/HCTZ treatment group. Most of the patient level protocol violations were due to either of the last two consecutive qualifying visits (A01, A99) having SeDBP < 110 mm Hg (22 patients). These patients included 62-1, 62-2, 76-2, 76-3, 81-3, 114-12, 118-24, 119-1, 128-2, 146-2, 146-3, 161-5, 167-5, 179-1, 191-1, 194-11, 202-1, 219-1, 249-1, 275-9, 275-10, and 282-1. Two patients received prohibited medications.

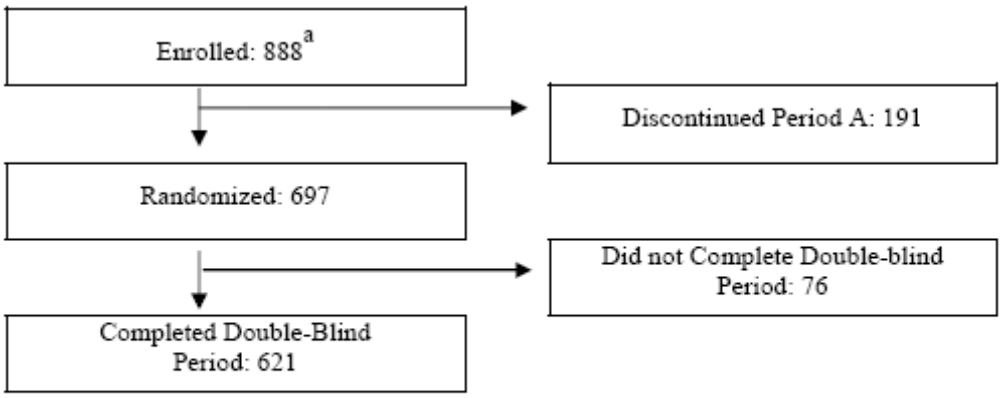
There were 17 patient level protocol violations and 3 visit level protocol violations in the Irbesartan monotherapy treatment group. Most of the patient level protocol violations were due to either of the last two consecutive qualifying visits (A01, A99) having SeDBP < 110 mm Hg (8 patients). Five patients received prohibited medications.

One subject (CV131176-48-4) in the Netherlands unblinded himself the day before his final study visit, but because the unblinding occurred at the end of the study, it did not affect data collection or analysis.

9.2.3.3 Disposition of Subjects

The disposition of subjects is graphically displayed in Figure 2. Table 27 displays the subject disposition for study CV131176. A total of 888 subjects were enrolled and 697 subjects were randomized to double-blind treatment, including 468 subjects randomized to irbesartan/HCTZ and 227 subjects randomized to irbesartan monotherapy. Two subjects were randomized to irbesartan monotherapy but were not treated. A total of 621 subjects (89.1%) completed the study, including 420 (89.7%) randomized to combination therapy and 201 (87.8%) randomized to irbesartan monotherapy.

Figure 2. Subject Disposition (CV131176)



[a] The IVRS system indicates 889; one subject was inadvertently assigned 2 different patient identification numbers and counted twice in the IVRS system, but only once in the database.

Source: Appendices 8.1.1 and 8.1.2

(Reproduced from Sponsor, Clinical Study Report, Figure 8.1, page 52)

Table 27. Agency Analysis: Subject Disposition (CV131176)

	Irb/HCTZ (n, %)	Irbesartan (n, %)	Total (n, %)
Total Number of Subjects Randomized	468 (100.0)	229 (100.0)	697 (100.0)
Number of Subjects Treated	468 (100.0)	227 (99.1)	695 (99.7)
Number of Subjects Discontinued from the Study during the Double-Blind Period	48 (10.3)	28 (12.2)	76 (10.9)
Adverse event*	10 (2.1)	5 (2.2)	15 (2.2)
Subject withdrew consent	9 (1.9)	4 (1.7)	13 (1.9)
Pregnancy	0	1 (0.4)	1 (0.1)
Lost to follow-up	4 (0.9)	3 (1.3)	7 (1.0)
Administrative reason by sponsor	1 (0.2)	0	1 (0.1)
Subject no longer meets study criteria	8 (1.7)	3(1.3)	11 (1.6)
Lack of efficacy	15 (3.2)	12 (5.2)	27 (3.9)
Poor/non-compliance	1 (0.2)	0	1 (0.1)
Number of Subjects Completing	420 (89.7)	201 (87.8)	621 (89.1)

***Table 8.1 in the Clinical Study Report on page 53 reports 10 subjects (2.1%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to "withdrawn consent" and 9 subjects (1.9%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to adverse events. Since I believe one of the irbesartan/HCTZ subjects (Subject 96-6) who was originally placed in the "withdrew consent" column in the sponsor's analysis should actually have been placed in the "adverse event" column, I retabulated the values for the "adverse event" and "withdrew consent" rows in this Table and made adjustments to the respective "Total" columns for these rows.**

Irb = Irbesartan

Analysis by Karen A. Hicks, M.D.

9.2.3.4 Demographics and Baseline Characteristics

Baseline demographics and baseline characteristics are displayed in Table 28. Baseline demographic characteristics were balanced between treatment groups except the irbesartan monotherapy treatment group had a greater percentage of women, subjects greater than 65 years of age, subjects with stable angina pectoris, and subjects with stroke or transient ischemic attack, compared with combination therapy. The irbesartan monotherapy treatment group also had a smaller percentage of men. The combination therapy group had a higher percentage of patients with SeDBP 120 - 129 and SeSBP 180 - 199, compared with the monotherapy group. The most commonly reported cardiovascular medical histories were hypertension (99.6%), hyperlipidemia (33.9%), and diabetes mellitus (11.8%).

The elderly population (age ≥ 65 years) and nonCaucasian races were underrepresented in both treatment groups.

Table 28. Baseline Demographic Characteristics (CV131176)

Characteristic		Irb/HCTZ (N = 468)	Irbesartan (N = 229)	Total (N = 697)
Age (years)	N	468	229	697
	Mean (SD)	52.2 (10.5)	52.9 (10.9)	52.5 (10.6)
	Range	23.0 – 81.0	25.0 – 83.0	23.0 – 83.0
Age Group	< 40 years	51 (10.9%)	24 (10.5%)	75 (10.8%)
	40 – 54 years	221 (47.2%)	107 (46.7%)	328 (47.1%)
	55 – 64 years	143 (30.6%)	59 (25.8%)	202 (29.0%)
	65 – 74 years	45 (9.6%)	33 (14.4%)	78 (11.2%)
	≥ 75 years	8 (1.7%)	6 (2.6%)	14 (2.0%)
Gender	Male	277 (59.2%)	124 (54.1%)	401 (57.5%)
	Female	191 (40.8%)	105 (45.9%)	296 (42.5%)
Race	White	395 (84.4%)	192 (83.8%)	587 (84.2%)
	Black/African American	67 (14.3%)	34 (14.8%)	101 (14.5%)
	American Indian/Alaska Native	2 (0.4%)	1 (0.4%)	3 (0.4%)
	Asian	3 (0.6%)	2 (0.9%)	5 (0.7%)
	Native Hawaiian/Other Pacific Islander	1 (0.2%)	0	1 (0.1%)
Weight (kg)	N	466	229	695
	Mean (SD)	89.7 (20.4)	91.8 (20.3)	90.3 (20.4)
	Range	48.0 – 164.3	44.0 – 151.5	44.0 – 164.3
Hypertension Duration (years)	N	464	229	693
	Mean (SD)	7.2 (8.2)	7.1 (7.5)	7.2 (8.0)
	Range	-0.7 – 48.9	0.0 – 35.8	-0.7 – 48.9
Region	North America	249 (53.2%)	117 (51.1%)	366 (52.5%)
	Western Europe	158 (33.8%)	80 (34.9%)	238 (34.1%)
	Other	61 (13.0%)	32 (14.0%)	93 (13.3%)

Characteristic		Irb/HCTZ (N = 468)	Irbesartan (N = 229)	Total (N = 697)
SeDBP (mm Hg)	N	467	227	694
	Mean (SD)	113.4 (3.7)	113.3 (3.5)	113.4 (3.7)
	Range	92.8 - 131.6	103.0 – 135.0	92.8 – 135.0
	< 110 mm Hg	17 (3.6%)	5 (2.2%)	22 (3.2%)
	110 – 114 mm Hg	326 (69.7%)	163 (71.2%)	489 (70.2%)
	115 – 119 mm Hg	90 (19.2%)	48 (21.0%)	138 (19.8%)
	120 – 129 mm Hg	33 (7.1%)	10 (4.4%)	43 (6.2%)
	≥ 130 mm Hg	1 (0.2%)	1 (0.4%)	2 (0.3%)
SeSBP (mm Hg)	N	467	227	694
	Mean (SD)	171.5 (16.3)	171.6 (16.9)	171.5 (16.5)
	Range	132.3 – 221.7	134.7 – 220.7	132.3 – 221.7
	< 140 mm Hg	4 (0.9%)	5 (2.2%)	9 (1.3%)
	140 – 159 mm Hg	100 (21.4%)	50 (21.8%)	150 (21.5%)
	160 – 179 mm Hg	224 (47.9%)	106 (46.3%)	330 (47.3%)
	180 – 199 mm Hg	113 (24.1%)	50 (21.8%)	163 (23.4%)
	200 – 219 mm Hg	25 (5.3%)	14 (6.1%)	39 (5.6%)
	≥ 220 mm Hg	1 (0.2%)	2 (0.9%)	3 (0.4%)
SeHR (beats/min)	N	465	226	691
	Mean (SD)	77.4 (10.5)	76.6 (10.2)	77.2 (10.4)
	Range	53.0 – 111.0	56.0 – 117.0	53.0 – 117.0
CV Specific Medical History		467 (99.8)	229 (100.0)	696 (99.9)
	Atrial Fibrillation	2 (0.4)	0	2 (0.3)
	Diabetes Mellitus	52 (11.1)	30 (13.1)	82 (11.8)
	Hyperlipidemia	158 (33.8)	78 (34.1)	236 (33.9)
	Hypertension	465 (99.4)	229 (100.0)	694 (99.6)
	Implanted Cardiovascular Defibrillator	1 (0.2)	0	1 (0.1)
	Myocardial Infarction	6 (1.3)	3 (1.3)	9 (1.3)
	PCI or CABG	6 (1.3)	0	6 (0.9)
	Permanent Pacemaker Implantation	1 (0.2)	0	1 (0.1)
	Renal Arterial Disease	2 (0.4)	0	2 (0.3)
	Stable Angina Pectoris	12 (2.6)	12 (5.2)	24 (3.4)
	Stroke or TIA	6 (1.3)	7 (3.1)	13 (1.9)
	Unstable Angina Pectoris	3 (0.6)	1 (0.4)	4 (0.6)
	Valvular Disease	2 (0.4)	3 (1.3)	5 (0.7)

SeDBP: seated diastolic blood pressure; SeSBP: seated systolic blood pressure; SeHR: seated heart rate
Reproduced from Sponsor, Clinical Study Report, Tables 8.3A, 8.3B, and 8.4, pages 55, 56, and 58)

9.2.3.5 Compliance

According to the protocol, the subject's compliance with study medication was to be reviewed and stressed at each visit. Subjects were compliant if they were taking between 80% and 120% of their medication.

Over the course of the study, 31 subjects in the irbesartan/HCTZ group were noncompliant 41 times and 14 subjects in the irbesartan monotherapy group were noncompliant 17 times. Week 7 had the greatest noncompliance in both treatment groups. At Week 7, 14 subjects in the irbesartan/HCTZ and 6 subjects in the irbesartan monotherapy treatment groups were noncompliant.

One patient (0.1%) (Subject 101-4) who had received irbesartan/HCTZ was discontinued from the study for noncompliance.

9.2.3.6 Extent of Exposure

In the Irbesartan/HCTZ and Irbesartan monotherapy treatment groups, the mean duration of exposure was 47.2 and 46.8 days, respectively. A total of 426 (91.0%) of patients in the Irbesartan/HCTZ group and 208 (91.6%) of patients in the Irbesartan monotherapy group received therapy for 31-60 days.

9.2.3.7 Concomitant Therapy

During Period A, the placebo run-in period, 302 (64.5%) Irbesartan/HCTZ subjects and 150 (66.1%) Irbesartan subjects received concomitant medications. Acetylsalicylic acid and acetaminophen were two of the most common medications taken by both treatment groups. A total of 24 (5.1%) subjects in the Irbesartan/HCTZ group and 13 (5.7%) subjects in the Irbesartan monotherapy group received acetaminophen. A total of 56 (12.0%) subjects in the Irbesartan/HCTZ group and 21 (9.3%) subjects in the Irbesartan monotherapy group received acetylsalicylic acid. Ibuprofen use was 2.9% overall. Systemic corticosteroid use occurred in $\leq$ 0.4% of subjects in both treatment groups. Topical nitrates were used in 0.2% of Irbesartan/HCTZ patients and in 0% of Irbesartan monotherapy patients. Concomitant antihypertensives (alpha adrenergic blockers, diuretics, beta blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and/or calcium channel blockers) were used by 121 subjects (25.9%) in the irbesartan/HCTZ treatment group and by 71 subjects (31.3%) in the irbesartan monotherapy group. Irbesartan was used by 20 subjects (4.3%) in the combination group and by 5 subjects (2.2%) in the monotherapy group. Amlodipine was used by 2 subjects (0.4%) in the combination group and by 8 subjects (3.5%) in the monotherapy group.

During Period B, the double-blind period, a total of 278 (59.4%) subjects in the Irbesartan/HCTZ group and 129 (56.8%) subjects in the Irbesartan monotherapy treatment group received concomitant medication. Acetaminophen and acetylsalicylic acid were used by 7.2% and 11.2% of the subjects, respectively. Ibuprofen was used by 4.3% of subjects overall. Systemic corticosteroid use was < 0.4% in both treatment groups. Organic nitrate use was 0% in the Irbesartan/HCTZ group and 0.4% (1 patient) in the Irbesartan monotherapy group. Concomitant antihypertensives were used in 9 subjects (1.9%) in the irbesartan/HCTZ group and in 5 subjects (2.2%) in the irbesartan monotherapy treatment group.

9.2.3.8 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with SeDBP < 90 mm Hg at Week 5 of the double-blind period. At Week 5 of the double-blind period, 47.2% of subjects randomized to irbesartan/HCTZ achieved trough SeDBP < 90 mm Hg, compared to 33.2% of subjects randomized to irbesartan (p = 0.0005), as shown in Table 29.

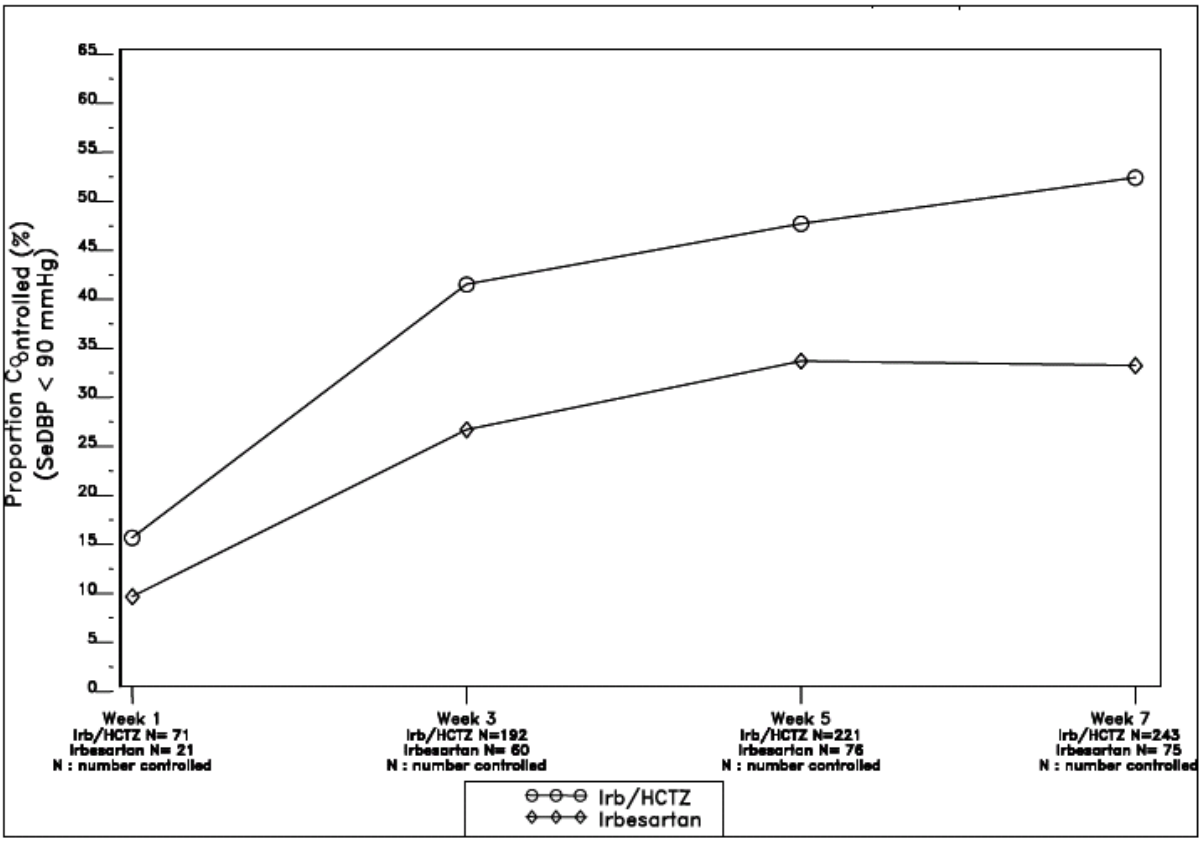
Table 29. Proportion of Subjects Controlled (SeDBP < 90 mm Hg) at Week 5 (CV131176)

	Trough Seated DBP < 90 mm Hg	
	Irb/HCTZ N = 468	**Irbesartan N = 229**
n at Baseline	468	229
n at Week 5	423	206
Proportion Controlled (No. Controlled)	0.472 (221)	0.332 (76)
Est. Difference between Treatments	0.140	
95% CI for Estimated Difference	(0.061, 0.220)	
P-value for Between Group Comparison	0.0005	

Reproduced from Sponsor, Clinical Study Report, Table 10.1, page 64. Source: Appendix 10A, Appendix 6, Supplemental Table S.10.1A.
N=number of subjects randomized
n=number of subjects with available efficacy data at Week 5
Proportion controlled=number controlled/number randomized.
Irb = Irbesartan
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

A graphical representation of the proportion of patients with SeDBP < 90 mm Hg at Week 5 is shown in Figure 3.

Figure 3. Proportion Controlled (SeDBP < 90 mm Hg) During Double-Blind Period (CV131176)



(Reproduced from Sponsor, Figure 10.1, Clinical Study Report, page 65)

9.2.3.9 Secondary Efficacy Endpoints

The other efficacy outcome measures were

- the proportion of subjects with SeDBP < 90 mm Hg (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)
- the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg (at Week 1, Week 3, Week 5, and Week 7).

Proportion of Subjects with Controlled SeDBP AND SeSBP at Weeks 1, 3, 5, and 7
The proportion of subjects in each treatment group with SeDBP < 90 mm Hg AND SeSBP < 140 mm Hg at Weeks 1, 3, 5, and 7 of the double-blind period is displayed in Table 30. Approximately 20% of the irbesartan monotherapy group at peak achieved this goal. At Weeks 3, 5, and 7, the percentage of patients who achieved this goal on irbesartan/HCTZ was approximately 14-19% higher than patients receiving irbesartan monotherapy.

Table 30. Treatment Comparison of Proportions Controlled during Double-Blind Period by Week (CV131176)

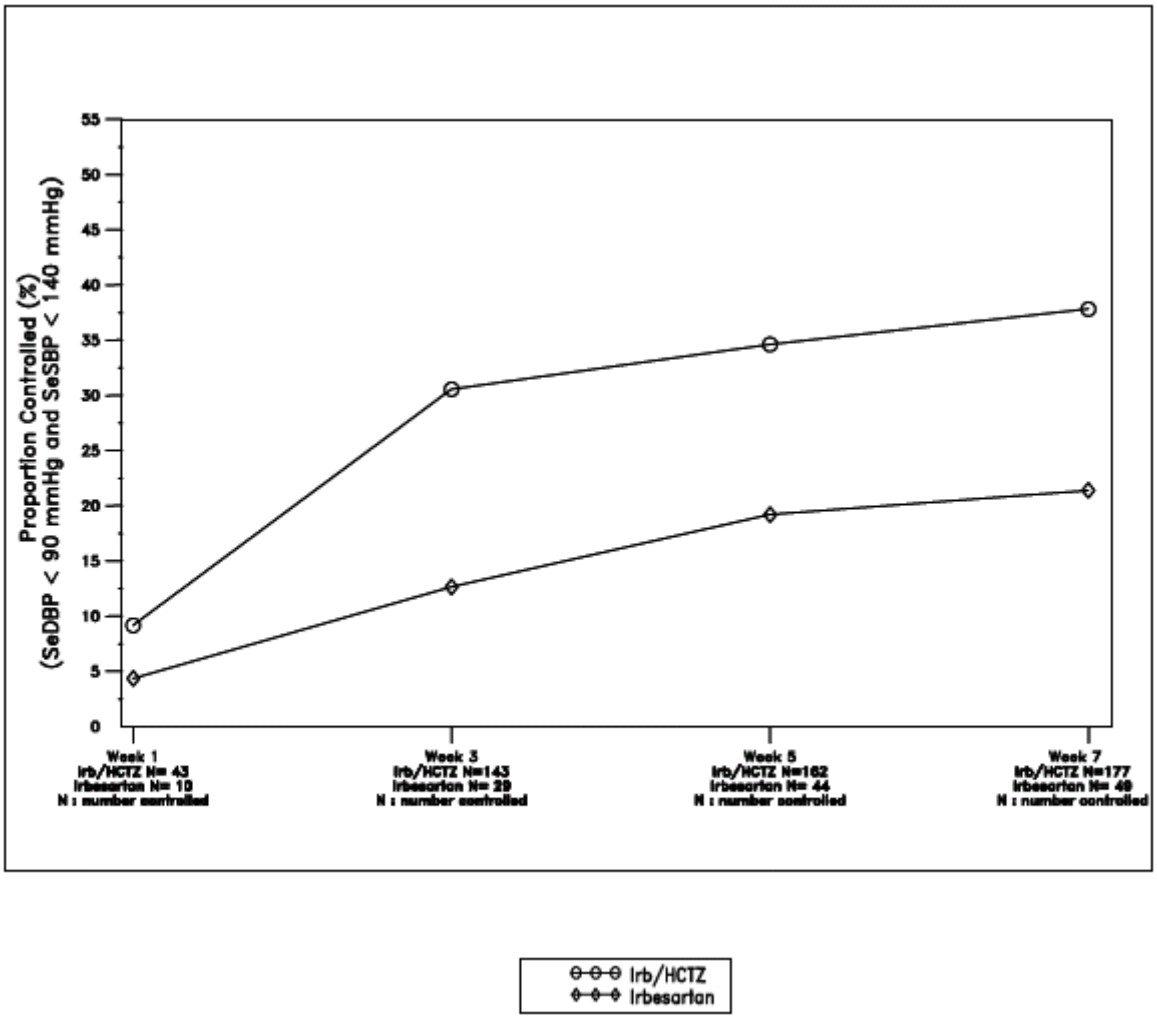
		Trough SeDBP < 90 mm Hg		Trough SeDBP < 90 mm Hg AND Trough SeSBP < 140 mm Hg	
Week	**Category**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
Week 1	**n at Baseline**	468	229	468	229
	n	460	219	460	219
	Proportion Controlled (No. Controlled)	0.152 (71)	0.092 (21)	0.092 (43)	0.044 (10)
	Est. Difference Between Treatments	0.060		0.048	
	95% CI for Estimated Difference	(0.007, 0.113)		(0.008, 0.089)	
	P-value for Between Group Comparison	0.0317		0.0230	
Week 3	**n at Baseline**	468	229	468	229
	n	452	219	452	219
	Proportion Controlled (No. Controlled)	0.410 (192)	0.262 (60)	0.306 (143)	0.127 (29)
	Est. Difference Between Treatments	0.148		0.179	
	95% CI for Estimated Difference	(0.073, 0.224)		(0.116, 0.242)	
	P-value for Between Group Comparison	0.0002		<0.0001	
Week 5	**n at Baseline**	468	229	468	229
	n	423	206	423	206
	Proportion Controlled (No. Controlled)	0.472 (221)	0.332 (76)	0.346 (162)	0.192 (44)
	Est. Difference Between Treatments	0.140		0.154	
	95% CI for Estimated Difference	(0.061, 0.220)		(0.084, 0.224)	
	P-value for Between Group	0.0005		< 0.0001	

		Trough SeDBP < 90 mm Hg		Trough SeDBP < 90 mm Hg AND Trough SeSBP < 140 mm Hg	
Week	**Category**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
	Comparison				
Week 7	**n at Baseline**	468	229	468	229
	n	426	203	426	203
	Proportion Controlled (No. Controlled)	0.519 (243)	0.328 (75)	0.378 (177)	0.214 (49)
	Est. Difference Between Treatments	0.192		0.164	
	95% CI for Estimated Difference	(0.113, 0.271)		(0.092, 0.236)	
	P-value for Between Group Comparison	< 0.0001		< 0.0001	

Reproduced from Sponsor, Clinical Study Report, Table 10.2, page 68. Source: Appendix 10A. Supplemental Tables S.10.1A, S.10.1B, S.10.2.
N=number of subjects randomized
n=number of subjects with available efficacy data at the week analyzed
Proportion controlled=number controlled/number randomized
Irb = Irbesartan
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

The graphical display of the proportion of subjects with SeDBP < 90 mm Hg AND Se SBP < 140 mm Hg during the double-blind period is shown in Figure 4.

Figure 4. Proportion Controlled (SeDBP < 90 mm Hg and SeSBP < 140 mm Hg) During Double-Blind Period (CV131176)



(Reproduced from Sponsor, Clinical Study Report, Figure 10.2, page 69)

Change from Baseline BP in SeSBP and SeDBP at Weeks 1, 3, 5, and 7

At Weeks 5 and 7, the mean systolic and diastolic blood pressure decreases from baseline were approximately 31/24 mm Hg for the irbesartan/HCTZ treatment group and 21/19 mm Hg for the irbesartan monotherapy treatment group, as displayed in Table 31.

For SeDBP, the differences between irbesartan/HCTZ and irbesartan groups in the adjusted mean changes from baseline were 2.5 mm Hg, 4.2 mm Hg, 4.7 mm Hg, and 4.6 mm Hg in favor of irbesartan/HCTZ at Weeks 1, 3, 5, and 7, respectively. The p-value was 0.0006 at Week 1 and < 0.0001 at Weeks 3, 5, and 7.

For SeSBP, the differences between irbesartan/HCTZ and irbesartan groups in the adjusted mean changes from baseline were 5.1 mm Hg, 9.4 mm Hg, 9.7 mm Hg, and 10.1 mm Hg in favor of

irbesartan/HCTZ at Weeks 1, 3, 5, and 7, respectively. The p-value was < 0.0001 at all time points.

Table 31. Mean Changes from Baseline in Trough SeDBP and SeSBP by Week (CV131176)

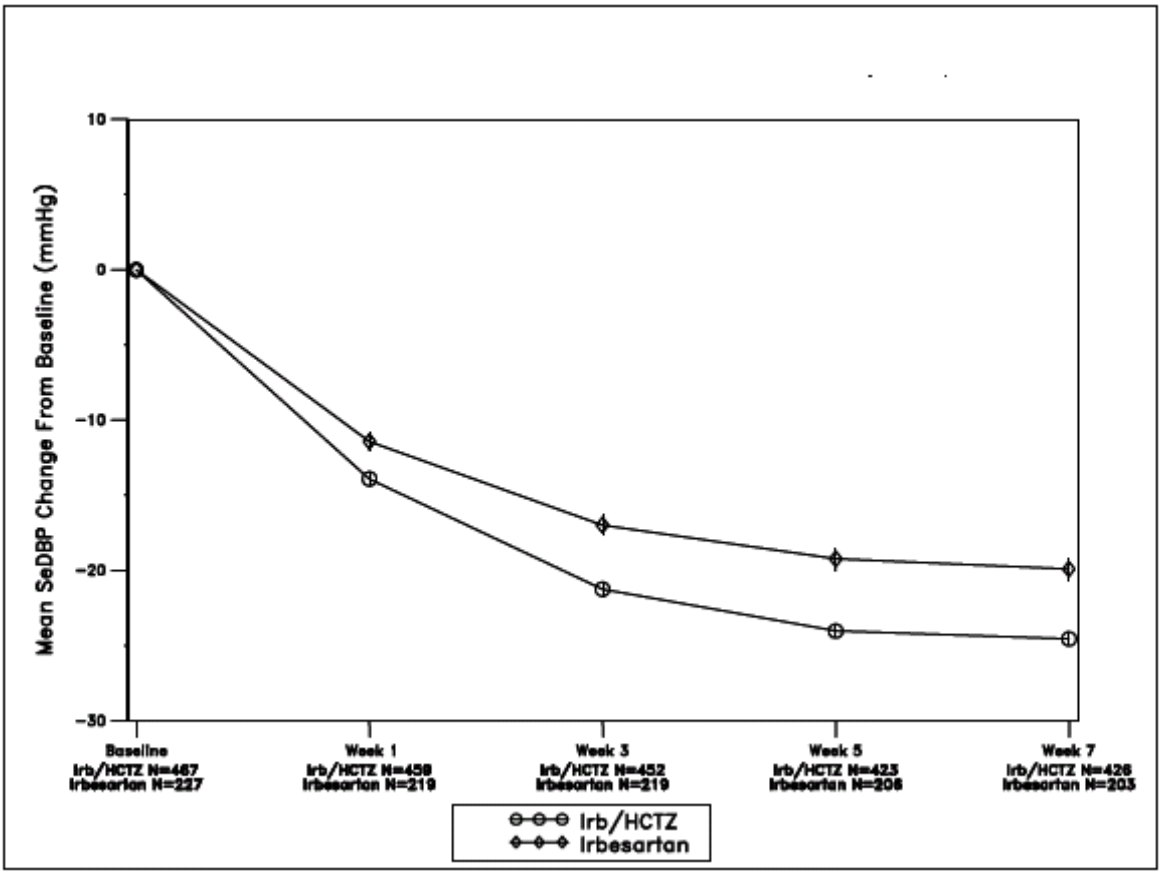
		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
Week 1	**n**	459	219	459	219
	Baseline Mean (SD)	113 (3.7)	113.4 (3.5)	171.4 (16.2)	171.9 (17.1)
	Period B On-Therapy Mean (SD)	99.5 (9.4)	102.0 (9.5)	154.5 (17.3)	160.0 (18.2)
	Adj. Mean Change from Baseline (SE)	-13.9 (0.4)	-11.4 (0.6)	-16.9 (0.6)	-11.8 (0.9)
	Difference in Adjusted Mean Change	-2.5		-5.1	
	95% CI for Estimated Difference	(-3.9, -1.1)		(-7.2, -3.0)	
	P-value	0.0006		< 0.0001	
Week 3	**n**	452	219	452	219
	Baseline Mean (SD)	113.4 (3.7)	113.2 (3.3)	171.5 (16.3)	171.5 (16.6)
	Period B On-Therapy Mean (SD)	92.2 (10.5)	96.3 (10.0)	144.4 (17.7)	153.8 (16.7)
	Adj. Mean Change from Baseline (SE)	-21.2 (0.5)	-17.0 (0.7)	-27.1 (0.7)	-17.7 (1.0)
	Difference in Adjusted Mean Change	-4.2		-9.4	
	95% CI for Estimated Difference	(-5.8, -2.6)		(-11.7, -7.0)	
	P-value	< 0.0001		< 0.0001	

		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
Week 5	**n**	423	206	423	206
	Baseline Mean (SD)	113.5 (3.5)	113.2 (3.2)	171.6 (16.4)	171.3 (16.3)
	Period B On-Therapy Mean (SD)	89.4 (9.3)	93.9 (10.2)	140.8 (15.3)	150.3 (16.9)
	Adj. Mean Change from Baseline (SE)	-24.0 (0.5)	-19.3 (0.7)	-30.8 (0.7)	-21.1 (1.0)
	Difference in Adjusted Mean Change	-4.7		-9.7	
	95% CI for Estimated Difference	(-6.3, 03.1)		(-12.0, -7.3)	
	P-value	< 0.0001		< 0.0001	
Week 7	**n**	426	203	426	223
	Baseline Mean (SD)	113.3 (3.5)	113.1 (3.2)	171.3 (16.3)	171.1 (16.6)
	Period B On-Therapy Mean (SD)	88.8 (9.4)	93.2 (10.6)	139.5 (16.1)	149.4 (17.1)
	Adj. Mean Change from Baseline (SE)	-24.5 (0.5)	-19.9 (0.7)	-31.7 (0.7)	-21.7 (1.0)
	Difference in Adjusted Mean Change	-4.6		-10.1	
	95% CI for Estimated Difference	(-6.2, -3.0)		(-12.5, -7.6)	
	P-value	< 0.0001		< 0.0001	

Reproduced from Sponsor, Clinical Study Report, Table 10.3, page 72)
Source: Appendix 10A, Appendix 6
Reference: Supplemental Tables S.10.3.A.1, S.10.3B
N=number of subjects randomized into Period B
n=number of subjects with available efficacy during Period B
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

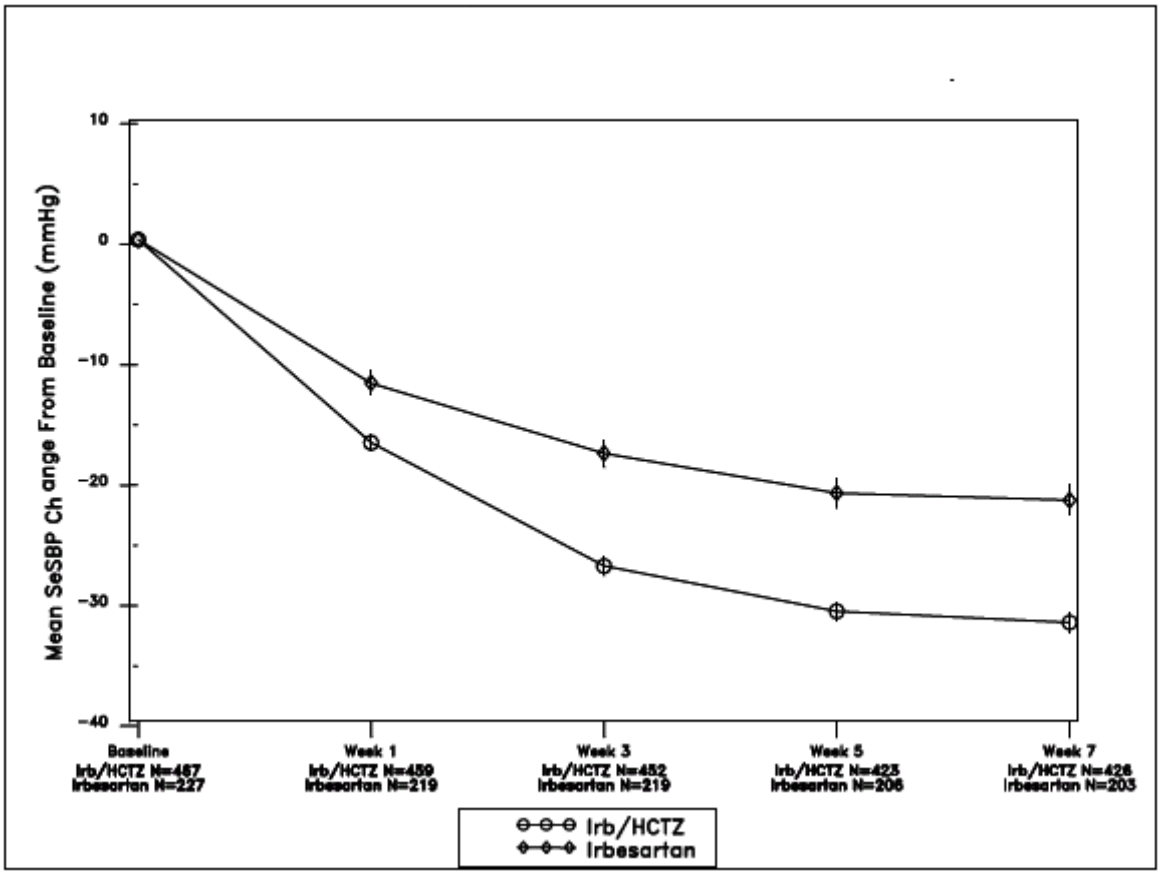
Graphical displays of mean changes from baseline in trough SeDBP and SeSBP are shown in Figure 5 and Figure 6, respectively.

Figure 5. Mean Changes from Baseline in Trough SeDBP During Double-Blind Period (CV131176)



(Reproduced from Sponsor, Clinical Study Report, Figure 10.3A, page 73)

Figure 6. Mean Changes from Baseline in Trough SeSBP During Double-Blind Period (CV131176)



(Reproduced from Sponsor, Clinical Study Report, Figure 10.3B, page 74)

Standing trough DBP and SBP results were similar to the seated trough DBP and SBP results; however, the adjusted mean changes from baseline were approximately 2-4 mm Hg lower with standing BP results, compared to sitting.

Since 10% of subjects randomized to the irbesartan monotherapy group did not have available data for the analysis of blood pressure changes at Week 5, the sponsor also performed last observation carried forward (LOCF) analyses at Weeks 5 and 7. For SeDBP, the difference between treatment groups in adjusted mean changes from baseline were 4.8 mm Hg and 5.0 mm Hg at weeks 5 and 7, respectively, in favor of irbesartan/HCTZ. For SeSBP, the difference between treatment groups in adjusted mean changes from baseline were 9.4 mm Hg and 10.1 mm Hg at weeks 5 and 7, respectively, in favor of irbesartan/HCTZ. The LOCF results were similar to the results obtained with the primary analyses. The results of the LOCF analysis are shown in Table 32.

Table 32. LOCF Analysis in Seated Blood Pressure During Week 5 and Week 7 of Double-Blind Period

		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
Week 5	**n**	463	225	463	225
	Baseline Mean (SD)	113.4 (3.72)	113.3 (3.52)	171.4 (16.31)	171.8 (16.97)
	Period B On-Therapy Mean (SD)	90.0 (9.92)	94.7 (10.91)	141.8 (16.49)	151.4 (17.85)
	Change from Baseline Mean (SD)	-23.4 (9.46)	-18.6 (10.84)	-29.6 (16.29)	-20.3 (18.21)
	Adj. Mean Change from Baseline (SE)	-23.4 (0.46)	-18.6 (0.66)	-29.6 (0.69)	-20.2 (0.99)
	Difference in Adjusted Mean Change	-4.8		-9.4	
	95% CI for Estimated Difference	(-6.4, -3.2)		(-11.8, -7.1)	
	P-value	< 0.0001		< 0.0001	
Week 7	**n**	463	225	463	225
	Baseline Mean (SD)	113.4 (3.72)	113.3 (3.52)	171.4 (16.31)	171.8 (16.97)
	Period B On-Therapy Mean (SD)	89.5 (10.26)	94.5 (11.45)	140.9 (17.23)	151.1 (18.38)
	Change from Baseline Mean (SD)	-23.9 (9.88)	-18.8 (11.15)	-30.6 (17.38)	-20.7 (18.22)
	Adj. Mean Change from Baseline (SE)	-23.9 (0.48)	-18.9 (0.69)	-30.6 (0.72)	-20.6 (1.04)
	Difference in Adjusted Mean Change	-5.0		-10.1	
	95% CI for Estimated Difference	(-6.6, -3.4)		(-12.6, -7.6)	
	P-value	< 0.0001		< 0.0001	

Means and mean changes are arithmetic means
Change from baseline = on-therapy value – baseline value
Analysis of covariance model: change = baseline treatment
N = number of subjects with available efficacy data at specified week and baseline
LOCF = Last Observation Carried Forward
Reproduced from Sponsor, Clinical Study Report, Tables S.10.3A.2, pages 210-211.

Heart Rate and Standing BP

Summary statistics by treatment group for change from baseline in seated heart rate (SeHR) (mean changes and 95% Confidence Interval) are shown in Table 33. Therapy with irbesartan/HCTZ or irbesartan alone did not affect heart rate. Trough standing heart rates were similar to seated heart rates, except the mean standing heart rates were approximately 3-4 bpm higher than the sitting HR measurements.

Table 33. Summary Statistics for Change from Baseline in Seated Heart Rate During Double-Blind Period by Week (CV131176)

Week	Randomized Group	N	Baseline Mean (SD)	Period: B On-Therapy Mean (SD)	Change from Baseline			
					Mean	(SD)	95% Confidence Interval	
							Lower	Higher
Trough SeHR								
Week 1	**Irb/HCTZ**	457	77.5 (10.56)	78.0 (11.73)	0.5	(8.02)	-0.2	1.2
	Irbesartan	218	76.7 (10.13)	75.8 (9.97)	-0.8	(8.38)	-2.0	0.3
Week 3	**Irb/HCTZ**	449	77.3 (10.53)	78.2 (11.70)	0.8	(9.51)	-0.0	1.7
	Irbesartan	218	76.5 (10.12)	75.4 (10.71)	-1.2	(8.99)	-2.4	0.0
Week 5	**Irb/HCTZ**	421	77.4 (10.40)	77.5 (11.18)	0.1	(8.78)	-0.7	1.0
	Irbesartan	205	76.6 (10.27)	75.6 (10.88)	-0.9	(8.74)	-2.1	0.3
Week 5 LOCF	**Irb/HCTZ**	461	77.4 (10.55)	77.5 (11.16)	0.1	(8.90)	-0.7	0.9
	Irbesartan	224	76.6 (10.17)	75.8 (10.72)	-0.8	(8.94)	-2.0	0.4
Week 7	**Irb/HCTZ**	424	77.1 (10.31)	77.6 (11.83)	0.5	(9.73)	-0.4	1.5
	Irbesartan	202	76.7 (10.23)	75.3 (10.95)	-1.4	(8.98)	-2.6	-0.2
Week 7 LOCF	**Irb/HCTZ**	461	77.4 (10.55)	77.5 (11.73)	0.1	(9.85)	-0.8	1.0
	Irbesartan	224	76.6 (10.17)	75.2 (10.90)	-1.4	(9.11)	-2.6	-0.2

SD: standard deviation
Reproduced from Sponsor, Clinical Study Report, Table S.10.3B, page 214.

9.2.3.10 Subgroup Analyses (age, gender, race, geographic region)

Proportions Controlled at Week 5

By age-group, the proportions of subjects whose SeDBP was controlled at Week 5 are displayed in Table 34. Regardless of the subgroup, except for "Race: Other," the irbesartan/HCTZ treatment group had a greater percentage of patients with SeDBP < 90 mm Hg at Week 5 than the irbesartan monotherapy treatment group. Results were similar for the percentage of patients achieving SeDBP < 90 mm Hg AND SeSBP < 140 mm Hg at Week 5.

Table 34. Proportions Controlled at Week 5 by Age-Group, Gender, Race, and Geographic Region (CV131176)

Group	Randomized Group	N at Specified Week	N	SeDBP < 90 mm Hg				SeDBP < 90 mm Hg AND SeSBP < 140 mm Hg			
				Number Controlled	Proportion Controlled	95% CI		Number Controlled	Proportion Controlled	95% CI	
						Lower	Upper			Lower	Upper
Age < 65 years	**Irb/HCTZ**	376	415	189	0.455	0.406	0.505	146	0.352	0.305	0.399
	Irbesartan	169	190	58	0.305	0.237	0.373	38	0.200	0.140	0.260
Age ≥ 65 years	**Irb/HCTZ**	47	53	32	0.604	0.463	0.745	16	0.302	0.169	0.435
	Irbesartan	37	39	18	0.462	0.292	0.631	6	0.154	0.028	0.280
Gender: Male	**Irb/HCTZ**	252	277	128	0.462	0.402	0.523	95	0.343	0.285	0.401
	Irbesartan	113	124	37	0.298	0.214	0.383	23	0.185	0.113	0.258
Gender: Female	**Irb/HCTZ**	171	191	93	0.487	0.413	0.560	67	0.351	0.280	0.421
	Irbesartan	93	105	39	0.371	0.274	0.469	21	0.200	0.119	0.281
Race: White	**Irb/HCTZ**	358	395	192	0.486	0.436	0.537	138	0.349	0.301	0.398
	Irbesartan	174	192	70	0.365	0.294	0.435	41	0.214	0.153	0.274
Race: Black/African American	**Irb/HCTZ**	59	67	27	0.403	0.278	0.528	22	0.328	0.208	0.448
	Irbesartan	29	34	5	0.147	0.013	0.281	2	0.059	-0.035	0.153
Race: Other	**Irb/HCTZ**	6	6	2	0.333	-0.127	0.794	2	0.333	-0.127	0.794
	Irbesartan	3	3	1	0.333	-0.367	1.033	1	0.333	-0.367	1.033
Region: North America	**Irb/HCTZ**	215	249	105	0.422	0.358	0.485	85	0.341	0.280	0.402
	Irbesartan	103	117	31	0.265	0.181	0.349	19	0.162	0.091	0.233
Region: Western Europe	**Irb/HCTZ**	152	158	82	0.519	0.438	0.600	55	0.348	0.271	0.426
	Irbesartan	76	80	37	0.463	0.347	0.578	20	0.250	0.149	0.351
Region: Other	**Irb/HCTZ**	56	61	34	0.557	0.425	0.690	22	0.361	0.232	0.489
	Irbesartan	27	32	8	0.250	0.084	0.416	5	0.156	0.015	0.298

N = number of subjects at baseline by age group. Irb = Irbesartan; HCTZ = Hydrochlorothiazide.
Proportion Controlled = Number controlled in specified group/N at Baseline in specified group
Reproduced from Sponsor, Clinical Study Report, Tables S.10.5.A1, S.10.5.B1, S.10.5.C1, and S.10.5.D1, pages 218, 220, 222, 224.

Summary Statistics (Age, Gender, Race, Geographic Region)

The summary statistics for changes from baseline in trough blood pressure at Week 5 by age-group are presented in Table 35. At Week 5, all subgroups treated with irbesartan/HCTZ achieved mean SeDBP < 90 mm Hg except for the following subgroups: Male Gender, Black/African American Race, Other Race, and North American Region. At Week 5, the only subgroups treated with irbesartan/HCTZ that achieved mean SeSBP < 140 mm Hg included the following subgroups: Female Gender and Other Region. The irbesartan/HCTZ combination treatment group had a greater mean reduction in blood pressure from baseline than the irbesartan monotherapy treatment group in all of the subgroups.

Table 35. Summary Statistics for Changes from Baseline in Trough BP at Week 5 by Age-Group, Gender, Race, and Geographic Region

Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period: B On-Therapy Mean (SD)	Change from Baseline			
					Mean	(SD)	95% Confidence Interval	
							Lower	Upper
Age < 65 years								
SeDBP	Irb/HCTZ	376	113.6 (3.59)	89.9 (9.30)	-23.6	(8.71)	-24.5	-22.7
SeDBP	Irbesartan	169	113.1 (3.14)	94.5 (9.95)	-18.6	(10.27)	-20.2	-17.1
SeSBP	Irb/HCTZ	376	170.5 (16.07)	140.3 (15.06)	-30.2	(15.61)	-31.8	-28.7
SeSBP	Irbesartan	169	170.3 (15.49)	149.2 (16.67)	-21.1	(16.50)	-23.6	-18.6
Age ≥ 65								
SeDBP	Irb/HCTZ	47	112.7 (2.61)	85.4 (8.46)	-27.3	(8.78)	-29.9	-24.7
SeDBP	Irbesartan	37	113.3 (3.72)	91.3 (11.26)	-22.0	(11.42)	-25.8	-18.2
SeSBP	Irb/HCTZ	47	180.6 (16.75)	144.9 (16.80)	-35.7	(13.48)	-39.6	-31.7
SeSBP	Irbesartan	37	176.0 (19.24)	155.2 (17.10)	-20.8	(23.71)	-28.7	-12.9
Gender: Male								
SeDBP	Irb/HCTZ	252	113.4 (3.65)	90.3 (9.86)	-23.2	(9.09)	-24.3	-22.1
SeDBP	Irbesartan	113	113.3 (2.85)	95.4 (10.23)	-17.9	(10.18)	-19.8	-16.0
SeSBP	Irb/HCTZ	252	170.8 (16.36)	141.5 (15.06)	-29.2	(15.31)	-31.1	-27.3
SeSBP	Irbesartan	113	171.1 (16.09)	152.2 (17.06)	-18.9	(16.70)	-22.0	-15.8

Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period: B On-Therapy Mean (SD)	Change from Baseline			
					Mean	(SD)	95% Confidence Interval	
							Lower	Upper
Gender: Female								
SeDBP	Irb/HCTZ	171	113.5 (3.28)	88.3 (8.32)	-25.2	(8.20)	-26.5	-24.0
SeDBP	Irbesartan	93	113.0 (3.67)	92.2 (10.04)	-20.9	(10.78)	-23.1	-18.6
SeSBP	Irb/HCTZ	171	172.9 (16.52)	139.7 (15.65)	-33.2	(15.45)	-35.6	-30.9
SeSBP	Irbesartan	93	171.6 (16.67)	148.0 (16.42)	-23.6	(19.12)	-27.5	-19.7
Race: White								
SeDBP	Irb/HCTZ	358	113.4 (3.21)	89.0 (8.98)	-24.4	(8.72)	-25.3	-23.5
SeDBP	Irbesartan	174	113.1 (2.83)	92.8 (9.74)	-20.3	(9.81)	-21.8	-18.9
SeSBP	Irb/HCTZ	358	171.9 (16.40)	140.4 (15.07)	-31.5	(15.58)	-33.1	-29.8
SeSBP	Irbesartan	174	171.4 (16.77)	149.3 (16.63)	-22.1	(18.30)	-24.9	-19.4
Race: Black/African American								
SeDBP	Irb/HCTZ	59	113.7 (4.62)	91.7 (10.67)	-22.0	(9.06)	-24.3	-19.6
SeDBP	Irbesartan	29	113.8 (5.16)	100.9 (10.77)	-12.9	(12.62)	-17.7	-8.1
SeSBP	Irb/HCTZ	59	169.4 (16.87)	142.6 (16.74)	-26.8	(14.65)	-30.6	-23.0
SeSBP	Irbesartan	29	170.0 (14.03)	156.3 (17.95)	-13.7	(14.39)	-19.2	-8.2
Race: Other								
SeDBP	Irb/HCTZ	6	117.4 (5.59)	95.9 (10.31)	-21.5	(8.05)	-29.9	-13.0
SeDBP	Irbesartan	3	112.3 (1.56)	95.7 (10.40)	-16.6	(11.37)	-44.9	11.6
SeSBP	Irb/HCTZ	6	179.8 (12.76)	146.0 (15.49)	-33.8	(12.41)	-46.8	-20.8
SeSBP	Irbesartan	3	179.2 (9.80)	150.6 (10.60)	-28.7	(12.68)	-60.2	2.8

Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period: B On-Therapy Mean (SD)	Change from Baseline			
					Mean	(SD)	95% Confidence Interval	
							Lower	Upper
Region: North America								
SeDBP	Irb/HCTZ	215	113.5 (4.02)	90.6 (10.54)	-22.8	(9.78)	-24.2	-21.5
SeDBP	Irbesartan	103	112.8 (3.43)	96.7 (10.82)	-16.1	(11.08)	-18.3	-14.0
SeSBP	Irb/HCTZ	215	168.6 (16.79)	140.3 (16.13)	-28.3	(16.34)	-30.5	-26.1
SeSBP	Irbesartan	103	166.6 (15.23)	151.1 (17.91)	-15.5	(17.31)	-18.9	-12.1
Region: Western Europe								
SeDBP	Irb/HCTZ	152	113.6 (2.88)	88.6 (7.43)	-24.9	(7.39)	-26.1	-23.8
SeDBP	Irbesartan	76	113.3 (2.91)	90.3 (8.45)	-23.1	(8.71)	-25.0	-21.1
SeSBP	Irb/HCTZ	152	175.3 (14.45)	142.5 (13.85)	-32.8	(13.67)	-35.0	-30.6
SeSBP	Irbesartan	76	174.3 (14.53)	147.6 (14.37)	-26.7	(14.68)	-30.1	-23.3
Region: Other								
SeDBP	Irb/HCTZ	56	113.1 (2.88)	87.1 (8.24)	-26.0	(7.65)	-28.0	-23.9
SeDBP	Irbesartan	27	114.1 (3.26)	93.8 (9.60)	-20.3	(9.61)	-24.1	-16.5
SeSBP	Irb/HCTZ	56	173.5 (18.12)	138.2 (15.63)	-35.2	(15.17)	-39.3	-31.2
SeSBP	Irbesartan	27	181.1 (19.17)	154.9 (18.48)	-26.2	(22.30)	-35.0	-17.4

SeDBP: Seated diastolic blood pressure; SeSBP: Seated systolic blood pressure; Irb = Irbesartan; HCTZ = Hydrochlorothiazide
Reproduced from Sponsor, Clinical Study Report, Tables S.10.5.A2, S.10.5.B2, S.10.5.C2, and S.10.5.D2, pages 219, 221, 223, and 225.

9.2.3.11 Additional Analyses

Efficacy by Blood Pressure Quartile and Treatment Group

Table 36 displays the number of subjects and percentages of subjects in each treatment group achieving SeDBP < 90 mm Hg at Week 5, according to baseline SeDBP quartile. The fourth quartile (highest baseline SeDBPs) in both treatment groups had the lowest efficacy.

Table 36. SeDBP Control at Week 5 by Baseline SeDBP Quartile and Treatment Group (CV131176)

Blood Pressure Quartile (Baseline SeDBP mm Hg)	Number of Patients Achieving a SeDBP < 90 mm Hg at Week 5
Treatment Group 1	**N = 468**
Quartile 1 (101.67 – 111.20 mm Hg)	61 (13.0%)
Quartile 2 (111.33 – 112.60 mm Hg)	60 (12.8%)
Quartile 3 (112.67 – 114.33 mm Hg)	63 (13.5%)
Quartile 4 (114.67 – 131.60 mm Hg)	37 (7.9%)
Total (Treatment Group 1)	**221 (47.2%)**
Treatment Group 2	**N = 229**
Quartile 1 (103.0 – 111.20 mm Hg)	19 (8.3%)
Quartile 2 (111.33 – 112.33 mm Hg)	19 (8.3%)
Quartile 3 (112.67 – 114.33)	24 (10.5%)
Quartile 4 (114.67 – 135.00)	14 (6.1%)
Total (Treatment Group 2)	**76 (33.2%)**
SeDBP: Seated diastolic blood pressure **Analysis by Karen A. Hicks, M.D.**	

Efficacy by Weight and Treatment Group

Table 37 displays the number of patients achieving SeDBP < 90 mm Hg at Week 5. In both treatment groups, efficacy was lowest in subjects weighing < 75 kg.

Table 37. Efficacy by Weight and Treatment Group (CV131176)

Weight (kg)	Number of Patients Achieving a SeDBP < 90 mm Hg at Week 5
Treatment Group 1	**N = 468**
Weight < 75 kg	55 (11.8%)
Weight ≥ 75 kg	165 (35.3%)
Total (Treatment Group 1)	**220***
Treatment Group 2	**N = 229**
Weight < 75 kg	21 (9.2%)
Weight ≥ 75 kg	55 (24.0%)
Total (Treatment Group 2)	**76 (33.2%)**
***One subject in Treatment Group 1 did not have a weight, so the numbers of patients achieving goal SeDBP at Week 5 adds up to 220 instead of 221.** **SeDBP: Seated diastolic blood pressure** **Analysis by Karen A. Hicks, M.D.**	

9.2.4 Summary (CV131176)

Irbesartan/HCTZ initiated at 150 mg/12.5 mg and titrated to 300 mg/25 mg after one week in severely hypertensive (SeDBP > 110 mm Hg) subjects lowered blood pressure more rapidly and to a greater extent than irbesartan monotherapy, started at 150 mg and titrated to 300 mg after one week. At 5 weeks, the proportion of subjects whose SeDBP was controlled (SeDBP < 90 mm Hg) was 47.2% in the irbesartan/HCTZ group compared to 33.2% in the irbesartan monotherapy group ($p = 0.0005$).

Study CV131176 had numerous secondary efficacy outcome measures. Although the sponsor did not make adjustments in the statistical analysis plan for multiple testing at each of the study visits, the p-values for the secondary efficacy outcome measures were highly significant and supported the efficacy of irbesartan/HCTZ in treating patients with severe hypertension. The proportion of subjects with SeDBP < 90 mm Hg at Weeks 1, 3, and 7 was significantly greater in the irbesartan/HCTZ treatment group, compared with the irbesartan monotherapy group ($p = 0.03$ at Week 1, $p = 0.0002$ at Week 3, and $p < 0.0001$ at Week 7). Similarly, the proportion of subjects with simultaneous SeSBP < 140 mmHg AND SeDBP < 90 mm Hg at Weeks 1, 3, 5, and 7 was significantly greater in the irbesartan/HCTZ treatment group, compared with the irbesartan monotherapy group ($p = 0.02$ at Week 1 and $p < 0.0001$ at Weeks 3, 5, and 7). Lastly, the mean change from baseline in trough SeDBP and trough SeSBP was significantly greater in the irbesartan/HCTZ treatment group, compared with irbesartan, at all time periods.

In addition to demonstrating the efficacy of irbesartan/HCTZ combination therapy, Study CV131176 demonstrated the efficacy of irbesartan monotherapy. At Week 1 in Study CV131176, when subjects were receiving either irbesartan 150 mg/HCTZ 12.5 mg or irbesartan 150 mg, 15.2% and 9.2% of subjects in the combination and monotherapy treatment groups, respectively, had trough SeDBP < 90 mm Hg. After one week, subjects were force titrated to either irbesartan 300 mg/HCTZ 25 mg or irbesartan 300 mg. By Week 3, 41.0% and 26.2% of subjects in the combination and monotherapy treatment groups, respectively, achieved SeDBP < 90 mm Hg. By Week 5, 47.2% and 33.2% of subjects and by Week 7, 51.9% and 32.8% of subjects in the combination and monotherapy treatment groups, respectively, had controlled SeDBP. Furthermore, the proportion of subjects achieving simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg on irbesartan monotherapy at Weeks 3, 5, and 7 was 12.7%, 19.2%, and 21.4%, respectively, compared with 30.6%, 34.6%, and 37.8% of subjects receiving irbesartan/HCTZ. These results support the efficacy of irbesartan monotherapy and irbesartan/HCTZ combination therapy.

9.3 Study CV131185, "The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Patients with Moderate Hypertension"

9.3.1 Protocol, Amendment and Post Hoc Changes

The study description was based upon the protocol dated July 14, 2004. There were no amendments. There were four administrative letters dated September 13, 2004, December 19, 2005, November 18, 2004, and March 24, 2005 which clarified the IND number (IND 46,214), exclusion criteria, and sites to which adverse events were reported.

9.3.2 Study Design

This was a multicenter, randomized, double-blind, active-controlled, 12-week, parallel group study in untreated and treated subjects with uncontrolled hypertension. Uncontrolled hypertension was defined as follows:

Untreated Subjects:

- averaged seated systolic blood pressure (SeSBP) ≥ 160 mm Hg and < 180 mm Hg and averaged seated diastolic blood pressure (SeDBP) < 110 mm Hg

or

- averaged SeDBP ≥ 100 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

Subjects Receiving Antihypertensive Monotherapy:

- averaged SeSBP ≥150 mm Hg and < 180 mm Hg and averaged SeDBP < 110 mm Hg

or

- averaged SeDBP ≥ 95 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

9.3.2.1 Objectives

The primary objective was to compare the change from baseline in SeSBP between the first line combination arm (irbesartan 150 mg/HCTZ 12.5 mg titrated to irbesartan 300 mg/HCTZ 25 mg) and each of the two monotherapy arms at Week 8. The monotherapy arms were irbesartan 150 mg (titrated to irbesartan 300 mg) or HCTZ 12.5 mg (titrated to HCTZ 25 mg).

Secondary objectives were

- to characterize the safety/tolerability in the three treatment regimens over twelve weeks of active therapy, examining in particular, 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
- to compare the change from baseline in SeDBP between the first line combination arm and each of the two monotherapy arms at Weeks 8 and 12

- to compare the change from baseline in SeSBP between the first line combination arm and each of the two monotherapy arms at Week 12
- to compare the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg between the first line combination arm and each of the two monotherapy arms at Weeks 8 and 12
- to examine the change from baseline in hs-CRP at Week 12

Other objectives were
- to examine the change from baseline in SeSBP and SeDBP at Weeks 2 and 4
- to examine the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg at Weeks 2 and 4
- to examine the change from baseline in hs-CRP at Week 8

9.3.2.2 Inclusion and Exclusion Criteria

Inclusion Criteria (must be present) (Based on Protocol, page 23)
1. Men and women, ages 18 and older, with women of childbearing potential (WOCBP) using an adequate method of contraception to avoid pregnancy throughout the study and for up to one week after the study to minimize the risk of pregnancy
2. Signed written informed consent
3. Subjects willing to discontinue their antihypertensive medication, if applicable
4. Subjects with uncontrolled hypertension defined as:

   Untreated Subjects (an untreated subject is defined as one who has not received antihypertensive medication for at least four weeks prior to enrollment):
   - averaged seated systolic blood pressure (SeSBP) ≥ 160 mm Hg and < 180 mm Hg and averaged seated diastolic blood pressure (SeDBP) < 110 mm Hg

   or
   - averaged SeDBP ≥ 100 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

   Subjects Receiving Antihypertensive Monotherapy (monotherapy is defined as treatment with one antihypertensive medication for at least four weeks; fixed combination therapy does not represent monotherapy)
   - averaged SeSBP ≥150 mm Hg and < 180 mm Hg and averaged SeDBP < 110 mm Hg

   or
   - averaged SeDBP ≥ 95 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

Exclusion Criteria (cannot be present) (Based on Protocol, page 25)

Sex and Reproductive Status

1. WOCBP who were **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for up to one week after the study.
2. Women who were pregnant or breastfeeding
3. Women with a positive pregnancy test on enrollment or prior to study drug administration

Target Disease Exceptions

4. SeSBP ≥ 180 mm Hg or SeDBP ≥ 110 mm Hg and/or evidence of malignant or accelerated hypertension or clinical evidence that the subject required immediate lowering of his/her blood pressure within hours, including, but not limited to coronary ischemia or neurological signs and symptoms
5. Known or suspected secondary hypertension

Medical History and Concurrent Diseases

6. Hypertensive encephalopathy, stroke, or transient ischemic attack within the past 12 months
7. Myocardial infarction, percutaneous transluminal coronary revascularization, coronary artery bypass graft, or unstable angina pectoris within the past six months
8. New York Heart Association functional class III-IV congestive heart failure, or LV dysfunction requiring ACE inhibitor
9. Hemodynamically significant cardiac valvular disease
10. Heart block greater than first degree atrioventricular block, preexcitation syndrome, sick sinus syndrome, chronic atrial fibrillation, or chronic atrial flutter, or other significant arrhythmias that may interfere with the blood pressure measurements
11. Significant chronic renal impairment, or renovascular disease
12. Significant liver disease
13. Systemic lupus erythematosus
14. Gastrointestinal disease or surgery that may interfere with drug absorption
15. Malignancy during the past five years excluding localized squamous cell or basal cell carcinoma of the skin
16. Currently pregnant or lactating
17. Mental condition (psychiatric or organic cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the study, or mental retardation or language barrier such that the subject is unable to give informed consent
18. Drug or alcohol abuse within the last five years
19. Any medical condition that in the judgment of the Investigator would jeopardize the subject's safety or evaluation of the study drug for efficacy and safety

Physical and Laboratory Test Findings

20. Obesity that would limit accurate blood pressure measurement
21. Positive pregnancy test
22. Serum creatinine ≥ 1.5 mg/dL
23. AST, ALT, or total bilirubin ≥ 3 times the upper limit of normal
24. Serum glucose > 240 mg/dL (if high, may be repeated once)
25. Hemoglobin A1c ≥ 10%

26. Serum potassium < 3.3 or > 5.5 mmol/l
27. White blood cell count < 2,600/µl
28. Platelet count < 100,000 µl
29. Hemoglobin < 10 g/dL
30. Any laboratory test value that in the judgment of the Investigator would jeopardize the subject's safety or the study drug's evaluation for efficacy and safety

Allergies and Adverse Drug Reactions

31. Known hypersensitivity to irbesartan, angiotensin receptor blockers (ARB), hydrochlorothiazide (HCTZ), or other thiazide diuretics

Prohibited Therapies and/or Medications (Reproduced from Protocol, page 27)

Concomitant vasoactive drugs, including the following, are not permitted throughout the study:

32. Nitrates
33. Angiotensin converting enzyme (ACE inhibitors), calcium antagonists, diuretics, angiotensin II receptor antagonists
34. Beta-adrenergic blocking agents including eye drops
35. Chronic sympathomimetic drugs including bronchodilators, nasal sprays, and oral decongestants
36. Other bronchodilators
37. Other antihypertensive drugs and arterial vasodilators
38. Oral or intramuscular corticosteroids and anabolic steroids were prohibited. Topical steroids and inhaled corticosteroids were allowed.
39. Potassium supplements
40. Antibiotics other than short (≤ 2 week) courses
41. Protease inhibitors and reverse transcriptase inhibitors
42. Oral contraceptive therapy (must have been initiated at least one month prior to study enrollment. If taking, oral contraception must have been at a stable dose throughout the study)
43. Antacid ingestion within two hours of study treatment
44. Lithium
45. Chronic nonsteroidal anti-inflammatory drugs (NSAIDs) (chronic defined as for seven days or more) with the exception of low-dose aspirin therapy (≤ 325 mg daily) and occasional aspirin or NSAID use in customary doses (not to exceed 7 days and not to be ingested within the 4 days preceding a clinic visit)
46. Psychotropic drug therapy (occasional anxiolytics and stable doses of selective serotonin reuptake inhibitors, except venflaxine, are permitted), anticonvulsant, and antidepressant drugs
47. Herbal medications, food supplements, vitamin or mineral supplements found to have ingredients, which have the potential to effect blood pressure, e.g., ephedra
48. Phosphodiesterase inhibitors for the treatment of erectile dysfunction (sildenafil, tadalafil, and vardenafil) should not be taken in the 24 hours prior to any study visits

Other Exclusion Criteria

49. Potential for non-compliance with the requirements of the protocol or geographic or social factors that made study participation impractical
50. Simultaneous or previous participation (in the 30 days prior to study entry) in a clinical study using an experimental drug or device, or previous participation in this study
51. Prisoners or subjects who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study

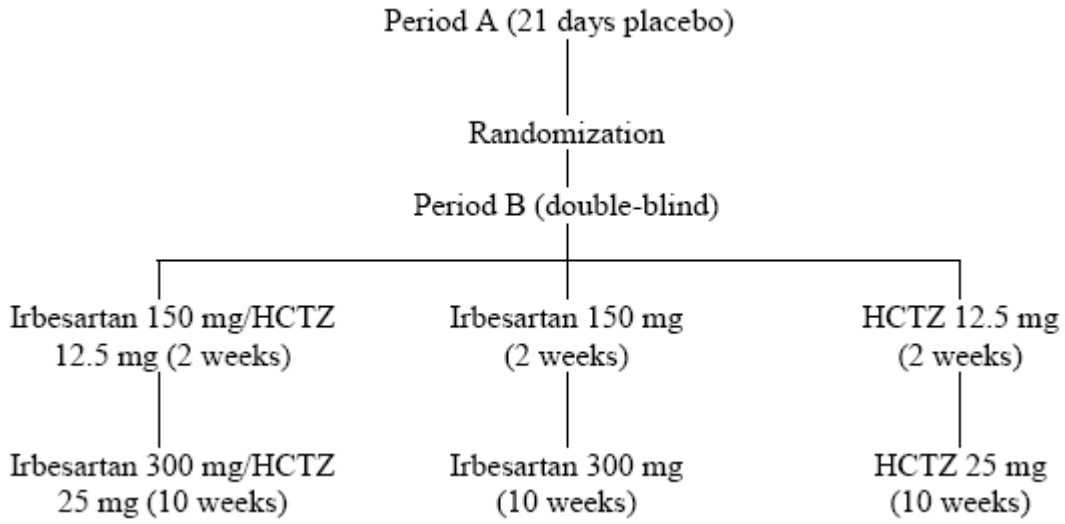
Restricted Therapies

- Chronic NSAIDs (chronic defined as for 7 days or more) with the exception of low-dose aspirin therapy (≤ 325 mg daily) and occasional aspirin or NSAID use in customary does (not to exceed 7 days and not to be ingested within the 4 days preceding a clinic visit
- Antibiotics other than short (≤ 2 week) courses
- Oral contraceptive therapy (must have been initiated at least one month prior to study enrollment. If taking, oral contraception must have been at a stable dose throughout the study)
- Antacid ingestion within 2 hours of study treatment
- Phosphodiesterase inhibitors for the treatment of erectile dysfunction (sildenafil, tadalafil, and vardenafil) were not to be taken in the 24 hours prior to any study visit.
- Herbal medications, food supplements, vitamin or mineral supplements were permitted unless the specific preparation was reviewed by the Investigator and found to have ingredients which had the potential to effect blood pressure, e.g., ephedra

9.3.2.3 Study Plan

Following screening and completion of the informed consent process, investigators or designees telephoned the central randomization system (IVRS) to enroll subjects into the study. The study was comprised of two periods, A and B. Period A was the single-blind placebo lead-in phase, and Period B was the double-blind treatment phase. The duration of Period A was 21 days, and the duration of Period B was 12 weeks. The study schema is displayed in Figure 7.

Figure 7. Study Schema (CV131185)



(Reproduced from Clinical Study Report, Figure 5.1, page 24)

During Period A, subjects who were currently untreated immediately began taking single-blind placebo therapy. Subjects currently receiving antihypertensive therapy were withdrawn in accordance with manufacturer recommendations and were to also immediately begin receiving single-blind placebo therapy.

Following Period A, subjects were randomized if they continued to meet the following blood pressure criteria off of therapy at **Visits A01 and A99**:

- Averaged SeSBP ≥ 160 mm Hg and M 180 mm Hg and averaged SeDBP < 110 mm Hg

or

- Averaged SeDBP ≥ 100 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg

Subjects were randomized in a 3:1:1 ratio to receive either combination therapy (irbesartan plus HCTZ), irbesartan monotherapy, or HCTZ monotherapy for twelve weeks (Period B). The starting dose of the regimens was irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 150 mg, or HCTZ 12.5 mg, respectively.

After two weeks of study treatment, subjects in the combination therapy arm were titrated to irbesartan 300 mg/HCTZ 25 mg, subjects in the irbesartan monotherapy arm were titrated to irbesartan 300 mg, and subjects in the HCTZ monotherapy arm were titrated to HCTZ 25 mg. All subjects were to continue taking their titrated dose for the remaining 10 weeks of the study.

During Periods A and B, study medication was to be taken between 6 am and 11 am. On the morning of all study visits, study medication was withheld so trough blood pressure was measured (24 ± 3 hours following the last dose of study medication). Following randomization, study visits occurred at Weeks 2 (B01), 4 (B02), 8 (B03), and 12 (B99).

The schedule of procedures/events is summarized in Table 38.

Table 38. Flow Chart/Time and Events Schedule (CV131185)

Procedure	Enrollment Visit A00	Qualifying Visit Day 14 A01	Randomization Visit Day 21 A99/B00	Titration Visit Week 2 B01	Week 4 B02	Week 8 B03	End of Treatment Week 12 B99
Eligibility Assessments							
Informed Consent	X						
Telephone IVRS	X		X				X
Inclusion/Exclusion Criteria	X	X	X				
Medical History	X						
Pregnancy Test	X		X			X	X
Efficacy/Safety Assessments							
Physical Examination and ECG	X						X
Blood Pressure/Heart Rate	X	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X	X
Laboratory Tests	X		X	X	X	X	X
Clinical Drug Supplies							
Dispense Study Medication	X		X	X	X	X	
Assessment of Medication Use		X	X	X	X	X	X

(Reproduced from Sponsor, Protocol, page 36. Source: Appendix 5.1A)

9.3.2.4 Discontinuation of Therapy

Subjects were to be discontinued from study therapy AND withdrawn from the study for the following reasons (Based on Protocol, page 31):

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy was not in the best interest of the subject
- Severe hypertension unresponsive to therapy. Severe hypertension is average SeSBP ≥ 180 mm Hg or average SeDBP ≥ 110 mm Hg. The parameter in question (whether SeSBP or SeDBP) should be confirmed above its threshold at two consecutive visits after B00. Both unscheduled and scheduled visits should be considered in this assessment.
  Response to therapy is a decline of at least 10 mm Hg SeSBP from visit B00.
- Clinical signs and symptoms which, in the opinion of the investigator, indicate a need for more aggressive blood pressure treatment than specified in the protocol
- Clinical signs and symptoms of hypotension to a degree which, in the opinion of the investigator, indicate a need for less aggressive blood pressure treatment than specified in the protocol
- Pregnancy
- Termination of the study by Bristol-Myers Squibb

- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

9.3.2.5 Dosage, Duration, and Adjustment of Therapy

The starting dose was irbesartan 150 mg/HCTZ 12.5 mg, irbesartan 150 mg, or HCTZ 12.5 mg.

After two weeks of study treatment, subjects in the combination therapy arm were titrated to irbesartan 300 mg/HCTZ 25 mg, subjects in the irbesartan monotherapy arm were titrated to irbesartan 300 mg, and subjects in the HCTZ monotherapy arm were titrated to HCTZ 25 mg for an additional 10 weeks.

9.3.2.6 Efficacy Endpoints

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

The secondary outcome measures 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 after 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 mm Hg and SeDBP < 90 mm Hg at Weeks 8 and 12
- the change from baseline in hs-CRP at Week 12

Other efficacy measurements were

- the change from baseline in SeSBP and SeDBP at Weeks 2 and 4
- the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg at Weeks 2 and 4, and
- the change from baseline in hs-CRP at Week 8

9.3.2.7 Statistical Considerations

No interim analyses were performed. The primary analysis included all randomized subjects (intention-to-treat) and used a one-way analysis of covariance, with the baseline blood pressure value as the covariate. A sample size of 298 subjects in the irbesartan/HCTZ group and 99 subjects in both irbesartan and HCTZ monotherapy groups would provide 90% power at a 1-sided significance level of 0.025 to detect a 6.0 mm Hg difference between combination and monotherapy groups in SeSBP changes from baseline at Week 8, assuming a 14 mm Hg standard deviation for the change in SeSBP and a 5% dropout rate. Additionally, this sample size would provide 90% power to detect a 3.2 mm Hg overall difference between the combination and monotherapy treatment groups in change from baseline in SeDBP at Week 8, assuming a 7.5 mm Hg standard deviation for the change in SeDBP.

9.3.3 Results

9.3.3.1 Sites, Investigators, and Study Dates

The study was conducted from October 7, 2004 through June 30, 2005. There were 135 investigators at a total of 135 sites, including 93 sites in the United States, 23 sites in Canada, 9 sites in Germany, and 10 sites in France.

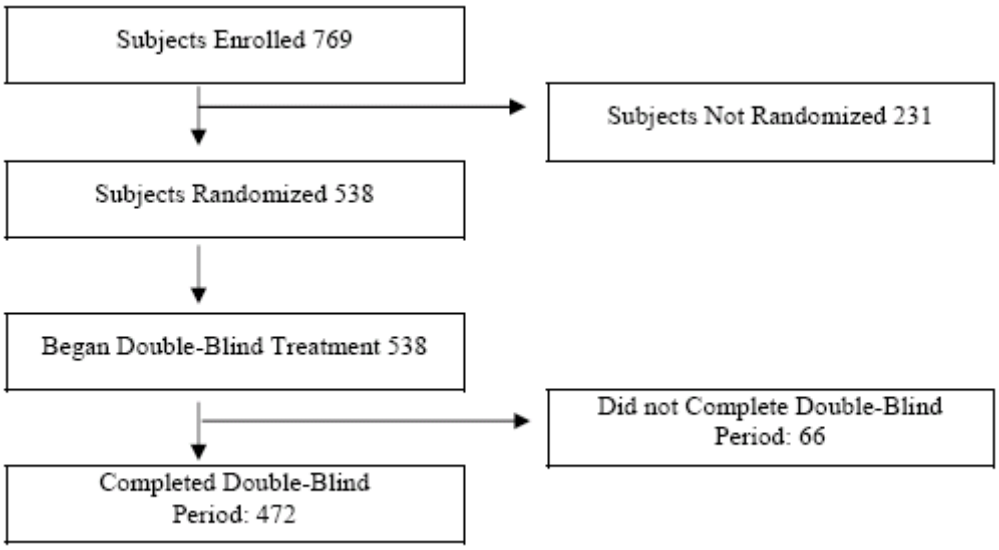
9.3.3.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the current Declaration of Helsinki.

9.3.3.3 Disposition of Subjects

A total of 769 subjects were enrolled into the placebo lead-in phase and 538 subjects were randomized into double-blind therapy (Period B), including 328 subjects in the irbesartan/HCTZ treatment group, 106 subjects in the irbesartan monotherapy treatment group, and 104 subjects in the HCTZ monotherapy treatment group. A total of 472 subjects completed the study, including 287 in the irbesartan/HCTZ treatment group, 94 subjects in the irbesartan monotherapy treatment group, and 91 subjects in the HCTZ monotherapy treatment group. Subject disposition is displayed graphically in Figure 8. Table 39 summarizes the subjects discontinued during Period B and the reasons for discontinuation.

Figure 8. Subject Disposition (CV131185)



(Reproduced from Sponsor, Clinical Study Report, Figure 8.1, page 56)

Table 39. Summary of Subjects Discontinued during Period B and Reason for Discontinuation (CV131185)

	Irb/HCTZ n, (%)	Irbesartan n (%)	HCTZ n (%)	Total n (%)
Total Number of Subjects Randomized	**328 (100.0)**	**106 (100.0)**	**104 (100.0)**	**538 (100.0)**
Number of Subjects Treated	**328 (100.0)**	**106 (100.0)**	**104 (100.0)**	**538 (100.0)**
Number of Subjects Discontinued from the Study	41 (12.5)	12 (11.3)	13 (12.5)	66 (12.3)
Adverse event	22 (6.7)	4 (3.8)	5 (4.8)	31 (5.8)
Subject withdrew consent	4 (1.2)	1 (0.9)	2 (1.9)	7 (1.3)
Lost to follow-up	7 (2.1)	2 (1.9)	3 (2.9)	12 (2.2)
Subject no longer meets study criteria	4 (1.2)	3 (2.8)	1 (1.0)	8 (1.5)
Lack of efficacy	1 (0.3)	1 (0.9)	1 (1.0)	3 (0.6)
Poor/non-compliance	1 (0.3)	0	1 (1.0)	2 (0.4)
Other	2 (0.6)	1 (0.9)	0	3 (0.6)
Number of Subjects Completing	**287 (87.5)**	**94 (88.7)**	**91 (87.5)**	**472 (87.7)**
Randomized Subjects **Source: Appendix 8.1.2** **Reproduced from Sponsor, Clinical Study Report, CV131185, Table 8.1, page 57.**				

9.3.3.4 Demographics and Baseline Characteristics

Baseline demographic characteristics are displayed in Table 40. Treatment groups were balanced with respect to baseline characteristics, except there was a higher percentage of Blacks and females randomized to the irbesartan monotherapy treatment group. The elderly (age ≥ 65 years) were underrepresented in all treatment groups.

Table 40. Baseline Demographic Characteristics (CV131185)

Characteristic	Irb/HCTZ (N = 328)	Irbesartan (N = 106)	HCTZ (N = 104)	Total
Age (years)				
N	328	106	104	538
Mean (SD)	55.1 (11.3)	55.3 (10.8)	56.0 (12.7)	55.3 (11.5)
Range	24.0 – 87.0	25.0 – 87.0	21.0 – 83.0	21.0 – 87.0
Age Group				
< 40 years	27 (8.2%)	7 (6.6%)	9 (8.7%)	43 (8.0%)
40-54 years	137 (41.8%)	50 (47.2%)	31 (29.8%)	218 (40.5%)
55-64 years	96 (29.3%)	30 (28.3%)	41 (39.4%)	167 (31.0%)
65-74 years	52 (15.9%)	13 (12.3%)	16 (15.4%)	81 (15.1%)
≥ 75 years	16 (4.9%)	6 (5.7%)	7 (6.7%)	29 (5.4%)
Gender				
Male	181 (55.2%)	49 (46.2%)	62 (59.6%)	292 (54.3%)
Female	147 (44.8%)	57 (53.8%)	42 (40.4%)	246 (45.7%)

Characteristic	Irb/HCTZ (N = 328)	Irbesartan (N = 106)	HCTZ (N = 104)	Total
Race				
White	271 (86.2%)	95 (89.6%)	86 (82.7%)	452 (84.0%)
Black/African American	50 (15.2%)	9 (8.5%)	15 (14.4%)	74 (13.8%)
American Indian/Alaska Native	0	1 (0.9%)	1 (1.0%)	2 (0.4%)
Asian	6 (1.8%)	0	2 (1.9%)	8 (1.5%)
Native Hawaiian/Other Pacific Islander	1 (0.3%)	0	0	1 (0.2%)
Other	0	1 (0.9%)	0	1 (0.2%)
Weight (kg)				
N	327	106	104	537
Mean (SD)	87.6 (19.1)	88.2 (20.7)	88.4 (18.3)	87.9 (19.2)
Range	46.0 – 152.0	47.0 – 146.1	55.0 – 146.1	46.0 – 152.0
Hypertension Duration (years)				
N	327	105	104	536
Mean (SD)	6.6 (6.9)	6.2 (7.3)	7.4 (7.9)	6.7 (7.2)
Range	0.0 – 45.1	0.0 – 40.0	0.0 – 35.8	0.0 – 45.1
Region				
North America	247 (75.3%)	78 (73.6%)	79 (76.0%)	404 (75.1%)
Western Europe	81 (24.7%)	28 (26.4%)	25 (24.0%)	134 (24.9%)
Reproduced from Sponsor, Clinical Study Report, Table 8.3A, page 59.				

Baseline efficacy measures are displayed in Table 41. Mean seated diastolic blood pressure, systolic blood pressure, and heart rate were balanced between treatment groups.

Table 41. Baseline Efficacy Measures (CV131185)

Characteristic	Irb/HCTZ (N = 328)	Irbesartan (N = 106)	HCTZ (N = 104)	Total (N = 538)
SeSBP (mm Hg)				
N	328	106	104	538
Mean (SD)	161.7 (12.1)	161.4 (10.0)	162.0 (10.6)	161.7 (11.4)
Range	127.7 – 203.3	135.7 – 178.0	136.0 – 180.0	127.7 – 203.3
< 140 mm Hg	20 (6.1%)	1 (0.9%)	4 (3.8%)	25 (4.6%)
140 - < 160 mm Hg	90 (27.4%)	31 (29.2%)	32 (30.8%)	153 (28.4%)
160 - < 180 mm Hg	215 (65.5%)	74 (69.8%)	67 (64.4%)	356 (66.2%)
≥ 180 mm Hg	3 (0.9%)	0	1 (1.0%)	4 (0.7%)
SeDBP (mm Hg)				
N	328	106	104	538
Mean (SD)	97.5 (8.3)	97.9 (7.6)	97.6 (7.5)	97.6 (8.0)
Range	66.0 – 114.7	74.3 – 109.3	74.7 – 110.7	66.0 – 114.7
< 90 mm Hg	58 (17.7%)	16 (15.1%)	15 (14.4%)	89 (16.5%)
90 - < 100 mm Hg	90 (27.4%)	30 (28.3%)	34 (32.7%)	154 (28.6%)
100 - < 110 mm Hg	177 (54.0%)	60 (56.6%)	54 (51.9%)	291 (54.1%)
≥ 110 mm Hg	3 (0.9%)	0	1 (1.0%)	4 (0.7%)

Characteristic	Irb/HCTZ (N = 328)	Irbesartan (N = 106)	HCTZ (N = 104)	Total (N = 538)
SeHR (beats/min)				
N	328	106	104	538
Mean (SD)	75.5 (10.4)	75.3 (10.5)	76.6 (12.4)	75.7 (10.8)
Range	48.0 – 110.0	52.0 – 100.0	50.0 – 108.0	48.0 – 110.0
hs-CRP				
N	285	91	91	467
Geometric Mean (SE)	3.1 (0.2)	2.9 (0.3)	2.8 (0.3)	3.0 (0.1)
Median	3.2	2.9	3.3	3.2
Range	0.1 – 57.8	0.2 – 150.0	0.3 – 113.0	0.1 – 150.0
Note: Natural logarithm of hs-CRP is used and then transformed back to raw scale. **Randomized Subjects** **Reproduced from Sponsor, Clinical Study Report, Table 8.3B, page 60.**				

The number (percent) of randomized subjects with specific cardiovascular histories is shown in Table 42. Hypertension (99.6%), hyperlipidemia (42.4%), and diabetes mellitus (13.8%) were the most commonly reported cardiovascular conditions.

Table 42. Number (Percent) of Randomized Subjects with Specific CV Histories (CV131185)

	Irb/HCTZ (N = 328) n (%)	Irbesartan (N = 106) n (%)	HCTZ (N = 104) n (%)	Total (N = 538) n (%)
Number of Subjects with CV Specific Medical History	**327 (99.7)**	**106 (100.0)**	**104 (100.0)**	**537 (99.8)**
Hypertension	327 (99.7)	105 (99.1)	104 (100.0)	536 (99.6)
Hyperlipidemia	146 (44.5)	45 (42.5)	37 (35.6)	228 (42.4)
Diabetes Mellitus	47 (14.3)	14 (13.2)	13 (12.5)	74 (13.8)
Stable Angina Pectoris	6 (1.8)	2 (1.9)	1 (1.0)	9 (1.7)
Stroke or TIA	6 (1.8)	0	1 (1.0)	7 (1.3)
Myocardial Infarction	5 (1.5)	1 (0.9)	2 (1.9)	8 (1.5)
PCI or CABG	4 (1.2)	2 (1.9)	0	6 (1.1)
Atrial Fibrillation	1 (0.3)	1 (0.9)	0	2 (0.4)
Permanent Pacemaker Implantation	1 (0.3)	0	0	1 (0.2)
Valvular Disease	1 (0.3)	0	1 (1.0)	2 (0.4)
Reproduced from Sponsor, Clinical Study Report, Table 8.4, page 62)				

Approximately 52.4%, 49.1%, and 45.2% of subjects in the irbesartan/HCTZ, irbesartan, and HCTZ groups, respectively, had received previous hypertensive therapy.

9.3.3.5 Compliance

One subject in the irbesartan/HCTZ group and one subject in the HCTZ group were discontinued from the study for lack of compliance.

9.3.3.6 Extent of Exposure

The mean duration of exposure was approximately 78 days for the 3 treatment groups. Approximately 85% of subjects in each of the three treatment groups were exposed for 61 to 90 days during the study.

Table 43. Extent of Exposure to Double-Blind Study Drug by Treatment Group (CV131185)

Days	Irb/HCTZ n (%)	Irbesartan n (%)	HCTZ n (%)
1 - 7	3 (0.9%)	2 (1.9%)	3 (2.9%)
8 - 14	6 (1.8%)	2 (1.9%)	0
15 - 30	12 (3.7%)	5 (4.7%)	4 (3.8%)
31 - 60	13 (4.0%)	2 (1.9%)	5 (4.8%)
61 - 90	279 (85.1%)	90 (84.9%)	88 (84.6%)
91 – 180	15 (4.6%)	5 (4.7%)	4 (3.8%)
Total	328	106	104
Mean Duration of Exposure (Days)	78.6	78.1	77.7
Reproduced from Sponsor, Clinical Study Report, Table 9.1, page 65.			

9.3.3.7 Concomitant Therapy

A total of 384 subjects (71.4%) across the 3 treatment groups received a total of 1189 concomitant medications during the double-blind period. The most commonly taken classes of medications during the double-blind period included vitamin/mineral supplements, acetylsalicylic acid, acetaminophen, ibuprofen, thyroid therapy, serum lipid-reducing agents, and histamine H_2 antagonists. A total of 13 (3.96%), 2 (1.9%), and 1 (0.96%) subject(s) in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively, received concomitant antihypertensive medications and/or nitrates during the double-blind period.

Table 44. Sponsor's Analysis: Most Frequently Used Concomitant Medications During Double-Blind Treatment (CV131185)

Medication	Irb/HCTZ (N = 328) n (%)	Irbesartan (N = 106) n (%)	HCTZ (N = 104) n (%)	Total (N = 538) n (%)
Acetylsalicylic acid (ASA)	48 (14.6)	12 (11.3)	19 (18.3)	79 (14.7)
Atorvastatin	30 (9.1)	10 (9.4)	8 (7.7)	48 (8.9)
Acetaminophen (APAP)	26 (7.9)	12 (11.3)	6 (5.8)	44 (8.2)
Ibuprofen	20 (6.1)	5 (4.7)	9 (8.7)	34 (6.3)
Levothyroxine	19 (5.8)	8 (7.5)	4 (3.8)	31 (5.8)
Metformin	19 (5.8)	3 (2.8)	2 (1.9)	24 (4.5)
Simvastatin	13 (4.0)	3 (2.8)	7 (6.7)	23 (4.3)
Reproduced from Sponsor, Clinical Study Report, Table 9.5, page 67.				

9.3.3.8 Primary Efficacy Endpoint

The primary efficacy outcome measure was the change from baseline in SeSBP at Week 8. Mean decreases in SeSBP at Week 8 were 27.1 mm Hg, 22.1 mm Hg, and 15.7 mm Hg in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively (mean difference of 5 mm Hg against irbesartan, p = 0.0016 and 11.3 mm Hg against HCTZ, p < 0.0001). The primary efficacy outcome measure results are presented in Table 45.

Table 45. Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP and SeDBP to Week 8 of Period B: Randomized Subjects (CV131185)

	Irb/HCTZ N = 328	**Irbesartan N = 106**	**HCTZ N = 104**
SeSBP			
n	303	95	95
Baseline Mean (SD)	161.8 (12.30)	161.5 (10.29)	161.6 (10.75)
On-Therapy Mean (SD)	134.7 (15.06)	139.5 (14.25)	145.9 (13.61)
Adjusted Mean Change from Baseline (SE)	-27.1 (0.76)	-22.1 (1.36)	-15.7 (1.36)
Estimated Difference between Combo and mono Group*		-5.0	-11.3
95% CI for Estimated Difference		(-8.0, -1.9)	(-14.4, -8.3)
P-value for Combo and Mono Group Comparison**		0.0016	< 0.0001
SeDBP			
n	303	95	95
Baseline Mean (SD)	97.6 (8.13)	98.0 (7.10)	97.4 (7.65)
On-Therapy Mean (SD)	83.0 (8.95)	86.2 (8.80)	90.2 (8.91)
Adjusted Mean Change from Baseline (SE)	-14.6 (0.45)	-11.6 (0.81)	-7.3 (0.81)
Estimated Difference between Combo and mono Group*		-3.0	-7.4
95% CI for Estimated Difference		(-4.8, -1.2)	(-9.2, -5.5)
P-value for Combo and Mono Group Comparison**		0.0013	< 0.0001

Reference: Supplemental Tables S.10.1A
Randomized Subjects
***Difference = Combo Group – Mono Group**
****p-value of two-sided tests**
Note: N = number of subjects randomized into Period B; n = number of subjects with available efficacy data at Week 8
Source: Appendix 6.0, Appendix 10A
Reproduced from Sponsor, Clinical Study Report, Table 10.1.1, page 69
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

For trough SeDBP, the mean decreases from baseline at Week 8 were 14.6 mm Hg, 11.6 mm Hg, and 7.3 mm Hg for the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy groups, respectively.

Since over 10% of the subjects included in the primary analysis had protocol violations in the irbesartan/HCTZ and HCTZ treatment groups, the sponsor also performed a sensitivity analysis at Week 8 using the per protocol population. The per protocol results were similar to the primary analysis results. For trough SeSBP, irbesartan/HCTZ lowered blood pressure 4.8 mm Hg more than irbesartan monotherapy ($p = 0.0044$) and 10.8 mm Hg more than HCTZ monotherapy ($p < 0.0001$). For SeDBP, irbesartan/HCTZ lowered blood pressure 2.7 mm Hg more than irbesartan monotherapy ($p = 0.0051$) and 7.2 mm Hg more than HCTZ monotherapy ($p < 0.0001$).

Since over 10% of the data in both monotherapy arms at Week 8 were not available, the sponsor performed a last observation carried forward (LOCF) analysis which was consistent with the primary analysis results. At week 8, irbesartan/HCTZ lowered blood pressure 5.6 mm Hg more than irbesartan monotherapy ($p = 0.0003$) and 11.0 mm Hg more than HCTZ monotherapy ($p < 0.0001$).

9.3.3.9 Secondary Efficacy Endpoints/Other Efficacy Endpoints

Secondary efficacy outcome measures were

- 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 mm Hg and SeDBP < 90 mm Hg at Weeks 8 and 12
- the change from baseline in hs-CRP at Week 12

Other efficacy outcome measures were

- the change from baseline in SeSBP and SeDBP at Weeks 2 and 4
- the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg at Weeks 2 and 4
- the change from baseline in hs-CRP at Week 8

Time Courses of Mean Changes from Baseline at Weeks 2, 4, 8, and 12: Trough SeSBP

The sponsor did not adjust for multiple comparisons in the statistical analysis plan. Nevertheless, the mean changes from baseline at Weeks 2, 4, 8, and 12 were highly significant and supported the efficacy of irbesartan/HCTZ in treating patients with moderate hypertension. The mean changes from baseline in trough SeSBP by week are displayed in Table 46. At 2, 4, 8, and 12 weeks, irbesartan/HCTZ reduced mean changes from baseline in trough SeSBP more than the irbesartan and HCTZ monotherapy groups.

Table 46. Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP By Week (CV131185)

Week		Trough SeSBP		
		Irb/HCTZ N = 328	Irbesartan N = 106	HCTZ N = 104
2	**n**	**316**	**102**	**103**
	Baseline Mean (SD)	161.8 (12.22)	161.4 (10.16)	161.9 (10.68)
	On-Therapy Mean (SD)	143.9 (14.85)	147.6 (14.55)	151.7 (14.16)
	Adjusted Mean Change from Baseline (SE)	-17.9 (0.69)	-13.9 (1.22)	-10.2 (1.22)
	Est. Difference between Combo and Mono Group*		-4.0	-7.7
	95 % CI for Estimated Difference		(-6.8, -1.3)	(-10.5, -5.0)
	P-value for Combo and Mono Group Comparison**		0.0044	< 0.0001
4	**n**	**316**	**100**	**100**
	Baseline Mean (SD)	161.7 (12.17)	161.5 (10.23)	161.7 (10.70)
	On-Therapy Mean (SD)	136.9 (14.91)	143.7 (14.88)	147.8 (11.95)
	Adjusted Mean Change from Baseline (SE)	-24.8 (0.71)	-17.8 (1.26)	-13.9 (1.26)
	Est. Difference between Combo and Mono Group*		-7.0	-10.9
	95 % CI for Estimated Difference		(-9.8, -4.1)	(-13.8, -8.1)
	P-value for Combo and Mono Group Comparison**		< 0.0001	< 0.0001
8	**n**	**303**	**95**	**95**
	Baseline Mean (SD)	161.8 (12.30)	161.5 (10.29)	161.6 (10.75)
	On-Therapy Mean (SD)	134.7 (15.06)	139.5 (14.25)	145.9 (13.61)
	Adjusted Mean Change from Baseline (SE)	-27.1 (0.76)	-22.1 (1.36)	-15.7 (1.36)
	Est. Difference between Combo and Mono Group*		-5.0	-11.3
	95 % CI for Estimated Difference		(-8.0, -1.9)	(-14.4, -8.3)
	P-value for Combo and Mono Group Comparison**		0.0016	< 0.0001
12	**n**	**291**	**94**	**91**
	Baseline Mean (SD)	161.7 (12.23)	161.5 (10.34)	161.3 (10.83)
	On-Therapy Mean (SD)	133.3 (13.77)	142.0 (15.59)	144.9 (13.08)
	Adjusted Mean Change from Baseline (SE)	-28.3 (0.73)	-19.5 (1.29)	-16.5 1.31)
	Est. Difference between Combo and Mono Group*		-8.7	-11.8
	95 % CI for Estimated Difference		(-11.7, -5.8)	(-14.7, -8.8)
	P-value for Combo and Mono Group Comparison**		< 0.0001	<0.0001

Reference: Supplemental Tables S.10.1A, S.10.1E
Randomized Subjects
***Difference = Combo Group – Mono Group**
****p-value of two-sided tests**
Note: N = number of subjects randomized into Period B; n = number of subjects with available efficacy during Period B.
Source: Appendix 10A, 6.0
Reproduced from Sponsor, Clinical Study Report, Table 10.1.2A, pages 71-72
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

The mean changes in trough SeDBP by week are displayed in Table 47. At 2, 4, 8, and 12 weeks, irbesartan/HCTZ reduced mean changes from baseline in trough SeDBP greater than the irbesartan and HCTZ monotherapy treatment groups.

Table 47. Sponsor's Analysis: Mean Changes in Trough SeDBP By Week (CV131185)

Week		Trough SeDBP		
		Irb/HCTZ N = 328	Irbesartan N = 106	HCTZ N = 104
2	**n**	**316**	**102**	**103**
	Baseline Mean (SD)	97.4 (8.39)	97.6 (7.60)	97.6 (7.53)
	On-Therapy Mean (SD)	88.1 (8.91)	90.3 (8.78)	92.1 (9.03)
	Adjusted Mean Change from Baseline (SE)	-9.3 (0.41)	-7.3 (0.72)	-5.5 (0.72)
	Est. Difference between Combo and Mono Group*		-2.0	-3.8
	95 % CI for Estimated Difference		(-3.7, -0.4)	(-5.4, -2.2)
	P-value for Combo and Mono Group Comparison**		0.0147	< 0.0001
4	**n**	**316**	**100**	**100**
	Baseline Mean (SD)	97.4 (8.13)	98.0 (7.49)	97.6 (7.54)
	On-Therapy Mean (SD)	84.5 (9.11)	88.0 (8.60)	90.2 (8.60)
	Adjusted Mean Change from Baseline (SE)	-13.0 (0.43)	-9.8 (0.77)	-7.4 (0.77)
	Est. Difference between Combo and Mono Group*		-3.1	-5.6
	95 % CI for Estimated Difference		(-4.8, -1.4)	(-7.3, -3.8)
	P-value for Combo and Mono Group Comparison**		0.0005	< 0.0001
8	**n**	**303**	**95**	**95**
	Baseline Mean (SD)	97.6 (8.31)	98.0 (7.10)	97.4 (7.65)
	On-Therapy Mean (SD)	83.0 (8.95)	86.2 (8.80)	90.2 (8.91)
	Adjusted Mean Change from Baseline (SE)	-14.6 (0.45)	-11.6 (0.81)	-7.3 (0.81)
	Est. Difference between Combo and Mono Group*		-3.0	-7.4
	95 % CI for Estimated Difference		(-4.8, -1.2)	(-9.2, -5.5)
	P-value for Combo and Mono Group Comparison**		0.0013	< 0.0001
12	**n**	**291**	**94**	**91**
	Baseline Mean (SD)	97.5 (8.19)	97.9 (7.12)	97.4 (7.80)
	On-Therapy Mean (SD)	82.3 (9.24)	86.6 (9.00)	89.7 (8.88)
	Adjusted Mean Change from Baseline (SE)	-15.2 (0.48)	-11.1 (0.84)	-7.8 (0.85)
	Est. Difference between Combo and Mono Group*		-4.1	-7.4
	95 % CI for Estimated Difference		(-6.0, -2.2)	(-9.3, -5.5)
	P-value for Combo and Mono Group Comparison**		< 0.0001	< 0.0001

Reference: Supplemental Tables S.10.1A, S.10.1E
Randomized Subjects
***Difference = Combo Group – Mono Group**
****p-value of two-sided tests**
Note: N = number of subjects randomized into Period B; n = number of subjects with available efficacy during Period B.
Source: Appendix 10A, 6.0
Reproduced from Sponsor, Clinical Study Report, Table 10.1.2B, pages 73-74
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Proportion of Subjects with Controlled SeSBP and SeDBP

The proportion of subjects achieving SeSBP < 140 mm Hg and SeDBP < 90 mm Hg at Weeks 2, 4, 8, and 12 is displayed in Table 48. Note that by Week 2, 21% and 14% of the subjects in the irbesartan monotherapy and HCTZ monotherapy treatment groups, respectively, had achieved trough SeDBP < 90 mm Hg and trough SeSBP < 140 mm Hg. By Week 8, 41% and 20% of the

subjects in the irbesartan monotherapy and HCTZ monotherapy treatment groups, respectively, had achieved a "controlled" SeSBP and SeDBP. If futility is defined as the achievement of goal blood pressure in ≤ 10% of subjects in a particular treatment group only, neither irbesartan monotherapy nor HCTZ monotherapy treatment groups satisfy this definition.

Table 48. Sponsor's Analysis: Proportion of Subjects Controlled By Week (CV131185)

Week		Trough SeDBP < 90 mm Hg and Trough SeSBP < 140 mm Hg		
		Irb/HCTZ N = 328	**Irbesartan N = 106**	**HCTZ N = 104**
2	**n (observed cases)**	**316**	**102**	**103**
	n (with data imputed)	328	106	104
	Proportion Controlled (No. of Responders)	0.265 (87)	0.208 (22)	0.144 (15)
	Est. Difference between Combo and Mono Group		0.058	0.121
	95 % CI for Estimated Difference		(-0.039, 0.155)	(0.032, 0.210)
	P-value for Combo and Mono Group Comparison		0.2492	0.0116
4	**n (observed cases)**	**316**	**100**	**100**
	n (with data imputed)	328	106	104
	Proportion Controlled (No. of Responders)	0.445 (146)	0.292 (31)	0.173 (18)
	Est. Difference between Combo and Mono Group		0.153	0.272
	95 % CI for Estimated Difference		(0.044, 0.261)	(0.175, 0.369)
	P-value for Combo and Mono Group Comparison		0.0062	< 0.0001
8	**n (observed cases)**	**303**	**95**	**95**
	n (with data imputed)	328	106	104
	Proportion Controlled (No. of Responders)	0.534 (175)	0.406 (43)	0.202 (21)
	Est. Difference between Combo and Mono Group		0.128	0.332
	95 % CI for Estimated Difference		(0.014, 0.242)	(0.231, 0.432)
	P-value for Combo and Mono Group Comparison		0.0254	< 0.0001
12	**n (observed cases)**	**291**	**94**	**91**
	n (with data imputed)	328	106	104
	Proportion Controlled (No. of Responders)	0.558 (183)	0.340 (36)	0.250 (26)
	Est. Difference between Combo and Mono Group		0.218	0.308
	95 % CI for Estimated Difference		(0.107, 0.330)	(0.203, 0.413)
	P-value for Combo and Mono Group Comparison		0.0001	< 0.0001

Reference: Supplemental Tables S.10.2A
Randomized Subjects
Note: N = number of subjects randomized into Period B; n = number of subjects with available efficacy during Period B. Number of subjects with imputed responses (not controlled) also shown.
Source: Appendix 10A, 6.0.
Reproduced from Sponsor, Clinical Study Report, Table 10.2, pages 77-78.

Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Mean Changes from Baseline in Trough hs-CRP to Week 8 and Week 12
According to the sponsor's analysis, at Week 12, the irbesartan/HCTZ treatment group had a significant increase in trough hs-CRP, compared with the irbesartan monotherapy group ($p = 0.0036$).

Heart Rate and Standing Blood Pressure
Across the 3 treatment groups, there were no substantial changes from baseline in seated and standing heart rate. Changes from baseline in standing systolic and diastolic blood pressure were similar to what was seen with the corresponding seated measures.

9.3.3.10 Subgroup Analyses (age, gender, race, geographic region)

Summary statistics for change from baseline in trough blood pressure at Week 8 by age, gender, race, and geographic region are presented in Table 49. Combination therapy with irbesartan/HCTZ was most effective in all subgroups. The HCTZ component of the irbesartan/HCTZ combination therapy had a marked effect on seated diastolic and systolic blood pressure in Blacks.

9.3.4 Summary (CV131185)

In patients with moderate hypertension, irbesartan/HCTZ (150mg/12.5 mg titrated to 300/25 mg at two weeks) significantly reduced seated systolic blood pressure from baseline at Week 8, compared with irbesartan monotherapy (150 mg titrated to 300 mg) and HCTZ monotherapy (12.5 mg titrated to 25 mg). The HCTZ component of the irbesartan/HCTZ combination was especially important in Blacks/African Americans for the reduction of seated systolic and diastolic blood pressure from baseline. Study CV131185 also demonstrated the efficacy of irbesartan monotherapy. At Week 8, the proportion of subjects with simultaneous systolic and diastolic blood pressure control was 53%, 41%, and 20% in the irbesartan/HCTZ, irbesartan monotherapy, and HCTZ monotherapy treatment groups, respectively.

Table 49. Summary Statistics for Change from Baseline in Trough BP at Week 8 by Subgroup (CV131185)

Group	Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period B On-Therapy Mean (SD)	Change from Baseline			
						Mean	(SD)	95% Confidence Interval	
								Lower	Upper
Age < 65 years	**SeSBP**	**Irb/HCTZ**	240	160.0 (12.46)	132.8 (14.73)	-27.2	(14.32)	-29.0	-25.3
	SeSBP	**Irbesartan**	78	159.6 (10.16)	138.7 (14.03)	-20.9	(13.41)	-23.9	-17.9
	SeSBP	**HCTZ**	74	161.2 (11.03)	145.1 (13.76)	-16.1	(14.90)	-19.6	-12.7
	SeDBP	**Irb/HCTZ**	240	99.0 (7.35)	84.0 (9.01)	-14.9	(8.97)	-16.1	-13.8
	SeDBP	**Irbesartan**	78	99.0 (6.51)	87.1 (8.60)	-11.9	(9.28)	-14.0	-9.8
	SeDBP	**HCTZ**	74	98.9 (6.95)	91.8 (8.80)	-7.1	(7.31)	-8.8	-5.4
Age ≥ 65 years	**SeSBP**	**Irb/HCTZ**	63	168.7 (8.80)	141.8 (14.24)	-26.9	(14.32)	-30.5	-23.3
	SeSBP	**Irbesartan**	17	169.8 (5.82)	142.9 (15.16)	-27.0	(15.53)	-35.0	-19.0
	SeSBP	**HCTZ**	21	162.8 (9.86)	148.7 (13.01)	-14.1	(15.15)	-21.0	-7.2
	SeDBP	**Irb/HCTZ**	63	92.1 (8.72)	78.8 (7.38)	-13.3	(8.28)	-15.4	-11.2
	SeDBP	**Irbesartan**	17	93.0 (7.75)	81.8 (8.65)	-11.2	(9.33)	-16.0	-6.4
	SeDBP	**HCTZ**	21	91.9 (7.64)	84.5 (6.82)	-7.4	(7.41)	-10.8	-4.0
Gender: Male	**SeSBP**	**Irb/HCTZ**	169	161.6 (12.95)	136.6 (14.48)	-25.0	(13.82)	-27.1	-22.9
	SeSBP	**Irbesartan**	42	162.9 (10.06)	143.8 (14.29)	-19.1	(14.26)	-23.6	-14.7
	SeSBP	**HCTZ**	58	160.2 (11.49)	147.0 (13.42)	-13.2	(15.24)	-17.2	-9.2
	SeDBP	**Irb/HCTZ**	169	99.2 (7.17)	84.3 (9.13)	-14.9	(8.55)	-16.2	-13.6
	SeDBP	**Irbesartan**	42	98.2 (7.48)	86.8 (9.96)	-11.4	(9.53)	-14.3	-8.4
	SeDBP	**HCTZ**	58	98.5 (7.19)	91.0 (8.51)	-7.5	(8.12)	-9.6	-5.4
Gender: Female	**SeSBP**	**Irb/HCTZ**	134	162.0 (11.47)	132.3 (15.47)	-29.8	(14.50)	-32.2	-27.3
	SeSBP	**Irbesartan**	53	160.3 (10.41)	136.0 (13.37)	-24.2	(13.35)	-27.9	-20.6
	SeSBP	**HCTZ**	37	163.8 (9.20)	144.3 (13.93)	-19.5	(13.67)	-24.1	-15.0
	SeDBP	**Irb/HCTZ**	134	95.5 (8.79)	81.2 (8.42)	-14.3	(9.22)	-15.9	-12.7
	SeDBP	**Irbesartan**	53	97.8 (6.84)	85.6 (7.81)	-12.1	(9.09)	-14.6	-9.6
	SeDBP	**HCTZ**	37	95.6 (8.08)	89.0 (9.48)	-6.6	(5.85)	-8.6	-4.7

Group	Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period B On-Therapy Mean (SD)	Change from Baseline			
						Mean	(SD)	95% Confidence Interval	
								Lower	Upper
Race: White	**SeSBP**	**Irb/HCTZ**	254	162.9 (11.77)	134.8 (14.78)	-28.1	(14.37)	-29.8	-26.3
	SeSBP	**Irbesartan**	86	161.4 (10.13)	138.7 (14.41)	-22.7	(14.05)	-25.8	-19.7
	SeSBP	**HCTZ**	80	161.5 (10.38)	144.6 (13.59)	-16.9	(14.39)	-20.1	-13.7
	SeDBP	**Irb/HCTZ**	254	97.1 (8.25)	82.4 (8.82)	-14.7	(8.65)	-15.7	-13.6
	SeDBP	**Irbesartan**	86	97.8 (7.25)	85.4 (8.67)	-12.4	(9.26)	-14.4	-10.4
	SeDBP	**HCTZ**	80	97.5 (7.76)	89.6 (8.65)	-7.9	(7.12)	-9.5	-6.4
Race: Black/African American	**SeSBP**	**Irb/HCTZ**	46	155.8 (13.28)	134.1 (16.95)	-21.7	(13.06)	-25.5	-17.8
	SeSBP	**Irbesartan**	7	160.7 (14.16)	148.3 (11.21)	-12.4	(10.68)	-22.3	-2.5
	SeSBP	**HCTZ**	12	162.3 (13.59)	156.4 (9.67)	-5.8	(16.43)	-16.2	4.6
	SeDBP	**Irb/HCTZ**	46	100.1 (7.11)	86.2 (9.27)	-13.9	(9.98)	-16.8	-10.9
	SeDBP	**Irbesartan**	7	101.3 (3.60)	94.8 (6.99)	-6.5	(7.79)	-13.7	0.7
	SeDBP	**HCTZ**	12	98.0 (5.63)	96.3 (7.53)	-1.7	(7.21)	-6.3	2.9
Race: Other	**SeSBP**	**Irb/HCTZ**	3	165.1 (19.00)	135.0 (10.21)	-30.1	(9.56)	-53.9	-6.4
	SeSBP	**Irbesartan**	2	164.5 (2.12)	141.2 (8.77)	-23.3	(6.65)	-83.0	36.4
	SeSBP	**HCTZ**	3	161.3 (12.45)	138.1 (8.69)	-23.2	(6.29)	-38.9	-7.6
	SeDBP	**Irb/HCTZ**	3	100.8 (5.35)	80.9 (3.53)	-19.9	(7.60)	-38.8	-1.0
	SeDBP	**Irbesartan**	2	94.0 (8.49)	89.0 (0.00)	-5.0	(8.49)	-81.2	71.2
	SeDBP	**HCTZ**	3	91.2 (11.80)	83.2 (12.50)	-8.0	(3.38)	-16.4	0.4
Region: North America	**SeSBP**	**Irb/HCTZ**	226	160.3 (13.00)	133.9 (14.79)	-26.5	(14.62)	-28.4	-24.6
	SeSBP	**Irbesartan**	69	160.0 (10.40)	139.7 (13.57)	-20.4	(12.94)	-23.5	-17.3
	SeSBP	**HCTZ**	72	160.0 (11.28)	146.5 (13.83)	-13.5	(15.07)	-17.1	-10.0
	SeDBP	**Irb/HCTZ**	226	98.8 (7.54)	84.1 (8.64)	-14.6	(8.84)	-15.8	-13.5
	SeDBP	**Irbesartan**	69	98.9 (6.60)	87.2 (8.63)	-11.7	(9.31)	-13.9	-9.4
	SeDBP	**HCTZ**	72	98.3 (7.22)	91.0 (8.40)	-7.3	(7.87)	-9.2	-5.5

Group	Efficacy Variable	Randomized Group	N	Baseline Mean (SD)	Period B On-Therapy Mean (SD)	Change from Baseline			
						Mean	(SD)	95% Confidence Interval	
								Lower	Upper
Region: Western Europe	**SeSBP**	**Irb/HCTZ**	77	166.1 (8.67)	137.2 (15.65)	-29.0	(13.22)	-32.0	-26.0
	SeSBP	**Irbesartan**	26	165.2 (9.14)	138.9 (16.17)	-26.3	(15.69)	32.7	-20.0
	SeSBP	**HCTZ**	23	166.7 (6.94)	144.2 (13.04)	-22.5	(12.30)	-27.8	-17.1
	SeDBP	**Irb/HCTZ**	77	94.0 (8.78)	79.5 (9.00)	-14.5	(8.91)	-16.5	-12.5
	SeDBP	**Irbesartan**	26	95.5 (7.86)	83.3 (8.79)	-12.1	(9.24)	-15.8	-8.4
	SeDBP	**HCTZ**	23	94.6 (8.41)	87.9 (10.18)	-6.7	(5.25)	-8.9	-4.4

Irb = Irbesartan; HCTZ = Hydrochlorothiazide; SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure
Reproduced from Sponsor, Clinical Study Report, Table S.10.4.A, S.10.4.B, S.10.4.C, S.10.4.D, pages 254-257.

10 REFERENCES

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/s/

Karen Hicks
9/1/2006 02:21:04 PM
MEDICAL OFFICER

MO ADDENDUM
REVIEW OF ECG TRACINGS

Medical Officer Review and Typographical Corrections
NDA 20,758
DFS Date: October 17, 2006

Submission SE1 (037) BM dated September 13, 2006
Submission SE1 (037) BM dated September 26, 2006

1. The review of the above submissions was completed on Friday, October 6, 2006. The submission dated September 13, 2006 contained the following ECG tracings:

   Study CV131176
   1. 80-003
   2. 121-004 (duplicate of a tracing submitted previously)

   Study CV131185
   1. 026-003

   The submission dated September 26, 2006 contained the following ECG tracings:

   Study CV131176
   1. 55-19
   2. 55-20

   Study CV131185
   1. 16-003
   2. 17-011

   Many of the tracings submitted were of poor quality, and a number of tracings were performed at nonstandard paper speeds. However, overall, there was no drug-related QTc prolongation.

   The above submissions failed to include previously requested tracings on Subject 10-4 (Study CV131176, irbesartan monotherapy). An e-mail communication dated October 17, 2006 was sent to the sponsor to request these final tracings.

2. Typographical Correction (Table 31 on page 66 of NDA 20,758 Efficacy Supplement Review)

Table 1. Mean Changes from Baseline in Trough SeDBP and SeSBP by Week (CV131176)

		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
Week 1	**n**	459	219	459	219
	Baseline Mean (SD)	113 (3.7)	113.4 (3.5)	171.4 (16.2)	171.9 (17.1)
	Period B On-Therapy Mean (SD)	99.5 (9.4)	102.0 (9.5)	154.5 (17.3)	160.0 (18.2)
	Adj. Mean Change from	-13.9 (0.4)	-11.4 (0.6)	-16.9 (0.6)	-11.8 (0.9)

		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
	Baseline (SE)				
	Difference in Adjusted Mean Change	-2.5		-5.1	
	95% CI for Estimated Difference	(-3.9, -1.1)		(-7.2, -3.0)	
	P-value	0.0006		< 0.0001	
Week 3	**n**	452	219	452	219
	Baseline Mean (SD)	113.4 (3.7)	113.2 (3.3)	171.5 (16.3)	171.5 (16.6)
	Period B On-Therapy Mean (SD)	92.2 (10.5)	96.3 (10.0)	144.4 (17.7)	153.8 (16.7)
	Adj. Mean Change from Baseline (SE)	-21.2 (0.5)	-17.0 (0.7)	-27.1 (0.7)	-17.7 (1.0)
	Difference in Adjusted Mean Change	-4.2		-9.4	
	95% CI for Estimated Difference	(-5.8, -2.6)		(-11.7, -7.0)	
	P-value	< 0.0001		< 0.0001	
Week 5	**n**	423	206	423	206
	Baseline Mean (SD)	113.5 (3.5)	113.2 (3.2)	171.6 (16.4)	171.3 (16.3)
	Period B On-Therapy Mean (SD)	89.4 (9.3)	93.9 (10.2)	140.8 (15.3)	150.3 (16.9)
	Adj. Mean Change from Baseline (SE)	-24.0 (0.5)	-19.3 (0.7)	-30.8 (0.7)	-21.1 (1.0)
	Difference in Adjusted Mean Change	-4.7		-9.7	
	95% CI for Estimated Difference	(-6.3, **-3.1**)		(-12.0, -7.3)	
	P-value	< 0.0001		< 0.0001	
Week 7	**n**	426	203	426	**203**
	Baseline Mean (SD)	113.3 (3.5)	113.1 (3.2)	171.3 (16.3)	171.1 (16.6)
	Period B On-Therapy Mean (SD)	88.8 (9.4)	93.2 (10.6)	139.5 (16.1)	149.4 (17.1)
	Adj. Mean Change from Baseline (SE)	-24.5 (0.5)	-19.9 (0.7)	-31.7 (0.7)	-21.7 (1.0)
	Difference in Adjusted Mean Change	-4.6		-10.1	

		Trough SeDBP (mm Hg)		Trough SeSBP (mm Hg)	
Week		**Irb/HCTZ N = 468**	**Irbesartan N = 229**	**Irb/HCTZ N = 468**	**Irbesartan N = 229**
	95% CI for Estimated Difference	(-6.2, -3.0)		(-12.5, -7.6)	
	P-value	< 0.0001		< 0.0001	

Reproduced from Sponsor, Clinical Study Report, Table 10.3, page 72.
Source: Appendix 10A, Appendix 6
Reference: Supplemental Tables S.10.3.A.1, S.10.3B
Irb: irbesartan
HCTZ: Hydrochlorothiazide
N=number of subjects randomized into Period B
n=number of subjects with available efficacy during Period B
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Please note the bolded change in Week 5, 95% CI (-6.3, **-3.1**), for estimated difference in Trough SeDBP as well as the bolded change in Week 7, n for irbesartan (**203**), under Trough SeSBP. Although the n for irbesartan was written as "223" in Sponsor's Table 10.3 on page 72 of the Clinical Study Report, the actual number is "203" as written in Table S.10.3A.1, page 209.

3. Typographical Correction (Table 46 on page 94 of NDA 20,758 Efficacy Supplement Review)

Table 2. Sponsor's Analysis: Mean Changes from Baseline in Trough SeSBP By Week (CV131185)

Week		Trough SeSBP		
		Irb/HCTZ N = 328	Irbesartan N = 106	HCTZ N = 104
2	**n**	**316**	**102**	**103**
	Baseline Mean (SD)	161.8 (12.22)	161.4 (10.16)	161.9 (10.68)
	On-Therapy Mean (SD)	143.9 (14.85)	147.6 (14.55)	151.7 (14.16)
	Adjusted Mean Change from Baseline (SE)	-17.9 (0.69)	-13.9 (1.22)	-10.2 (1.22)
	Est. Difference between Combo and Mono Group*		-4.0	-7.7
	95 % CI for Estimated Difference		(-6.8, -1.3)	(-10.5, -5.0)
	P-value for Combo and Mono Group Comparison**		0.0044	< 0.0001
4	**n**	**316**	**100**	**100**
	Baseline Mean (SD)	161.7 (12.17)	161.5 (10.23)	161.7 (10.70)
	On-Therapy Mean (SD)	136.9 (14.91)	143.7 (14.88)	147.8 (11.95)
	Adjusted Mean Change from Baseline (SE)	-24.8 (0.71)	-17.8 (1.26)	-13.9 (1.26)
	Est. Difference between Combo and Mono Group*		-7.0	-10.9
	95 % CI for Estimated Difference		(-9.8, -4.1)	(-13.8, -8.1)
	P-value for Combo and Mono Group Comparison**		< 0.0001	< 0.0001
8	**n**	**303**	**95**	**95**
	Baseline Mean (SD)	161.8 (12.30)	161.5 (10.29)	161.6 (10.75)
	On-Therapy Mean (SD)	134.7 (15.06)	139.5 (14.25)	145.9 (13.61)
	Adjusted Mean Change from Baseline (SE)	-27.1 (0.76)	-22.1 (1.36)	-15.7 (1.36)
	Est. Difference between Combo and Mono Group*		-5.0	-11.3
	95 % CI for Estimated Difference		(-8.0, -1.9)	(-14.4, -8.3)
	P-value for Combo and Mono Group Comparison**		0.0016	< 0.0001
12	**n**	**291**	**94**	**91**
	Baseline Mean (SD)	161.7 (12.23)	161.5 (10.34)	161.3 (10.83)
	On-Therapy Mean (SD)	133.3 (13.77)	142.0 (15.59)	144.9 (13.08)
	Adjusted Mean Change from Baseline (SE)	-28.3 (0.73)	-19.5 (1.29)	-16.5 **(1.31)**

Week		Trough SeSBP		
		Irb/HCTZ N = 328	Irbesartan N = 106	HCTZ N = 104
	Est. Difference between Combo and Mono Group*		-8.7	-11.8
	95 % CI for Estimated Difference		(-11.7, -5.8)	(-14.7, -8.8)
	P-value for Combo and Mono Group Comparison**		< 0.0001	<0.0001

Reference: Supplemental Tables S.10.1A, S.10.1E
Randomized Subjects
***Difference = Combo Group – Mono Group**
****p-value of two-sided tests**
Note: N = number of subjects randomized into Period B; n = number of subjects with available efficacy during Period B.
Source: Appendix 10A, 6.0
Reproduced from Sponsor, Clinical Study Report, Table 10.1.2A, pages 71-72
Analysis verified by Jialu Zhang, Ph.D. and Karen A. Hicks, M.D.

Please note the bolded change in Week 12, under HCTZ, Adjusted Mean Change from Baseline (SE), which should be **(1.31)**.

4. Clarifications
    a. Section 6.1.3.4 Prespecified Adverse Events, page 28, under Hypotension: **Three subjects** (not two) experienced hypotension on irbesartan/HCTZ combination therapy, including Subject 248-1 who experienced "hypotension," Subject 293-2 who experienced "symptomatic hypotension," and Subject 288-4 who experienced "orthostatic hypotension." There were no reports of hypotension in the irbesartan monotherapy group.

    b. Please see Revised Table 10 (page 29) for Study CV131176:

Table 3. Agency Analysis: Subjects with Prespecified Adverse Events (CV131176)

Adverse Events	**Irbesartan/HCTZ**		**Irbesartan**	
Preferred Term	**(N = 468) n (%)**	**95% CI (Lower, Upper)**	**(N = 227) n (%)**	**95% CI (Lower, Upper)**
Subjects with Selected Adverse Events	41 (8.8)	(6.4, 11.7)	26 (11.5)	(7.6, 16.3)
Headache	20 (4.3)	(2.6, 6.4)	15 (6.6)	(3.7, 10.6)
Headache	19 (4.1)		15 (6.6)	
Migraine	1 (0.2)		0	
Dizziness	17 (3.6)	(2.1, 5.7)	9 (4.0)	(1.8, 7.3)
Dizziness	16 (3.4)		9 (4.0)	
Dizziness Postural	1 (0.2)		0	
Hypotension	3 (0.6)	(0.1, 1.8)	0	(0.0, 1.6)
Hypotension	1 (0.2)		0	
Hypotension, Symptomatic	1 (0.2)		0	
Orthostatic Hypotension	1 (0.2)		0	
Hypokalemia/Decreased Potassium	3 (0.6)	(0.1, 1.8)	1 (0.4)	(0.0, 2.4)
Blood Potassium Decreased	2 (0.4)		1 (0.4)	
Hypokalemia	1 (0.2)		0	

Adverse Events Preferred Term	Irbesartan/HCTZ (N = 468) n (%)	Irbesartan/HCTZ 95% CI (Lower, Upper)	Irbesartan (N = 227) n (%)	Irbesartan 95% CI (Lower, Upper)
Hyperkalemia/Increased Potassium	1 (0.2)	(0.0, 1.2)	0	(0.0, 1.6)
Hyperkalemia	1 (0.2)		0	
Syncope	0	(0.0, 0.8)	0	(0.0, 1.6)
Serum Potassium < 3.0	0	(0.0, 0.8)	0	(0.0, 1.6)
Serum Potassium > 6.0	3 (0.6)	(0.1, 1.8)	3 (1.3)	(0.3, 3.8)

CI: Confidence Interval
***Please note that although hyperkalemia was reported as an adverse event in one subject randomized to irbesartan/HCTZ only, there were three subjects (0.6 %) in the irbesartan/HCTZ group and three subjects in the irbesartan monotherapy group (1.3%) who achieved elevated potassium levels meeting the "laboratory marked abnormality criteria." Please see** Error! Reference source not found. **for full details.**
Source: Clinical Study Report (CV131176), Table 12.5.1A, page 93.
Analysis verified by Karen A. Hicks, M.D.. Source: Derived Adverse Event Data set.

c. Section 6.1.7 Vital Signs (Clarification of Paragraphs 3 through 5):

According to the adverse events data set, Subjects 248-1, 288-4, and 293-2 experienced hypotension on Days 30, 19, and 16, respectively. Subjects 248-1 and 288-4 did not have vital signs recorded when they were on medication and symptomatic.

Subject 248-1 experienced "hypotension" from February 12, 2005 (Day 30) through February 18, 2005 and subsequently discontinued the study due to this adverse event. The patient received the final dose of study medication on February 17, 2005. Vital signs were checked on February 10, 2005 and on February 18, 2005. On February 10, 2005, seated blood pressure was 136/86 with a heart rate of 78 bpm. Standing blood pressure was 136/87 with a heart rate of 74 bpm. On February 18, 2005, seated blood pressure was 139/96 with a heart rate of 81 bpm. Standing blood pressure was 125/91 with a heart rate of 76 bpm. There were no additional blood pressures or heart rates recorded from February 12, 2005 through February 17, 2005 when the patient was on medication and symptomatic. Although her systolic blood pressure dropped 15 mm Hg with standing on February 18, 2005, her heart rate did not increase. It is possible her blood pressure and heart rate changes would have been more prominent if vital signs were checked on medication during peak symptoms.

Subject 288-4 experienced "dizziness" on April 5, 2005 and "orthostatic hypotension" on April 8, 2005. There were no vital signs recorded on these dates. On April 11, 2005, the average sitting blood pressure was 131/79 with a heart rate of 65 bpm. Standing blood pressure on this date was 123/76 with a heart rate of 71 bpm. The patient completed the study. The patient received the final dose of study medication on May 10, 2005.

Subject 293-2 experienced weakness and sleepiness from April 2, 2005 through April 10, 2005 but went on to complete the study. The patient received the final dose of

study medication on May 3, 2005. The investigator interpreted the weakness and sleepiness to be symptomatic of hypotension. This subject began the study on March 14, 2005. From April 2, 2005 through April 10, 2005, the subject experienced "symptomatic hypotension." The symptoms were reportedly mild, and no action was taken. On April 6, 2005, average sitting blood pressure was 133/97 with a heart rate of 88 bpm. Standing blood pressures were 138/108, 135/102, and 134/102 with a heart rate of 98 bpm. Based on these blood pressures, the patient was not hypotensive, although she had been diagnosed by the study physician as having "symptomatic hypotension."

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/s/

Karen Hicks
10/17/2006 03:26:01 PM
MEDICAL OFFICER

MO ADDENDUM
ECG TRACING FOR SUBJECT 10-4

NDA 20,758
Avalide® (irbesartan/hydrochlorothiazide)
EDR Submission
Correspondence Date: October 24, 2006
Date of Review: November 7, 2006
Reviewer: Karen A. Hicks, Medical Officer

This submission included the baseline and final visit 12-lead ECG tracings for Subject 10-4 from the irbesartan monotherapy group for Study CV131176. The ECGs demonstrated no evidence of drug-related QTc prolongation.

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/s/

Karen Hicks
11/7/2006 10:52:26 AM
MEDICAL OFFICER

MO ADDENDUM
FINANCIAL DISCLOSURE

sNDA 20-758 Efficacy Review
Irbesartan/Hydrochlorothiazide (Avalide®)
Clinical Reviewer: Karen A. Hicks, M.D.

Date: October 20, 2006
Addendum

Section 4.6, Financial Disclosures, page 14:
Both studies were conducted by Bristol-Myers Squibb Company. The sponsor provided categorical assurance there were no financial arrangements with the clinical investigators, and I am in agreement with this assessment.

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/s/

Karen Hicks
10/20/2006 04:09:59 PM
MEDICAL OFFICER

EFFICACY DISCUSSION DOCUMENT

October 6, 2006

Study CV131176: "The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Severe Hypertension"

Design: Multicenter, randomized, double-blind, active-controlled, parallel group trial in untreated uncontrolled hypertensive (SeDBP ≥ 110 mm Hg) subjects and in subjects with uncontrolled hypertension (SeDBP ≥ 100 mm Hg) who were currently treated with antihypertensive monotherapy.

Total patients: 697 patients
Irbesartan/HCTZ: 468 patients
Irbesartan: 229 patients

Inclusion Criteria:
Currently untreated with an SeDBP ≥ 110 mm Hg or treated with SeDBP ≥ 100 mm Hg

Lead In: 7-10 days
7 Weeks Double-Blind (1 week of Irb/HCTZ 150/12.5 or Irbesartan 150 mg; 6 weeks of Irb/HCTZ 300/25 or Irbesartan 300 mg)

Primary Efficacy Endpoint:
The proportion of subjects whose SeDBP was controlled (SeDBP < 90 mm Hg) at Week 5

Secondary Efficacy Endpoints:
- The proportion of subjects with SeDBP < 90 mm Hg (at Weeks 1, 3, and 7)
- The change from baseline in SeSBP and SeDBP (at Weeks 1, 3, 5, and 7)
- The proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg (at Weeks 1, 3, 5, and 7)

Safety Endpoints:
- The frequency of treatment discontinuations due to adverse events
- The frequencies of hypotension, dizziness, and syncope
- The frequency of headaches
- The frequencies of hypokalemia and hyperkalemia

Study CV131185: "The Efficacy and Safety of Irbesartan/HCTZ Combination Therapy as First Line Treatment for Patients with Moderate Hypertension"

Design: Multicenter, randomized, double-blind, active-controlled, 12-week parallel group study in untreated and treated subjects with uncontrolled hypertension. Uncontrolled HTN was defined as follows:

Inclusion Criteria:
Untreated Subjects:

- **averaged seated systolic blood pressure (SeSBP) ≥ 160 mm Hg and < 180 mm Hg and averaged seated diastolic blood pressure (SeDBP) < 110 mm Hg**

or

- **averaged SeDBP ≥ 100 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg**

Subjects Receiving Antihypertensive Monotherapy:

- **averaged SeSBP ≥150 mm Hg and < 180 mm Hg and averaged SeDBP < 110 mm Hg**

or

- **averaged SeDBP ≥ 95 mm Hg and < 110 mm Hg and averaged SeSBP ≥ 130 mm Hg and < 180 mm Hg**

Total Patients: 538 subjects
Irbesartan/HCTZ: 328 subjects
Irbesartan: 106 subjects
HCTZ: 104 subjects

21 Days Placebo
12 Weeks Double-Blind including **2 weeks** of Irb/HCTZ 150/12.5 or Irb 150 or HCTZ 12.5 mg
And **10 weeks** of Irb/HCTZ 300/25 or Irb 300 or HCTZ 25 mg

Primary Efficacy Endpoint
Change from Baseline in SeSBP at Week 8

Secondary Efficacy Endpoints

- 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 after 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 mm Hg and SeDBP < 90 mm Hg at Weeks 8 and 12
- the change from baseline in hs-CRP at Week 12

Other Efficacy Endpoints

- the change from baseline in SeSBP and SeDBP at Weeks 2 and 4
- the proportion of subjects with simultaneous SeSBP < 140 mm Hg and SeDBP < 90 mm Hg at Weeks 2 and 4, and
- the change from baseline in hs-CRP at Week 8

Table 1. Proportion of Subjects Controlled (SeDBP < 90 mm Hg) by Week (Study CV131176)

Treatment	n at Baseline	n at Week	Proportion Controlled (Number Controlled)	Estimated Difference Between Treatments	95% Confidence Interval	P- Value for Between Group Comparison
Week 1						
Irbesartan/HCTZ	468	460	15.2% (71)	6.0	(0.007, 0.113)	0.0317
Irbesartan	229	219	9.2% (21)			
Week 3						
Irbesartan/HCTZ	468	452	41.0% (192)	14.8	(0.073, 0.224)	0.0002
Irbesartan	229	219	26.2% (60)			
Week 5*						
Irbesartan/HCTZ	468	423	47.2% (221)	14.0	(0.061, 0.220)	0.0005
Irbesartan	229	206	33.2% (76)			
Week 7						
Irbesartan/HCTZ	468	426	51.9% (243)	19.2	(0.113, 0.271)	< 0.0001
Irbesartan	229	203	32.8% (75)			
***Primary Endpoint**						

Table 2. Treatment Comparison of Proportions Controlled During Double-Blind Period by Week (CV131176)

Treatment	n at Baseline	n at Week	Proportion Controlled (Number Controlled) (Trough SeDBP < 90 mm Hg AND Trough SeSBP < 140 mm Hg)	Estimated Difference Between Treatments	95% Confidence Interval	P- Value for Between Group Comparison
Week 1						
Irbesartan/HCTZ	468	460	9.2% (43)	4.8	(0.008, 0.089)	0.0230
Irbesartan	229	219	4.4% (10)			
Week 3						
Irbesartan/HCTZ	468	452	30.6% (143)	17.9	(0.116, 0.242)	< 0.0001
Irbesartan	229	219	12.7% (29)			
Week 5						
Irbesartan/HCTZ	468	423	34.6% (162)	15.4	(0.084, 0.224)	< 0.0001
Irbesartan	229	206	19.2% (44)			
Week 7						
Irbesartan/HCTZ	468	426	37.8% (177)	16.4	(0.092, 0.236)	< 0.0001
Irbesartan	229	203	21.4% (49)			

Table 3. Mean Changes from Baseline in Trough SeDBP by Week (CV131176)

Treatment	n at Baseline	n at Week	Baseline Mean (SD)	Double-Blind On Therapy Mean (SD)	Adjusted Mean Change from Baseline (SE)	Difference in Adjusted Mean Change	95% Confidence Interval	P- Value for Between Group Comparison
Week 1								
Irbesartan/HCTZ	468	459	113 (3.7)	99.5 (9.4)	-13.9 (0.4)	-2.5	(-3.9, -1.1)	0.0006
Irbesartan	229	219	113.4 (3.5)	102.0 (9.5)	-11.4 (0.6)			
Week 3								
Irbesartan/HCTZ	468	452	113.4 (3.7)	92.2 (10.5)	-21.2 (0.5)	-4.2	(-5.8, -2.6)	<0.0001
Irbesartan	229	219	113.2 (3.3)	96.3 (10.0)	-17.0 (0.7)			
Week 5								
Irbesartan/HCTZ	468	423	113.5 (3.5)	89.4 (9.3)	-24.0 (0.5)	-4.7	(-6.3, -3.1)	<0.0001
Irbesartan	229	206	113.2 (3.2)	93.9 (10.2)	-19.3 (0.7)			
Week 7								
Irbesartan/HCTZ	468	426	113.3 (3.5)	88.8 (9.4)	-24.5 (0.5)	-4.6	(-6.2, -3.0)	<0.0001
Irbesartan	229	203	113.1 (3.2)	93.2 (10.6)	-19.9 (0.7)			

Table 4. Mean Changes from Baseline in Trough SeSBP by Week (CV131176)

Treatment	n at Baseline	n at Week	Baseline Mean (SD)	Double-Blind On Therapy Mean (SD)	Adjusted Mean Change from Baseline (SE)	Difference in Adjusted Mean Change	95% Confidence Interval	P- Value for Between Group Comparison
Week 1								
Irbesartan/HCTZ	468	459	171.4 (16.2)	154.5 (17.3)	-16.9 (0.6)	-5.1	(-7.2, -3.0)	< 0.0001
Irbesartan	229	219	171.9 (17.1)	160.0 (18.2)	-11.8 (0.9)			
Week 3								
Irbesartan/HCTZ	468	452	171.5 (16.3)	144.4 (17.7)	-27.1 (0.7)	-9.4	(-11.7, -7.0)	<0.0001
Irbesartan	229	219	171.5 (17.6)	153.8 (16.7)	-17.7 (1.0)			
Week 5								
Irbesartan/HCTZ	468	423	171.6 (16.4)	140.8 (15.3)	-30.8 (0.7)	-9.7	(-12.0, -7.3)	<0.0001
Irbesartan	229	206	171.3 (16.3)	150.3 (16.9)	-21.1 (1.0)			
Week 7								
Irbesartan/HCTZ	468	426	171.3 (16.3)	139.5 (16.1)	-31.7 (0.7)	-10.1	(-12.5, -7.6)	<0.0001
Irbesartan	229	203	171.1 (16.6)	149.4 (17.1)	-21.7 (1.0)			

Table 5. Mean Changes from Baseline in Trough SeSBP by Week (CV131185)

Treatment	n at Baseline	n at Week	Baseline Mean (SD)	On Therapy Mean (SD)	Adjusted Mean Change from Baseline (SE)	Estimated Difference Between Combo and Mono Group	95% Confidence Interval for Estimated Difference	P- Value for Combo and Mono Group Comparison
Week 2								
Irbesartan/HCTZ	328	316	161.8 (12.22)	143.9 (14.85)	-17.9 (0.69)			
Irbesartan	106	102	161.4 (10.16)	147.6 (14.55)	-13.9 (1.22)	-4.0	(-6.8, -1.3)	0.0044
HCTZ	104	103	161.9 (10.68)	151.7 (14.16)	-10.2 (1.22)	-7.7	(-10.5, -5.0)	<0.0001
Week 4								
Irbesartan/HCTZ	328	316	161.7 (12.17)	136.9 (14.91)	-24.8 (0.71)			
Irbesartan	106	100	161.5 (10.23)	143.7 (14.88)	-17.8 (1.26)	-7.0	(-9.8, -4.1)	<0.0001
HCTZ	104	100	161.7 (10.70)	147.8 (11.95)	-13.9 (1.26)	-10.9	(-13.8, -8.1)	<0.0001
Week 8*								
Irbesartan/HCTZ	328	303	161.8 (12.30)	134.7 (15.06)	-27.1 (0.76)			
Irbesartan	106	95	161.5 (10.29)	139.5 (14.25)	-22.1 (1.36)	-5.0	(-8.0, -1.9)	<0.0001
HCTZ	104	95	161.7 (10.70)	147.8 (11.95)	-13.9 (1.26)	-10.9	(-13.8, -8.1)	<0.0001
Week 12								
Irbesartan/HCTZ	328	291	161.7 (12.23)	133.3 (13.77)	-28.3 (0.73)			
Irbesartan	106	94	161.5 (10.34)	142.0 (15.59)	-19.5 (1.29)	-8.7	(-11.7, -5.8)	<0.0001
HCTZ	104	91	161.3 (10.83)	144.9 (13.08)	-16.5 (1.31)	-11.8	(-14.7, -8.8)	<0.0001
***Primary Efficacy Endpoint**								

Table 6. Mean Changes from Baseline in Trough SeDBP by Week (CV131185)

Treatment	n at Baseline	n at Week	Baseline Mean (SD)	On Therapy Mean (SD)	Adjusted Mean Change from Baseline (SE)	Estimated Difference Between Combo and Mono Group	95% Confidence Interval for Estimated Difference	P- Value for Combo and Mono Group Comparison
Week 2								
Irbesartan/HCTZ	328	316	97.4 (8.39)	88.1 (8.91)	-9.3 (0.41)			
Irbesartan	106	102	97.6 (7.60)	90.3 (8.78)	-7.3 (0.72)	-2.0	(-3.7, -0.4)	0.0147
HCTZ	104	103	97.6 (7.53)	92.1 (9.03)	-5.5 (0.72)	-3.8	(-5.4, -2.2)	<0.0001
Week 4								
Irbesartan/HCTZ	328	316	97.4 (8.13)	84.5 (9.11)	-13.0 (0.43)			
Irbesartan	106	100	98.0 (7.49)	88.0 (8.60)	-9.8 (0.77)	-3.1	(-4.8, -1.4)	0.0005
HCTZ	104	100	97.6 (7.54)	90.2 (8.60)	-7.4 (0.77)	-5.6	(-7.3, -3.8)	<0.0001
Week 8*								
Irbesartan/HCTZ	328	303	97.6 (8.31)	83.0 (8.95)	-14.6 (0.45)			
Irbesartan	106	95	98.0 (7.10)	86.2 (8.80)	-11.6 (0.81)	-3.0	(-4.8, -1.2)	0.0013
HCTZ	104	95	97.4 (7.65)	90.2 (8.91)	-7.3 (0.81)	-7.4	(-9.2, -5.5)	<0.0001
Week 12								
Irbesartan/HCTZ	328	291	97.5 (8.19)	82.3 (9.24)	-15.2 (0.48)			
Irbesartan	106	94	97.9 (7.12)	86.6 (9.00)	-11.1 (0.84)	-4.1	(-6.0, -2.2)	<0.0001
HCTZ	104	91	97.4 (7.80)	89.7 (8.88)	-7.8 (0.85)	-7.4	(-9.3, -5.5)	<0.0001

Table 7. Proportion of Subjects Controlled by Week (CV131185)

Treatment	n at Baseline	n at Week	Proportion Controlled (Number of Responders) (Trough SeDBP < 90 mm Hg AND Trough SeSBP < 140 mm Hg)	Estimated Difference Between Combo and Mono Groups	95% Confidence Interval for Estimated Difference	P- Value for Combo and Mono Group Comparison
Week 2						
Irbesartan/HCTZ	328	316	26.5% (87)			
Irbesartan	106	102	20.8% (22)	5.8	(-0.039, 0.155)	0.2492
HCTZ	104	103	14.4% (15)	12.1	(0.032, 0.210)	0.0116
Week 4						
Irbesartan/HCTZ	328	316	44.5% (146)			
Irbesartan	106	100	29.2% (31)	15.3	(0.044, 0.261)	0.0062
HCTZ	104	100	17.3% (18)	27.2	(0.175, 0.369)	<0.0001
Week 8						
Irbesartan/HCTZ	328	303	53.4% (175)			
Irbesartan	106	95	40.6% (43)	12.8	(0.014, 0.242)	0.0254
HCTZ	104	95	20.2% (21)	33.2	(0.231, 0.432)	<0.0001
Week 12						
Irbesartan/HCTZ	328	291	55.8% (183)			
Irbesartan	106	94	34.0% (36)	21.8	(0.107, 0.330)	0.0001
HCTZ	104	91	25.0% (26)	30.8	(0.203, 0.413)	<0.0001

SAFETY DISCUSSION

Study CV131176: Safety

Table 1. Agency Analysis: Summary of Subjects Discontinued During Period B and Reason for Discontinuation (CV131176)

	Irb/HCTZ (n, %)	Irbesartan (n, %)	Total (n, %)
Total Number of Subjects Randomized	468 (100.0)	229 (100.0)	697 (100.0)
Number of Subjects Treated	468 (100.0)	227 (99.1)	695 (99.7)
Number of Subjects who Discontinued the Study during the Double-Blind Period	48 (10.3)	28 (12.2)	76 (10.9)
Adverse event*	10 (2.1)	5 (2.2)	15 (2.2)
Subject withdrew consent*	9 (1.9)	4 (1.7)	13 (1.9)
Pregnancy	0	1 (0.4)	1 (0.1)
Lost to follow-up	4 (0.9)	3 (1.3)	7 (1.0)
Administrative reason by sponsor	1 (0.2)	0	1 (0.1)
Subject no longer meets study criteria	8 (1.7)	3(1.3)	11 (1.6)
Lack of efficacy	15 (3.2)	12 (5.2)	27 (3.9)
Poor/non-compliance	1 (0.2)	0	1 (0.1)
Number of Subjects Completing	420 (89.7)	201 (87.8)	621 (89.1)

***Table 8.1 in the Clinical Study Report on page 53 reports 10 subjects (2.1%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to "withdrawn consent" and 9 subjects (1.9%) in the irbesartan/HCTZ treatment group discontinuing the study during the double-blind period due to adverse events. Since I believe one of the irbesartan/HCTZ subjects (Subject 96-6) who was originally placed in the "withdrew consent" column in the sponsor's analysis should actually have been placed in the "adverse event" column, I retabulated the values for the "adverse event" and "withdrew consent" rows in this Table and made adjustments to the respective "Total" columns for these rows.**
Irb = Irbesartan
Analysis by Karen A. Hicks, M.D.

Table 2. Sponsor's Analysis: Overall Incidence of Adverse Events During Double-Blind Treatment Period (CV131176)

Event	Irbesartan/HCTZ (N = 468) N (%)	Irbesartan (N = 227) N (%)
Total Subjects with Adverse Events (AE)‡	140 (29.9%)	82 (36.1%)
Total Subjects with Treatment-Related AE	53 (11.3%)	23 (10.1%)
Total Subjects with Serious Adverse Events (SAE)	**1 (0.2%)†**	1 (0.4%)
Total Subjects with Discontinuations due to AE	**9 (1.9%)***	5 (2.2%)
Deaths	0	0

‡Adverse Event = unique subjects experiencing adverse events. Total unique subjects experiencing adverse events = 222.
†If one includes Subject 240-4, the 74 year old white female who experienced a transient ischemic attack one day after her study medication was increased to irbesartan 300 mg/HCTZ 25 mg, the irbesartan/HCTZ combination group has 2 serious adverse events (0.43%).
***In the irbesartan/HCTZ treatment group, I counted 10 discontinuations due to AE (2.2%), not 9 (1.9%). The additional AE involved Subject 96-6 who had been coded as a "withdrew consent" as opposed to "withdrew due to an adverse event."**
Reproduced from Sponsor, Clinical Study Report, Table 12.1, page 76.
Source: Supplemental Tables S.12.1.1, S.12.1.2, S.12.2, S.12.3; Appendix 12.4.
Analysis verified by Karen A. Hicks, M.D.

Table 3. Most Common Adverse Events as Reported by at Least 1% of Subjects in Either Treatment Group During Double-Blind Period, by Preferred Term (Study CV131176)

	Number (%) of Subjects	
Preferred Term (PT) (%)	**Irbesartan/HCTZ N = 468**	**Irbesartan N = 227**
Total Subjects with at least 1 Adverse Event	**140 (29.9%)**	**82 (36.1%)**
Headache	19 (4.1%)	15 (6.6%)
Dizziness	16 (3.4%)	9 (4.0%)
Nasopharyngitis	8 (1.7%)	10 (4.4%)
Bronchitis	6 (1.3%)	6 (2.6%)
Fatigue	6 (1.3%)	1 (0.4%)
Upper Respiratory Tract Infection	6 (1.3%)	4 (1.8%)
Erectile Dysfunction	5 (1.1%)	0
Nausea	5 (1.1%)	5 (2.2%)
Diarrhea	4 (0.9%)	3 (1.3%)
Sinusitis	4 (0.9%)	3 (1.3%)
Cough	3 (0.6%)	4 (1.8%)
Muscle Spasms	2 (0.4%)	3 (1.3%)

Table 4. Number (Percent) of Subjects with Pre-Specified Adverse Events During Double-Blind Period by Adverse Event and Preferred Term (Study CV131176)

Adverse Events	**Irbesartan/HCTZ**		**Irbesartan**	
Preferred Term	**(N = 468) n (%)**	**95% CI (Lower, Upper)**	**(N = 227) n (%)**	**95% CI (Lower, Upper)**
Subjects with Selected Adverse Events	**41 (8.8)**	**(6.4, 11.7)**	**26 (11.5)**	**(7.6, 16.3)**
Headache	**20 (4.3)**	**(2.6, 6.4)**	**15 (6.6)**	**(3.7, 10.6)**
Headache	19 (4.1)		15 (6.6)	
Migraine	1 (0.2)		0	
Dizziness	**17 (3.6)**	**(2.1, 5.7)**	**9 (4.0)**	**(1.8, 7.3)**
Dizziness	16 (3.4)		9 (4.0)	
Dizziness Postural	1 (0.2)		0	
Hypotension	**3 (0.6)**	**(0.1, 1.8)**	**0**	**(0.0, 1.6)**
Hypotension	1 (0.2)		0	
Hypotension, Symptomatic	1 (0.2)			
Orthostatic Hypotension	1 (0.2)		0	
Hypokalemia/Decreased Potassium	**3 (0.6)**	**(0.1, 1.8)**	**1 (0.4)**	**(0.0, 2.4)**
Blood Potassium Decreased	2 (0.4)		1 (0.4)	
Hypokalemia	1 (0.2)		0	
Hyperkalemia/Increased Potassium	**1 (0.2)**	**(0.0, 1.2)**	**0**	**(0.0, 1.6)**
Hyperkalemia	1 (0.2)		0	
Syncope	**0**	**(0.0, 0.8)**	**0**	**(0.0, 1.6)**
Serum Potassium < 3.0	**0**	**(0.0, 0.8)**	**0**	**(0.0, 1.6)**
Serum Potassium > 6.0	**3 (0.6)**	**(0.1, 1.8)**	**3 (1.3)**	**(0.3, 3.8)**
CI: Confidence Interval				

Study CV131185: Safety

Table 5. Summary of Subjects Discontinued during Period B and Reason for Discontinuation (CV131185)

	Irb/HCTZ n, (%)	Irbesartan n (%)	HCTZ n (%)	Total n (%)
Total Number of Subjects Randomized	**328 (100.0)**	**106 (100.0)**	**104 (100.0)**	**538 (100.0)**
Number of Subjects Treated	**328 (100.0)**	**106 (100.0)**	**104 (100.0)**	**538 (100.0)**
Number of Subjects Discontinued from the Study	41 (12.5)	12 (11.3)	13 (12.5)	66 (12.3)
Adverse event	22 (6.7)	4 (3.8)	5 (4.8)	31 (5.8)
Subject withdrew consent	4 (1.2)	1 (0.9)	2 (1.9)	7 (1.3)
Lost to follow-up	7 (2.1)	2 (1.9)	3 (2.9)	12 (2.2)
Subject no longer meets study criteria	4 (1.2)	3 (2.8)	1 (1.0)	8 (1.5)
Lack of efficacy	1 (0.3)	1 (0.9)	1 (1.0)	3 (0.6)
Poor/non-compliance	1 (0.3)	0	1 (1.0)	2 (0.4)
Other	2 (0.6)	1 (0.9)	0	3 (0.6)
Number of Subjects Completing	**287 (87.5)**	**94 (88.7)**	**91 (87.5)**	**472 (87.7)**
Randomized Subjects **Source: Appendix 8.1.2** **Reproduced from Sponsor, Clinical Study Report, CV131185, Table 8.1, page 57.**				

Table 6. Overview of Adverse Events During Period B (CV131185)

Event	Irbesartan/HCTZ (N = 328 n (%)	Irbesartan (N = 106) n (%)	HCTZ (N = 104) n (%)
Total Subjects with Adverse Events (AE)	154 (47.0)	48 (45.3)	41 (39.4)
Total Subjects with Treatment-Related AE	47 (14.3)	12 (11.3)	8 (7.7)
Total Subjects with Serious Adverse Events (SAE)	6 (1.8)	0	3 (2.9)
Total Subjects with Discontinuations due to AE	22 (6.7)	4 (3.8)	5 (4.8)
Deaths	0	0	0
Source: Table 2.12.1.1B, Table S.12.1.1C, Table @.12.2, Table S.12.3, Table S.12.4 **Reproduced from Sponsor, Clinical Study Report, Table 12.1, page 83.**			

Table 7. Number (Percent) of Subjects with Pre-Specified Adverse Events During Double-Blind Period by AE and PT (CV131185)

Adverse Events (AE) Preferred Term (PT)	Irbesartan/HCTZ		Irbesartan		HCTZ	
	(N = 328) n (%)	95% CI	(N = 106) n (%)	95% CI	(N = 104) n (%)	95% CI
Subjects with Selected Adverse Events	**35 (10.7)**	**(7.5, 14.5)**	**7 (6.6)**	**(2.7, 13.1)**	**7 (6.7)**	**(2.7, 13.4)**
Headache	18 (5.5)	(3.2, 8.4)	4 (3.8)	(1.0, 9.3)	5 (4.8)	(1.6, 10.8)
Headache	14 (4.3)		3 (2.8)		5 (4.8)	
Sinus Headache	4 (1.2)		1 (0.9)		0	
Dizziness	10 (3.0)	(1.4, 5.4)	4 (3.8)	(1.0, 9.3)	1 (1.0)	(0.0, 5.2)
Hypotension	3 (0.9)	(0.2, 2.6)	0	(0.0, 3.4)	0	(0.0, 3.5))
Hypotension	1 (0.3)		0		0	
Orthostatic Hypotension	2 (0.6)		0		0	

Adverse Events (AE) Preferred Term (PT)	Irbesartan/HCTZ		Irbesartan		HCTZ	
	(N = 328) n (%)	95% CI	(N = 106) n (%)	95% CI	(N = 104) n (%)	95% CI
Hypokalemia/Decreased Potassium	3 (0.9)	(0.2, 2.6)	0	(0.0, 3.4)	0	(0.0, 3.5)
Blood Potassium Decreased	1 (0.3)		0		0	
Hypokalemia	2 (0.6)		0		0	
Hyperkalemia/Increased Potassium	4 (1.2)	(0.3, 3.0)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.2)
Blood Potassium Increased	2 (0.6)		0		1 (1.0)	
Hyperkalemia	2 (0.6)		0		0	
Syncope	0	(0.0, 1.1)	0	(0.0, 3.4)	1 (1.0)	(0.0, 5.2)
Syncope Vasovagal	0		0		1 (1.0)	
Serum Potassium < 3.0	0	(0.0, 1.1)	0	(0.0, 3.4)	0	(0.0, 3.5)
Serum Potassium > 6.0	4 (1.2)	(0.3, 3.0)	0	(0.0, 3.4)	0	(0.0, 3.5)

Reproduced from Sponsor, Clinical Study Report, Table S.12.1.1A, page 259.
Analysis verified by Karen A. Hicks, M.D.

DRAFT
QUESTIONS TO THE COMMITEE

Questions

Irbesartan/HCTZ
April 18, 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Advisory Committee is asked to opine on the basis for granting first-line use to combination antihypertensives, and to apply the principles to AVALIDE (irbesartan/HCTZ). For the most part, combination antihypertensive products, formulations of two or more drugs for hypertension, have been given an indication for second-line use, similar to what AVALIDE now has:

> "**INDICATIONS AND USAGE**
>
> "AVALIDE (irbesartan-hydrochlorothiazide) Tablets is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**)."
>
> …
>
> "**DOSAGE AND ADMINISTRATION**
>
> "To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.
>
> "The side effects (see **WARNINGS**) of irbesartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of irbesartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects."

The general principle was that someone should not accept the risk of "dose-independent" adverse events associated with a second drug until he had wrung what value was possible with the first drug.

Exceptions to recommending single initial therapy assessments are:

- Capazide (captopril/HCTZ) was approved for first line therapy because it reduced the need to dose 2 or three times per day to once a day.
- ZIAC (bisoprolol/HCTZ) earned a first-line claim through demonstration that one got better blood pressure reduction with low doses of the drugs in combination than you got with single

agents at high doses, *and* had less of either individual agent's adverse effects.

- HYZAAR (losartan/HCTZ earned a first-line claim by demonstrating that the combination was effective and well-tolerated in a patient population with extremely elevated blood pressures, very unlikely to reach a blood pressure goal on either drug alone and in a population where a delay of control was most likely to lead to adverse outcomes even during short periods of inadequate blood pressure effect. By agreement with the Division, "very unlikely to reach goal" was defined as <10% reaching goal on monotherapy. For showing this, HYZAAR got a limited first-line indication: "This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients."

It was this latter pathway that was followed for AVALIDE (irbesartan/HCTZ). The study easily showed better blood pressure control on the combination than on monotherapy, and the combination regimen was well tolerated. However, irbesartan alone was effective in achieving goal in 33% of these subjects; thus, this population failed to meet the "very unlikely to reach goal" criterion.

The Division recognized that there were many problems with the current basis for achieving first-line claim, and invited SPONSOR to make a case for altering the paradigm. Among the issues are:

- The arbitrariness of the blood pressure goals.
- The goals being independent of patient risk factors (e.g. diabetic patients have different goal BPs).
- The arbitrariness of the "very unlikely" criterion
- The actual risks of "dose-independent" adverse events
- The ambiguity in what constitutes tolerability to starting two drugs
- The fact that most hypertensive patients are on multiple drugs.
- The fact that many people need multiple drugs at the time of initiating treatment.

The Cardio-Renal Advisory Committee is asked to consider …

- … how these and any other pertinent considerations should be weighed in deciding when to use combination products for first-line use.
- … whether the data for AVALIDE suffice to obtain such a claim.

- … how the properties of a combination product can be described in labeling to give physicians the best possible insight into how best to use it.

To address the general issue of a sensible basis for approving a combination product for first-line use, please consider the following questions:

1. All of the studies on the benefit of antihypertensive drugs in the prevention of cardiovascular events incorporated a stepped therapy approach using single drugs at low doses with titration to the maximum tolerated dose prior to adding a second and third medication. How does that affect your thinking about first-line use for combinations?
2. Please comment on the evidence to support and relevance of the following factors that might commend initial or early use of antihypertensive combinations:
    - Even at the time of initial diagnosis, most patients require more than one antihypertensive product to control blood pressure.
    - Lower blood pressure, at least until hypotension becomes symptomatic, is associated with a lower risk of cardiovascular events.
    - Antihypertensive drugs are, for the most part, among the safest drugs around.
    - The specific nature of the combination product. For example, would the rules be different if neither of the components were ACE-I or ARBs where the dose dependent adverse effects are minimal?
    - Are there other factors to consider?
3. What is the role of a study targeting a refractory population, like the one done with Avalide?
    - Is it necessary? Would the usual factorial study have been sufficient?
    - What population would be most appropriate to assess the safety consequences of initiating therapy with more than one drug? Should it, for instance, be enriched in elderly patients, who, one might expect, would be less tolerant of excessive pharmacological effect?
4. What adverse effects of AVALIDE would support a slower approach to combination therapy?
    - Symptomatic hypotension or syncope

- Hypokalemia
- Are there other adverse consequences to consider?

5. Demonstrating blood pressure effects in clinical trials requires many subjects, many replications, and carefully controlled conditions unlike clinical practice. Is there a value in terms of expected clinical outcomes to reducing the number of titration steps a physician is expected to make?
6. Is there a quantitative risk-benefit assessment that provides credible support for the initial use of AVALIDE? If so, should initial use be limited to a specific population?
7. On the basis of available data, should AVALIDE be approved for first-line use? Please vote. If you do not believe the data are adequate to support approval, describe what additional data would be needed?
8. If AVALIDE were approved for first-line use, should it have an INDICATION with constraints similar to those for HYZAAR or is it possible to give better advice? A major element of better advice is a better description of the expectations of using irbesartan alone and in combination.
    - The placebo effect observed in controlled clinical trials has at least two components. Please comment on whether either component is relevant to clinical practice.
        i. Regression to the mean
        ii. Accommodation to the clinical setting
    - Should the description in the label be based on placebo-subtracted data?
    - Labeling for outcome claims (previously discussed with the Advisory Committee) will include general language about the goal for blood pressure being a function of other cardiovascular risk factors. Should the description of the effects of AVALIDE take various goals into consideration?
    - Should the description take into consideration the likelihood of getting to goal on each component alone, or just irbesartan?
    - Did subgroup analyses show other factors—like age or race—that should be considered?
    - Should the description take into consideration the dose of each component, or just a dosing strategy?
    - Should the description focus or systolic pressure, diastolic pressure, or both simultaneously?

- Please identify any data presentation you saw that you felt best communicated the necessary information in a manner understandable by a practicing physician.